Technology Assessment

Technology Assessment Program

Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment

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Report on the Evidence Regarding Off-Label Indications for Targeted Therapies used in Cancer Treatment

Technology Assessment Report

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Duke Evidence-based Practice Center

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Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Executive Summary

Background

The term "targeted therapies" refers to antineoplastic treatments designed not to kill cells but, more precisely, to attack growth factors, cell surface receptors, and intracellular proteins that mediate the cancer cell's ability to proliferate, grow, or evade cell death. Examples of targeted therapies include small molecule inhibitors, monoclonal antibodies, and conjugated agents. Intended to damage or destroy cancer cells while minimizing the effects on normal cells, several targeted therapies have been successfully brought into routine clinical use, with approval from the U.S. Food and Drug Administration (FDA) for specific indications. The use of these FDA-approved agents has expanded to include multiple indications other than those for which they received FDA approval (i.e., "off-label indications"); in current clinical practice in oncology, off-label prescribing is common.

The primary purpose of this technology assessment is to evaluate the state of the evidence for/against the use of selected targeted therapies for off-label indications. Secondarily, the report also considers the practicality of the traditional systematic review approach, when applied to examine the evidence in rapidly evolving therapeutic areas such as targeted therapies for various cancers.

Methods

Through review of four drug compendia – the American Society of Health-System Pharmacists' *American Hospital Formulary Service-Drug Information* (AHFS-DI; 2006 version); National Comprehensive Cancer Network's (NCCN) *Drugs and Biologics Compendium* (online version); *United States Pharmacopeia Drug Information* (USP-DI; 2006 version); and Elsevier Gold Standard's *Clinical Pharmacology* (online version) – 19 off-label indications for eight targeted therapies were identified that were (1) FDA-approved, (2) marketed in or before January 2007, and (3) clearly recommended by at least one of the four compendia. MEDLINE® was searched through September 14, 2007, for potentially relevant publications. Studies were included if they were conducted in humans, investigated one of the 19 drug/disease combinations of interest, and reported at least one of the following outcomes: survival, disease-free survival, tumor response (any criteria acceptable), quality of life, or adverse effects. All study designs were included. This search of the published literature was supplemented by a search for relevant unpublished conference abstracts from the 2006 and 2007 annual meetings of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH).

Data were abstracted from included journal articles and abstracts directly into summary tables for each drug/disease combination by one investigator and over-read by another. Abstracted data included: study design, phase, selection/randomization, and eligibility criteria; number of patients, median age, previous treatment, stage of disease, drug dose per day, and outcomes sought; tumor response (number with tumor response assessed, complete response, partial response, stable disease, progressive disease); survival (overall, median, disease-free); and adverse events and tolerability. Study quality was assessed in relation to both internal validity

(e.g., randomization and allocation concealment; similarity of compared groups at baseline; specification of eligibility criteria; blinding of assessors, care providers, and patients) and external validity (e.g., description of the patient population, similarity to the target population of the report, use of highly selective criteria). In addition to data abstraction and quality analysis, a narrative description of study findings was prepared.

Results

Results for each of the 19 systematic reviews undertaken for this technology assessment are presented in summary tables in an Appendix to the main report. Here we provide results of the overarching endeavor to describe the state of the evidence for/against the use of targeted therapies for specified off-label indications in oncology.

In this set of systematic reviews of off-label indications for targeted therapies used in oncology, data relevant to the efficacy of any given drug varied greatly in quantity and quality. A high degree of heterogeneity in the data often prevented the combining of data, as required by traditional systematic review methodology, and complicated comparisons of results across studies. The variable and often inadequate quality of available data in this area also impeded efforts to draw definitive conclusions regarding safety or efficacy.

This technology assessment comprised 19 discrete systematic reviews; as such, it represents a large-scale undertaking. A principal difficulty encountered repeatedly was that of establishing a cut-off date for study inclusion. New evidence – with data that might potentially change conclusions, and hence warranted consideration for inclusion – continued to emerge after each of three arbitrarily chosen cut-off dates for study inclusion.

Discussion

Systematic reviews are not always a feasible and/or reliable way to answer questions regarding clinical effectiveness of new therapies. In areas where the pace of research is rapid, such as targeted therapies for off-label indications in oncology, the sheer volume of research and its heterogeneity make the process of systematic review challenging, if not impossible, within a reasonable timeframe.

In fields where the evidence is rapidly emerging and where the disease or condition entails clinical urgency, timeliness of evidence review is seriously challenged when using traditional systematic review methodology. Systematic reviews require "drawing a line in the sand," i.e., establishing an arbitrary cut-off date for study inclusion. Publication of new, potentially relevant, studies led the authors of this report to redefine the inclusion period three different times in the effort to include potentially relevant new information. Yet establishing a final cut-off date is eventually a necessity; this means that the results of any systematic review may be out of date even before completion of that review or its publication.

The compendia, a primary source of synthesized evidence for practicing clinical oncologists, are a vital, albeit imperfect, component of current evidence-based practice. The exercise represented by this technology assessment, i.e., the effort to describe the current evidence supporting/refuting the use of targeted therapies, represents an attempt to conduct on a limited scale the task performed by the compendia for the full off-label armamentarium in oncology.

The difficulties encountered on the smaller scale of this technology assessment suggest that the compendia's task is monumental and fraught with challenge. Considering the difficulties inherent in their purpose, the compendia perform an impressive service. Until a tested system is established to ensure access to comprehensive, timely, high-quality data, it is important to work with the compendia to continue to provide clinicians with a source of evidence that can guide their clinical decisions – while recognizing that this evidence synthesis is imperfect.

This technology assessment had several limitations. Variability in the quality and quantity of data made the drawing of conclusions regarding either the efficacy or the safety of the included drugs and respective indications difficult (if possible) and uncertain. Publication bias may have skewed results, because publication of negative results typically lags behind publication of positive results. The literature examined fell within a 10-year window, and reviews may have excluded relevant studies published before or after the endpoints. In particular, the literature reviews did not include published reports indexed in MEDLINE® after September 14, 2007.

Several areas for potential improvement in the current system of evidence development and review emerged through the conduct of this technology assessment. First, better definition of what constitutes "evidence" could help to minimize opinion and subjectivity in the process of evidence reporting. Second, the establishment of a standard approach for reporting on factors relevant to quality (e.g., study phase [e.g., Phase II, Phase III], presence/absence of a control group, blinding) could facilitate critical evaluation and weighting of published evidence. Third, an articulated consensus on the role of comparative effectiveness research in the evaluation of cancer treatments could strengthen both evidence generation and review. Finally, concerted national attention is well-directed toward the development and implementation of a new system for evidence review, one that is designed for rapid learning and expedient translation of research results into clinical practice improvements, and that features evaluation of the comparative effectiveness of available treatments in real-world clinical populations.

Chapter 1. Background

Clinical Context

Traditional anticancer treatment has relied on cytotoxic chemotherapy as a primary intervention. Chemotherapy has proven effective for many cancer diagnoses because it is toxic to rapidly proliferating cells such as tumor cells. As a systemic treatment, however, it also affects normal cells in the surrounding or peripheral area, and can alter, impair, or destroy those cells. Rather than damaging only the tumor, it typically causes multiple undesirable side effects which impair the patient's function, quality of life, and even survival.

Over the past 10 years, seeking to develop antineoplastic treatments with less associated toxicity, scientists and clinicians have tested a number of more specific agents termed "targeted therapies." These agents are designed not to kill cells but, more precisely, to attack growth factors, cell surface receptors, and intracellular proteins that mediate a malignancy's ability to proliferate, grow, or evade cell death. Examples of targeted therapies include small molecule inhibitors, monoclonal antibodies, and conjugated agents. Several of these agents have been successfully brought into routine clinical use.

Targeted therapies have been heralded as a promising new approach to cancer treatment; they have raised hopes and expectations of cure for previously intractable cancers, without the toxicity associated with traditional chemotherapy. They can be used as single agents, in combination with chemotherapy, or in combination with other targeted therapies. Their toxicity profile and scope of applicability differs from that of traditional chemotherapies. As new agents, with intensive research and development preceding their introduction into the market, they are currently very expensive.

Scientific enthusiasm surrounding targeted therapies has prompted a flurry of research activity focused on harnessing their potential. Consequently, the list of potential uses for targeted therapies has expanded, and continues to expand rapidly, beyond the original FDA-approved indications for these new drugs. The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following Evidence-based Practice Center: Duke (Contract Number: HHSA 290-02-0025). This technology assessment has been conducted to evaluate the state of the evidence supporting the use of targeted therapies outside of their FDA-approved indications; it also evaluates the practicality of traditional systematic review approaches in rapidly evolving therapeutic areas such as targeted therapies for various cancers.

Technology Assessed

The advent of targeted therapies has raised hopes of a new approach to cancer treatment – one that does not entail the deleterious collateral damage, adverse effects, or symptom side effects of traditional chemotherapy and radiation therapy. Targeted therapies that specifically damage or destroy cancer cells, while minimizing the effects on normal cells, currently include antibody therapies and small molecules, with gene therapies potentially an additional approach on the horizon.

Types of Therapies Considered

Antibody therapies use targeted antibodies to bind to a specific protein, thereby blocking its activity. Other mechanisms may also factor into the success of antibody therapies in treating cancer. For example, the complement and immune systems can recognize antibodies, and may destroy the cells to which the antibodies are bound.

Monoclonal antibodies are classes of identical antibodies produced by a single type of immune cell, and that have an affinity for a specific antigen. Attaching to tumor cells, monoclonal antibodies mark the cell for attack by the immune system, block specific transmembrane receptors, or deliver chemotherapeutic or radioactive drugs. Bevacizumab, now the standard of care for treatment of metastatic colon cancer, is an example of a monoclonal antibody in widespread clinical use.

Conjugated agents, another antibody therapy, represent a class of targeted therapies in which an antibody or protein is linked to a toxin or radioisotope. The antibody or protein component brings the entire cytotoxic agent to the cancer cell of interest, hopefully without binding to normal cells. This approach is designed to provide the benefit of radiation or chemotherapy on a cell-specific basis. An example is tositumomab, where an anti-CD20 antibody is covalently bound to ^{131}I, indicated for use in refractory follicular lymphoma. Since these drugs are rarely used off-label at present, they are not discussed further in this technology assessment.

Small molecule targeted therapies are drugs specially designed to bind certain receptors that inhibit signaling pathways for growth and proliferation within tumor cells. Small molecule inhibitors enter cells and disrupt protein functions and interactions. An example of a small molecule is imatinib, which has become standard of care for chronic myelogenous leukemia and gastrointestinal stromal tumors (GIST).

Many small molecules, including imatinib, inhibit the function of tyrosine kinases. Normally, the binding of various soluble factors outside normal tissue to cell surface receptors activates tyrosine kinases. These tyrosine kinases may either be a component of the receptor or an associated protein. When activated, they turn on a cascade of other proteins inside the cell, ultimately increasing the cells' ability to grow and divide. One way in which cancer cells proliferate and become resistant to cell death is by increasing the number of cell surface receptors, thus amplifying pro-survival signals. Another mechanism is mutatation of the tyrosine kinases associated with these receptors, thereby resulting in constitutively active kinases, ultimately causing uncontrolled cell proliferation. In either situation, tyrosine kinase inhibitors locate and bind to specific proteins, thereby causing a desirable effect, such as inhibiting vascular endothelial growth.

Another category of small molecule inhibitor is the proteosome inhibitor. Cellular functions such as proliferation and cell death in normal cells are dependent on levels of various intracellular proteins. The levels of these proteins are controlled in part by degradation, a function performed by the proteosome. Treatment with a proteosome inhibitor blocks the degradation of proteins; in cancer cells, this can push the cell towards cell death.

Gene therapies deliver genetic material into an individual's cells using a vector, usually a virus. The purpose of these treatments is to block expression of genes that promote tumor development, and/or to replace missing or defective tumor-suppressor genes. Such treatments may make tumor cells more susceptible to standard chemotherapy or radiotherapy. They may make normal tissues less susceptible to the damage induced by conventional treatments. Or, by eliminating specific abnormalities that triggered the normal cell to become neoplastic, they may

remove the tumor cell's ability to proliferate unchecked. Because gene therapy is, as yet, an experimental treatment that is not available outside of a clinical trial, gene therapies are not included in this technology assessment.

Inclusion criteria for targeted therapies

This technology assessment evaluates the strength of the evidence for targeted therapies. To include a maximum number of agents being used for off-label indications in oncology, we included medications that were: (1) FDA-approved targeted agents; (2) marketed in January 2007 or before; and (3) with compendia-listed indications other than the FDA-approved indication as of December 2006.

Consistent with the rapid evolution of this technology, some indications that were off-label in December 2006 are now FDA-approved; these reviews are still included in this summary since they provide insight into the nature of the literature as a whole.

The concept of a disease-specific indication for a drug is fluid. For some drug/disease indications the relationship represents a one-to-one relationship. For others, there are multiple different treatment situations within a disease category such that defining "indication" as the disease in which the drug is used is too broad and makes it difficult to draw conclusions about the data (e.g., alemtuzumab for NHL). Conversely, the indication may need to be sharply narrowed to reflect appropriate use of a drug only in certain times in a disease trajectory (e.g., for refractory disease after prior specified therapy, or in the setting of a positive biomarker). For this report, we used the drug/disease indication as specified within the compendia, since that reflects the indication considered for reimbursement purposes.

Policy Context

Targeted therapies are increasingly used in cancer treatment because of (1) their potential for improved efficacy in comparison to traditional chemotherapies, and (2) their association with fewer side effects. Heralded as the centerpiece of cancer care of the future, targeted therapies are the subject of a large volume of recent and current research. Research on targeted therapies is proceeding at a rapid pace. Between January 1, 2000, and September 1, 2008, the U.S. Food and Drug Administration (FDA) approved 41 anticancer drugs; 17 of these were targeted agents.[1]

Like other pharmaceutical treatments, targeted therapies must be approved by the FDA before being prescribed outside of the clinical trial setting. A major purpose of FDA review is to ensure patient safety; the National Cancer Institute Common Toxicity Criteria for Adverse Event reporting (CTCAE) provides standard terminology and definitions for adverse event reporting. Once FDA-approved, however, drugs may be used in new contexts as indicated by the available literature, based on the judgment of the prescribing physician rather than on specific requirements dictated by the FDA. When a drug is prescribed for an indication other than that for which it has obtained FDA approval, the prescription is termed "off-label." Third-party reimbursement for off-label uses of medications varies. For drugs falling within a category reimbursed by CMS (e.g., injection or Medicare Part D), payment for an off-label use of a drug is guided by whether that drug is listed for the particular off-label indication in one of the approved drug compendia.

Off-label prescribing in oncology is facilitated by Medicare insurability of off-label uses of anticancer drugs and biologics, stipulated under Social Security Act Section 1861(t)(2)(B)(ii)(I) and (II), under the Omnibus Budget Reconciliation Act of 1993. This statute recognized certain compendia as authoritative sources for determining a "medically-accepted indication" of drugs and biological agents used off-label in an anticancer chemotherapeutic regimen, unless the Secretary of Health and Human Services (HHS) determines otherwise. For purposes of the legislation, a compendium was defined as "a comprehensive listing of FDA-approved drugs and biologicals or a comprehensive listing of a specific subset of drugs and biologicals in a specialty compendium" (§414.930). The statute originally indicated that medically-accepted indications would be determined by three designated compendia: American Medical Association Drug Evaluations (AMA-DE), American Hospital Formulary Service Drug Information (AHFS-DI),[2] and United States Pharmacopeia Drug Information (USP-DI).[3] While the statute pertained specifically to CMS, most other third-party payers and state legislatures have followed suit.[4]

Implementation of the legislation has shifted in the course of compendia history. The AMA-DE is no longer published; its contents were incorporated into the USP-DI. Publication of the USP-DI ceased in 2007, with contents rolled into a successor compendium, DrugPoints. On June 6, 2008, CMS announced that it would recognize an additional compendium produced by the National Comprehensive Cancer Network (NCCN), the NCCN Drugs & Biologics Compendium, as a mandated reference for establishing coverage policy and coverage decisions regarding the use of drugs and biologics in cancer care. As of the time of this technology assessment report, the current recognized authoritative compendia are: National Comprehensive Cancer Network's (NCCN) *Drugs and Biologics Compendium*; Thompson Micromedex' *DrugDex*; Elsevier Gold Standard's *Clinical Pharmacology*; and American Society of Health-System Pharmacists' (ASHP) *American Hospital Formulary Service-Drug Information (AHFS-DI)*.[5] It should be noted that there is no standardized approach across the various compendia to determining which off-label indications should be included.

Many of the newly developed targeted therapies have been studied, or are currently being studied, for use in disease scenarios other than those for which they originally received FDA approval. Based on this emerging evidence, certain off-label indications are listed in drug compendia; these listings are significant in that oncologists often refer to the compendia when prescribing drugs for off-label uses.

Against this backdrop of off-label prescribing based on compendia listings of non-FDA-approved indications for cancer drugs, CMS requested a technology assessment of the efficacy and safety of selected targeted therapies when prescribed for off-label indications. Given the rapid evolution of this literature, a secondary purpose of the technology assessment was to conduct a horizon scan of early-stage trials (Phase I or prominent preclinical studies) of these agents. This limited horizon scan was intended to complement information gained through systematic review of the current body of literature, and to identify expected future directions. CMS will consider this information as background to its further discussion of coverage for and policies regarding targeted therapies.

Scope of Study

The scope of this technology assessment is limited to eight targeted therapy drugs and 19 respective off-label indications (Table 1). These drug/indication combinations were derived

from a list of all targeted therapy drugs available through the end of 2006. Four compendia – AHFS-DI (2006 version), NCCN Drugs & Biologics Compendium (online version), USP-DI (2006 version), and Clinical Pharmacology (online version) – were searched for listings of off-label indications for these drugs. The drug/indication combinations selected for inclusion in the current technology assessment are those for which these compendia provided clear recommendations. FDA-approved indications of these eight drugs are listed in Table 2.

Table 1. Drugs and off-label indications included in the technology assessment

Targeted therapy	Off-label indication(s)
Alemtuzumab (Campath®)	Cutaneous T-cell lymphoma
	Non-Hodgkin lymphoma
	T-cell prolymphocytic leukemia
Bevacizumab (Avastin®)	Breast cancer*
	Epithelial ovarian cancer
	Pancreatic adenocarcinoma
	Renal cancer*
Bortezomib (Velcade®)	Non-Hodgkin lymphoma
Cetuximab (Erbitux®)	Pancreatic adenocarcinoma
Erlotinib (Tarceva®)	Head and neck cancer
Gefitinib (Iressa®)	Head and neck cancer
Imatinib (Gleevec®)	Acute lymphoblastic leukemia*
	Chronic eosinophilic leukemia*
	Dermatofibrosarcoma protuberans*
	Myelodysplastic syndrome*
	Systemic mastocytosis*
Rituximab (Rituxan®)	Chronic lymphocytic leukemia
	Nodular lymphocyte-predominant Hodgkin disease
	Waldenstrom's macroglobulinemia*

* Indications that were approved by the FDA at some point during the completion of this technology assessment.

Table 2. FDA-approved indications of drugs included in the technology assessment, as of January 2007*

Drug	FDA-approved indication(s)
Alemtuzumab (Campath®)	• B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy
Bevacizumab (Avastin®)	• First-line treatment of patients with metastatic carcinoma of the colon or rectum
Bortezomib (Velcade®)	• Multiple myeloma patients who have received at least one prior therapy • Relapsed/refractory mantel cell lymphoma
Cetuximab (Erbitux®)	• In combination with radiation therapy, indicated for locally or regionally advanced squamous cell carcinoma of the head and neck. As a single agent, indicated for recurrent or metastatic head and neck carcinoma when prior platinum-based therapy has failed. • In combination with irinotecan, indicated in patients with colorectal carcinoma refractory to irinoctecan-based chemotherapy. As a single agent, indicated for metastatic colorectal carcinoma intolerant to irinotecan-based chemotherapy.
Erlotinib (Tarceva®)	• As a single agent, indicated for locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen • In combination with gemcitabine, indicated for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer
Gefitinib (Iressa®)	• As a single agent, indicated for continued treatment of locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxal chemotherapies among patients who are benefiting or have benefited from gefitinib
Imatinib (Gleevec®)	• Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors GIST • PH+ CML in chronic phase or in blast crisis, accelerated phase after failure of interferon-alpha therapy, or whose disease has recurred after stem cell transplant, or who are resistant to interferon-alpha therapy
Rituximab (Rituxan®)	• Relapsed or refractory low-grade or follicular, CD20-positive, B-cell, non-Hodgkin's lymphoma • First-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens

* Note: Drugs may be approved for use in combination with other agents not on this list.

Chapter 2. Methods

Selection Criteria

Selection of Drugs

Medications currently being used for off-label indications in oncology were included in the systematic review if they met the following inclusion criteria:

- Targeted agent;
- FDA-approved;
- Marketed in January 2007 or before; and,
- Having compendia-listed indications other than the FDA-approved indication, in one of the following four compendia as of December 2006: AHFS-DI (2006 version), NCCN (online version), USP-DI (2006 version), and Clinical Pharmacology (online version).

Selection of Studies

Each citation identified from the search strategies was evaluated by the investigators according to the following selection criteria.

Studies were included in the evidence tables if they met all of the following *inclusion criteria:*

- Conducted in humans;
- Investigated use of the candidate drug for the off-label indication;
- Addressed one of the off-label indications listed in Table 1 for included drugs;
- Reported at least the following outcomes for efficacy: survival, disease-free survival, tumor response, quality of life, or adverse effects.

All study designs – case reports, retrospective case series, clinical trials (Phase I, Phase II, Phase III, Phase IV), and large database (outcomes) studies – were included. Any type of tumor response criteria was considered to meet the eligibility criterion regarding efficacy outcome.

Studies were not included if they met any of the following *exclusion criteria:*

- Described only predictors of response;
- Was a pharmacokinetic study (i.e., a study in which outcomes are drug levels);
- Was conducted in a non-human setting (i.e., animal model or *in vitro*).

Our previous review of the quality of the compendia found that the compendia used information from abstracts, review articles, and other types of reports, in addition to randomized controlled trials, to support their listed recommendations. Hence, to ensure that our dataset was complete, we also included this level of information in our review. Studies that did not meet the eligibility criteria for inclusion in the evidence tables, or that were presented in abstract form only (i.e., without a companion published manuscript), were summarized in horizon scan and abstract tables only.

Search Strategy

A systematic MEDLINE® search employed the following algorithm:

1 alemtuzumab.mp. (1034)
2 campath.mp. (669)
3 exp lymphoma, t-cell, cutaneous/ (6371)
4 exp lymphoma, non-hodgkin/ (68316)
5 leukemia, prolymphocytic/ (391)
6 leukemia, t-cell, chronic/ (185)
7 leukemia, lymphocytic, chronic/ (8687)
8 (1 or 2) and (or/3-7) (421)
9 (bortezomib or velcade).mp. (1733)
10 exp lymphoma, non-hodgkin/ (68316)
11 9 and 10 (128)
12 (bevacizumab or avastin).mp. (2720)
13 exp Breast Neoplasms/ (165832)
14 ovarian neoplasms/ (49018)
15 exp pancreatic neoplasms/ (42132)
16 exp kidney neoplasms/ (46624)
17 12 and (or/13-16) (489)
18 (cetuximab or erbitux).mp. (1497)
19 exp pancreatic neoplasms/ (42132)
20 18 and 19 (61)
21 (erlotinib or tarceva).mp. (1300)
22 exp "Head and Neck Neoplasms"/ (195248)
23 21 and 22 (73)
24 (gefitinib or iressa).mp. (2337)
25 exp "Head and Neck Neoplasms"/ (195248)
26 24 and 25 (143)
27 (imatinib or gleevec).mp. (5493)
28 exp leukemia, lymphocytic, acute/ or exp leukemia, t-cell, acute/ (16285)
29 chronic eosinophilic leukemia.mp. (115)
30 dermatofibrosarcoma/ or dermatofibrosarcoma protuberans.mp. (1065)
31 exp Myelodysplastic Syndromes/ (12465)
32 exp mastocytosis, systemic/ (383)
33 27 and (or/28-32) (417)
34 (rituximab or rituxan).mp. (5132)
35 exp leukemia, lymphocytic, chronic/ (8687)
36 hodgkin disease/ or "nodular lymphocyte predominant hodgkin$ disease".mp. (28136)
37 waldenstrom macroglobulinemia/ (4062)
38 (waldenstr$ adj1 macroglobulinemia).mp. (4395)
39 34 and (or/35-38) (523)

Because we were frequently notified of new reports that might have been missed if the search were not updated, the above search strategy was conducted at multiple timepoints during the

conduct of this technology assessment. With respect to collecting abstracts and published reports for review in the literature synthesis, the search was last run on September 14, 2007.

Because the literature was evolving rapidly, and because the compendia frequently referenced unpublished conference abstracts from key international meetings such as the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) annual conferences, we supplemented the literature search with searches of conference abstracts for 2006 and 2007 (ASH and ASCO). We did not repeat this in 2008 or 2009, because the conference abstracts were minimally instructive to our overall understanding of the literature. In order to search the abstracts, we used the professional organizations' online databases, searching by drug name cross-matched with disease and using the same search terms as outlined above.

Data Abstraction

Data were abstracted from journal articles and abstracts directly into standardized data tables by four investigators independently. One data table was completed for each drug/disease combination (i.e., a targeted therapy and a specific off-label use of that targeted therapy). Each data table was over-read by an investigator other than the one who originally abstracted the data for that drug/disease combination.

The following data were abstracted from included studies: study design, phase, selection/randomization, and eligibility criteria; number of patients, median age, previous treatment, stage of disease, drug dose per day, and outcomes sought; tumor response (number with tumor response assessed, complete response, partial response, stable disease, progressive disease); survival (overall, median, disease-free); adverse events and tolerability; and quality assessment (see below). Data tables were created using Microsoft Excel (Microsoft, Inc.; Redmond, WA).

Please note the following additional details:

- Journal articles which reported results of Phase I dosing studies were considered as horizon scan reports rather than as full-text reports; hence these reports were not included in the primary data tables.
- For most drug/disease combinations reviewed, data populating the adverse events tables were abstracted from full reports only, and not from abstracts. Due to space constraints, abstracts do not typically include information on adverse events.

Quality Assessment

The quality of included studies was assessed on the following quality elements: internal validity (e.g., randomization and allocation concealment; similarity of compared groups at baseline; specification of eligibility criteria; blinding of assessors, care providers, and patients) and external validity (e.g., description of the patient population, similarity to the target population of the report, use of highly selective criteria). We adopted as a framework the quality assessment criteria used in a 2003 British report on imatinib mesylate for unresectable and/or metastatic gastrointestinal stromal tumors (GIST).[6] These criteria were, in turn, drawn from a 2001 methodological publication of the British National Health Service Centre for Reviews and Dissemination.[7] The specific quality criteria we selected cover the range of study designs used

in this report including experimental studies, cohort studies, case-control studies, and case series. Point scores were allocated by assigning one point for each quality category. There were a total of six possible categories. Quality ratings of "yes" to a quality criteria were assigned 1 point; no and unknown were both assigned 0 points. The last category, adequate description of subseries, was not applicable to all studies. Hence, the total possible quality points were 5 or 6 depending upon the applicability of the subseries category. High quality studies were those with ≥ 3/5 or 4/6 points. Abstract quality was not scored.

Data Synthesis

In addition to data abstraction and quality analysis, a narrative description of study findings was prepared. Results are presented in Chapter 3, immediately below.

Chapter 3. Results

Velocity of Evolution of the Literature

An important outcome of this technology assessment is its description of the state of the evidence in a single, quickly evolving, field of biomedical research. The body of literature surrounding targeted therapies is growing at a rapid rate (Table 3). Significant difficulty was encountered in the conduct of this study due to the continuous change in the available evidence; akin to drawing a line in the sand, we placed time boundaries for study inclusion – a necessity in order to proceed with any search strategy. As new information became available, however, we felt compelled to redraw the line in the interests of performing the most complete systematic review possible. This approach is largely infeasible and delayed completion of the study. In a larger sense, the "moving target" nature of evidence calls into question the feasibility of a time-bounded, static, evidence review process based on systematic review, in an environment where the evidence pool is continuously expanding.

Illustrating this challenge, Table 3 presents the number of identified publications available by December of the search year. The searches included only those drug/disease combinations planned for this technology assessment, using the search strategy outline above; total number of papers are presented by agent (summing across diseases, if more than one drug/disease combination was evaluated for that particular agent).

Table 3. Number of identified publications reporting on select off-label indications of each targeted therapy

Targeted therapy	2005	2006	2007	2008	2009*
Alemtuzumab (Campath®)	238	290	343	395	447
Bevacizumab (Avastin®)	82	148	257	420	558
Bortezomib (Velcade®)	32	52	82	119	137
Cetuximab (Erbitux®)	22	28	38	58	64
Erlotinib (Tarceva®)	15	31	49	68	78
Gefitinib (Iressa®)	58	87	110	137	149
Imatinib (Gleevec®)	173	228	306	383	451
Rituximab (Rituxan®)	286	352	418	481	565

*2009 figures are extrapolated using 6-month figures, as follows: 2009 estimate = 2008 estimate + [(total through June 2009) – (total through 2008)] x 2.

Systematic Literature Review for Drug/Disease Combinations

The Appendix summarizes the literature identified through the final search date of September 14, 2007. Each section covering a specific drug/disease combination follows the same structure, namely:

» Background
- Overview of drug
- Overview of disease
- Rationale for use of drug in disease

» Methods
» Results
- Studies identified
- Efficacy
- Survival
- Adverse Events
- Horizon Scan

» Discussion (Summary of findings)
» Supporting tables
- Appendix Table 1 – Full published reports of studies for drug/disease combination
    - Study
    - Study design
    - Patients
    - Tumor response
    - Survival
    - Other including quality assessment
- Appendix Table 2 – ASH & ASCO abstracts (2006/2007) presenting studies for drug/disease combination
    - Study
    - Study design
    - Patients
    - Tumor response
    - Survival
    - Other including adverse events and tolerability
- Appendix Table 3 – Horizon scan studies for drug/disease combination
    - Study
    - Study design
    - Drug dose per day
    - Sample size
    - Comments
- Appendix Table 4 – Adverse events (grade 3 & 4 only) from full published reports of studies for drug/disease combination

The summary of findings by indication presented here (Table 4) recapitulates the discussion section of each drug/disease section.

Table 4. Indications and summary of the systematic evidence review (last search date September 14, 2007)

Targeted therapy	Off-label indication(s)	Summary discussion
Alemtuzumab (Campath®)	Cutaneous T-cell lymphoma	There are emerging data for the role of alemtuzumab in the treatment of patients with progressive CTCL. Historically, single and combination chemotherapies for advanced disease (e.g., gemcitabine; methotrexate; cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone [CHOP]) have had variable response rates, high risk of neutropenic infections, and short median survivals. In Phase II reports, alemtuzumab compares favorably to these existing treatment options. This review identified four published Phase II reports suggesting some efficacy, with PR rates ranging as high as 79% and median survival reaching 35 months (though a median survival rate as low as four months was also reported). The ASH abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. Toxicities were predominantly hematological and as expected. Over time, our understanding of the CMV risk with alemtuzumab is improving; this clarity stands out as the main emerging information in the most recently published abstracts.
	Non-Hodgkin lymphoma	These are some of the most mature and disparate data reflecting the efficacy of alemtuzumab for the treatment of patients with progressive lymphoma, most notably because this dataset encompasses the mix of studies from both before and after the FDA-approval of alemtuzumab for one NHL sub-type, CLL. Further, these data reflect the use of alemtuzumab in a variety of settings; e.g., as monotherapy for relapsed/refractory NHL and as a conditioning regimen for stem cell transplantation. As a result, the efficacy results are divergent and difficult to interpret. Key messages of the published dataset are the following: 1) alemtuzumab may have a place in the therapy of general NHL for heavily pre-treated patients who can tolerate the adverse event profile (e.g., patients with good performance status) and for whom there are no other established options; 2) alemtuzumab may have a significant role in the preparatory management for stem cell transplantation; 3) new NHL sub-classifications particularly responsive to alemtuzumab, such as monotherapy for newly diagnosed peripheral T-cell lymphoma, are likely to emerge; and, 4) adverse events for alemtuzumab are as expected (i.e., predominantly hematological), with data supporting the importance of CMV reactivation as a major concern with alemtuzumab. Demonstration of the alemtuzumab target, CD52, was not a requisite for study entry and not clearly linked to outcomes, although in nearly all of the NHL settings where alemtuzumab was used, the presence of CD52 could be confidently assumed.
	T-cell prolymphocytic leukemia	There are emerging data for the role of alemtuzumab in the treatment of patients with T-PLL. Historically, single-agent pentostatin therapy has resulted in reasonable response rates, though response duration is often short and disease progression and death occur relatively quickly. Second-line therapies remain unsatisfactory for this disease in most cases. In Phase II reports, alemtuzumab appears to be active in the second-line therapy of this disease, though disease-free and overall survival outcomes are were not adequately reported. A role for alemtuzumab as front-line therapy for T-PLL was not evaluated in the trials identified during this review. This review identified four published Phase II reports suggesting significant efficacy, with CR rates as high as 60% and median overall survival reaching 19 months in one report. The ASH/ASCO abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. As expected, toxicities were predominantly hematological and infectious. Over time, our understanding of the risk of CMV and other opportunistic infections with alemtuzumab is improving, resulting in appropriate prophylactic strategies and early detection and treatment of infectious complications.

Targeted therapy	Off-label indication(s)	Summary discussion
Bevacizumab (Avastin®)	Breast cancer*	Because multiple treatment regimens are available to patients with metastatic breast cancer, and patients with no visceral involvement will sometimes live for years with their disease, demonstration of survival benefit from the addition of a VEGF inhibitor to the treatment regimen will be difficult. This review identified a single clinical trial that assessed the marginal benefits and harms associated with bevacizumab as adjunctive therapy in the treatment of breast cancer. That trial compared capecitabine alone to capecitabine with bevacizumab among patients with previously treated metastatic breast cancer. Bevacizumab contributed to improved response rates but not progression-free survival. The existing literature suggests that bevacizumab is relatively well tolerated at doses of 10 to 15 mg/kg every two to three weeks. Leukopenia and hypertension were the two most common serious adverse events. The ASCO 2007 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. Additional research is needed to determine whether the addition of a VEGF antibody, which has clearly been shown to be effective in the treatment of some cancers, and for which there is biological plausibility for the treatment of breast cancer, adds significantly to the current treatment options for metastatic breast cancer in terms of survival benefit. The FDA approved the use of bevacizumab for breast cancer in 2008 based upon emerging data, some of which were not available at the time of the most recent literature search presented in this report.
	Epithelial ovarian cancer	There are compelling reasons to evaluate the use of monoclonal antibodies to VEGF in the treatment of epithelial ovarian cancer, especially in light of ovarian cancer's high mortality rate and the proven efficacy of this class of targeted therapies in the treatment of colon, rectal, non-small cell lung, and breast cancers, and glioma.. However, to date there are limited data that support the use of bevacizumab in the treatment of epithelial ovarian cancer. The published case series and case reports suggest that bevacizumab may contribute to clinical response, including reduction in CA125 levels. These studies were not designed to directly evaluate the efficacy of bevacizumab, however, and there is inherent bias in relying on case reports or retrospective case series to assess either efficacy or safety of interventions, especially those typically used in combination with other treatments. The ASCO abstract and horizon scan articles did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. There were insufficient data identified in this review to comment on toxicities potentially associated with bevacizumab in the treatment of ovarian cancer.
	Pancreatic adenocarcinoma	The findings from the Phase II studies suggest that bevacizumab does little to improve clinical outcomes in the treatment of pancreatic adenocarcinoma. Complete responses ranged from 0 to 1% in these studies. The single Phase III trial, which enrolled 602 patients and compared gemcitabine plus bevacizumab 10 mg/kg to gemcitabine plus placebo, did not demonstrate a survival benefit associated with bevacizumab. These findings are consistent with recently published expert opinion that there is no consensus about second-line therapy after pancreatic cancer progression after gemcitabine failure.

Targeted therapy	Off-label indication(s)	Summary discussion
	Renal cancer*	Given the upregulation of VEGF associated with the mutated version of the von Hippel–Lindau tumor suppressor gene in the majority of renal cell cancers, drugs that target the inhibition of angiogenesis are logical therapeutic agents. The findings from this review support the use of bevacizumab in the treatment of renal cell cancer. The three fully published trials as well as the published abstracts demonstrated that bevacizumab appears to be both well tolerated and efficacious. The Phase III clinical trial published in abstract form demonstrated a 30.6% complete response associated with bevacizumab, compared to 12.4% associated with placebo when administered along with interferon therapy. Hypertension and proteinuria are among the more common adverse events associated with bevacizumab therapy.
Bortezomib (Velcade®)	Non-Hodgkin lymphoma	Although preclinical studies suggest a potential role for proteasome inhibitors in the treatment of hematologic malignancies, the studies identified in this review do not provide sufficient evidence to recommend the use of bortezomib in the treatment of NHL and related diseases. The quality of the uncontrolled Phase II studies was generally poor, and there were no randomized controlled trials that compared bortezomib to alternative therapies. Clinical response was highly variable, with CR and PR rates ranging from 0 to 90%. The patient populations represented in the studies were heterogeneous, as were the history of prior treatments and the other interventions used concurrently with bortezomib. Dosing of bortezomib ranged from 1.3 to 1.8 mg/m^2 at intervals ranging from 3 to 10 days. The ASH 2006, ASH 2007, and ASCO 2007 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. The horizon scan revealed reports of cardiovascular toxicities, including arrhythmias, as well as a potentially higher incidence of varicella herpes zoster among patients being treated with bortezomib. Further research is needed to determine what role, if any, bortezomib should have in the treatment of NHL, with the exception of mantle cell lymphoma.
Cetuximab (Erbitux®)	Pancreatic adenocarcinoma	Results from the clinical trials published as abstracts demonstate that the use of cetuximab as an adjunct in the treatment of pancreatic adenocarcinoma is associated with an increase in partial response from 8% to 16%. Only a single subject who received cetuximab had a complete response. Further research is needed to evaluate the efficacy and safety of cetuximab for patients with this cancer.
Erlotinib (Tarceva®)	Head and neck cancer	The overexpression of EGFR in 80% to 100% of HNSCC makes erlotinib a logical targeted therapy for HNSCC. The two full reports and the four abstracts in this review provide emerging evidence for the role of erlotinib in the treatment of patients with HNSCC. Historically, single and combination chemotherapies for advanced disease have had low response rates and short median survivals. In Phase II reports, erlotinib compares favorably to existing treatment options. This review identified two published Phase II reports suggesting some efficacy, with partial response and stable disease rates of 19% and 49%, respectively, in one of the studies. Complete response rates were highly variable across the six studies, ranging from 0 to 84%. There was a relatively low rate of toxicities reported in the two full reports, with dermatitis being the most commonly reported adverse event. The reports identified in this review did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates.

Targeted therapy	Off-label indication(s)	Summary discussion
Gefitinib (Iressa®)	Head and neck cancer	The paucity of published reports and the heterogeneity of the patient populations and the dosages studied preclude drawing conclusions at this time regarding the role of gefitinib in the treatment of HNSCC. Data available do not support its off-label use. Access to this drug has been severely restricted in the United States following the FDA approved labeling change in June 2005, such that gefitinib is seldom used either on-label for lung cancer or off-label for HNSCC. Interest in further clinical trials of this agent has also waned in the United States due to issues of access.
Imatinib (Gleevec®)	Acute lymphoblastic leukemia*	The constitutively activated tyrosine kinase bcr-abl, a product of the Philadelphia chromosome, is present in 20% to 30% of ALL cases. Because imatinib specifically targets cells with the Philadelphia chromosome, it is potentially useful as adjuvant therapy for patients with Ph+ ALL. This review identified two randomized clinical trials and 22 uncontrolled trials involving 1,430 patients with ALL, the vast majority of whom were previously untreated and were Philadelphia chromosome positive. Neither of the two randomized clinical trials identified in this review evaluated the efficacy of imatinib for ongoing treatment. One randomized trial demonstrated improved median survival when imatinib was added to ongoing to the induction regimen; all patients received imatinib during the ongoing treatment period in this study (the other randomized study did not have response or survival data available yet at the time of this review). The evidence from the Phase II trials suggests that this targeted therapy may be effective either as monotherapy or as combination therapy in the treatment of ALL, across the treatment settings studied, with CR rates in some studies reaching 100%. These favorable results must be considered in the context of the expected treatment success rates of existing therapies, which are generally high in the initial treatment of Ph+ ALL, maintained across treatment plans in children, and lead to treatment failure in adults; it follows that imatinib is usually used in adults with Ph+ ALL. The ASH/American Society of Clinical Oncology (ASCO) abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. These reports did, however, suggest that imatinib may be associated with a variety of different adverse events, including acute tumor lysis syndrome, cardiotoxicity, or pleural effusion.
	Chronic eosinophilic leukemia*	Each of the nine case reports or series considered in the horizon scan reported favorable responses to imatinib without significant toxicity in the treatment of chronic eosinophilic leukemia. The RT-PCR analysis suggests that there is sensitivity of the PDGFR alpha fusion to imatinib.

Targeted therapy	Off-label indication(s)	Summary discussion
	Dermatofibrosarcoma protuberans*	The vast majority of DFSP tumors have a chromosomal translocation that fuses the collagen gene with the PDGF gene, the result of which is the production of a self-stimulatory growth signal, rapid cell division, and tumor formation. This process involves the constitutive activation of the PDGF receptor, which provides a rationale for targeted inhibition of the PDGF receptor as a treatment strategy for patients with unresectable locally advanced or metastatic DFSP. This review identified two Phase II reports involving 35 patients with DFSP treated with imatinib as monotherapy. Neutropenia and maculopapular rash were the only Grade 3 adverse events reported. Fifty percent of patients in the full report demonstrated a PR and 36% of patients in the trial published as an abstract demonstrated a clinical response. In these Phase II reports, imatinib compares favorably to existing treatment options. The ASCO 2007 abstract and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. Given the rarity of DFSP tumors, the substantial mortality risk for those that transform into a sarcoma or metastasize, the lack of other systemic therapeutic interventions for DFSP, and the presence of the PDGF receptor as a target in DFSP, treatment with imatinib in DFSP is a sensible strategy even in the setting of few published reports and incomplete exploration in clinical trials identified in this review.
	Myelodysplastic syndrome*	Recent research suggests that some MDS patients express the PDGF receptor oncogene, and that PDGF has been implicated in the pathogenesis of various myeloproliferative disorders. This offers a rationale for targeted inhibition of the c-kit and PDGF receptor oncogenes as an MDS treatment strategy. This rationale, combined with the fact that MDS is often refractory to existing treatments, suggests that imatinib may be a potentially important targeted therapy for MDS. The published data described in this review suggest that imatinib is well tolerated in this patient population, with the only commonly occurring adverse event being neutropenic fever (21%). The two studies involving a total of fewer than 50 patients provide insufficient data to support firm conclusions, but their findings suggest that imatinib is not effective in the treatment of MDS. Complete response was achieved in a single patient, and only one patient achieved a partial response.
	Systemic mastocytosis*	Over the past few years, clinical research initiatives aimed at developing more tolerable and effective therapies for SM have investigated treatments, including imatinib, that specifically target the constitutive kinase activity of the mutated c-kit proto-oncogene and the FIP1L1-PDGFRα fusion gene. This review identified three Phase II reports involving 29 patients with SM treated with imatinib as monotherapy or in combination with prednisone. The results suggest that imatinib is well tolerated among patients with SM, with the only commonly occurring Grade 3/4 adverse event (7%) being toxicoderma. These three reports provide insufficient data to support firm conclusions, but their findings suggest some efficacy of imatinib in the treatment of SM, with PR rates ranging between 30% and 100%. The ASH 2006 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. Given the rarity of SM (and lack of patients for clinical trials), the need for systemic therapeutic interventions among some patients with severe and/or highly symptomatic disease, and the presence of a target for imatinib in this disease, treatment with imatinib in SM is a sensible strategy even in the setting of few published data and the incomplete exploration in clinical trials identified in this review.

Targeted therapy	Off-label indication(s)	Summary discussion
Rituximab (Rituxan®)	Chronic lymphocytic leukemia	As an anti-CD20 immunoglobulin, rituximab is theoretically well suited to treating CD20-positive CLL. Nearly all of the reports identified in this review included only patients with CLL known to have CD20-positive status. These reports provide relatively compelling evidence in support of the role of rituximab in the treatment of CLL. The quality of the studies was generally poor, and there is great variability in the clinical response rates, but in the aggregate the reports suggest some efficacy. CR and PR rates ranged from 0 to 70% and 15% to 67%, respectively, among the 16 fully published studies, and no clear pattern of the type or nature of adverse events possibly associated with rituximab use among patients with CLL was evident. Comparative effectiveness trials are needed to better determine the appropriate role of rituximab in the treatment of CLL.
	Nodular lymphocyte-predominant Hodgkin disease	Because rituximab is an anti-CD20 immunoglobulin that antagonizes the high-density CD20 surface antigens characteristic of the malignant cell population of NLPHD patients, it has emerged as a promising treatment option since its first off-label use in 1999 for a patient with difficult refractory NLPHD. Subsequent case reports and Phase II studies identified in this review provide further evidence that rituximab appears to be both effective in the short term and well tolerated, but that the duration of response may be limited. The observed CR and PR rates of 45% to 69% and 28% to 54%, respectively, compare favorably to existing treatment options, as do the estimated 10- and 20-year overall survival rates of 97% and 85% reported in a published abstract. The ASH 2006 and 2007 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. Only one out of 14 patients (7%) experienced a Grade 3/4 adverse event in the single study that reported adverse events.
	Waldenstrom's macroglobulinemia	Rituximab, an anti-CD20 immunoglobulin that targets the CD20 surface antigens that are expressed on malignant lymphocytes in WM, was used as an off-label treatment for WM from the late 1990s until its recent approval by the FDA. This review identified 13 published Phase II reports suggesting some efficacy, with one reported CR rate reaching 18% and PR rates ranging as high as 90%. Historically, single and combination chemotherapies for advanced disease have had variable response rates and short median survivals. In Phase II reports, rituximab was generally well-tolerated, and it compares favorably to these existing treatment options. The ASH 2006, ASH 2007, and ASCO 2007 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates.

* Indications that were approved by the FDA at some point during the completion of this technology assessment.

Chapter 4. Discussion

In this technology assessment, we attempted to provide complete and comprehensive reviews of 19 different drug/diseases indications. At the time of their selection, these indications were all off-label. Over the time course of doing this project, the literature evolved quickly (e.g., the number of potentially relevant articles related to alemtuzumab published in a calendar year increased from 290 to 447 from 2006 to 2009) and the FDA approved several indications (e.g., all five of the indications for imatinib were approved over that period). For some indications there was both biological plausibility of the drug/disease combination as well as relatively compelling evidence to support the prescription of that particular drug in that particular disease (e.g., alemtuzumab in cutaneous T cell lymphoma [CTCL]), and in other indications evidence was scant or not at all supportive (e.g., bevacizumab in pancreatic cancer).

This technology assessment constituted, in effect, a series of 19 systematic reviews of the medical literature on off-label indications of selected antineoplastic drugs. In terms of sheer labor effort, the scope of this undertaking was vast. A first and important observation is, therefore, recognition of the quantity of work expected of the compendia which are charged with continuously performing and updating systematic reviews on the comprehensive list of FDA-approved drugs and biologics. Moreover, this study confirmed the pervasive sense among clinicians that the drug landscape in oncology is frequently changing, not only as new indications arise but also as public support and interest shift to focus on specific drugs (e.g., gefitinib fell out of favor over the course of this review).

In listing off-label indications, the compendia function as a stepping stone between (1) drug development and research that produces substantial supporting evidence, and (2) FDA approval.

For many of the indications included in this technology assessment, FDA listing was in progress. Here, the drug's accessibility, via the mechanism of compendia off-label listing, jibes with this intended role of the compendia. We found that the volume of identified data was variable even for those agents that secured FDA approval, although those approved were primarily those with the more robust datasets identified in this review (e.g., the large number of studies for imatinib for acute lymphoblastic leukemia (ALL), and Phase III studies of bevacizumab for renal cell carcinoma). From our reviews, we could discern which drugs should not be accessible for the studied indication, and in general, their listing in the compendia was rescinded (e.g., bevacizumab for pancreatic cancer). The extent of review varied depending on expected usage and cost; expensive drugs likely to be used in common cancers (e.g., bevacizumab) tended to undergo full FDA review, whereas uncommon cancers did not.

Each discrete systematic review yielded interesting information on the off-label use(s) of a specific targeted therapy. However, the quality of studies varied tremendously, and the low quality of many published studies made it difficult to draw conclusions regarding the agent's effectiveness or safety. Study quality varied both across and within drugs. Because of the paucity of high-quality evidence, the data available – though voluminous – may have little meaning or value for informing clinical practice. Similarly, our horizon scan yielded little useful evidence; review of this level of evidence may serve better as an early warning system, alerting clinicians to potential adverse events (e.g., CMV in alemtuzumab) than as a viable source of data on efficacy.

The indication of alemtuzumab for Non-Hodgkin Lymphoma (NHL) illustrates many of the issues encountered in a systematic review of the literature in the rapidly evolving field of

targeted therapies. Clinical indication for use of alemtuzumab varied; specifically, we found the agent used at diverse stages of disease presentation. Four of the 11 published reports included alemtuzumab as a part of a stem cell transplant conditioning regimen, to reduce toxicity from donor lymphocyte infusion, or in conjunction with some other aspect of transplant therapy. Similarly, transplant was frequently the indication in abstracts and the horizon scan. In the remainder of studies, participants generally had relapsed or refractory NHL, or minimal residual disease after other standard therapies. Two abstracts presented the choice of alemtuzumab as first-line therapy in NHL; both involved patients with peripheral T cell lymphoma as their NHL subtype. In this wide variety of contexts, it is difficult – though necessary for the practicing clinician – to try to interpret efficacy outcomes and tolerability from the available evidence. In this drug/disease combination, reported response rates varied tremendously, from 4 percent to 80 percent. This variation could be due to the fact that many studies were not limited to a single disease or a single drug regimen; in studying alemtuzumab for NHL, as with other drug/disease combinations, patients with a variety of diseases were included in clinical trials.

The quantity, as well as quality, of data varied widely across the included indications. Practical considerations may account for some of this disparity in quality. Targeted therapies treat diseases that are frequently rare (e.g., alemtuzumab for T-cell prolymphocytic leukemia or imatinib for dermatofibrosarcoma protuberans [DFSP]); hence it is difficult to get many cases at one institution. Clinical trials are costly; hence it is impractical to expect cooperative clinical trials or industry-funded research of every permutation. In certain drug/disease combinations, (e.g., bevacizumab for epithelial ovarian cancer [EOC]), the data are severely limited. A published case series and case reports suggest that bevacizumab may contribute to clinical response in EOC, including reduction in CA125 levels. However, these studies were not designed to directly evaluate the efficacy of bevacizumab, and there is inherent bias in relying on case reports or retrospective case series to assess either efficacy or safety of interventions, especially those typically used in combination with other treatments. A larger quantity of data supported more mature drugs (e.g., imatinib). Given the complexities of completing clinical trials, and the small number of patients available at any single institution, the level of data for some drug/disease combinations was remarkable – and likely reflective of public enthusiasm for those drugs.

In some diseases, despite limited, lower quality, and/or ambiguous data, the use of an off-label indication may be a reasonable clinical decision. For example, given the rarity of dermatofibrosarcoma protuberans (DFSP) tumors, the substantial mortality risk for those tumors that progress into a sarcoma or metastasize, the lack of other systemic therapeutic interventions for DFSP, and the presence of the PDGF receptor as a target in DFSP, treatment with imatinib in DFSP is a sensible strategy even in the setting of few published reports, incomplete exploration in clinical trials, or data coming only from uncontrolled Phase II trials. Here, in a very immediate sense, the clinician's judgment of best treatment choice for an individual patient must take into account whatever evidence is available, and base the decision on that data, albeit limited. Likewise, in certain diseases with long survival estimates, the short time period of drug development makes calculation of median survival impossible (e.g., rituximab for nodular lymphocyte-predominant Hodgkin disease) and clinicians must evaluate the evidence in the absence of survival data. The balance of adverse effects versus potential clinical benefit presses another clinical judgment on oncologists; for example, despite risk of adverse events, targeted therapies may be a good choice for heavily pre-treated NHL patients who can tolerate the

adverse event profile and for whom there are no other established options (e.g., NHL patients with good performance status may benefit from alemtuzumab or bortezumab).

In interpreting some studies, there may be a temptation to assume that efficacy is implied by the presence of a logical target (e.g., bevacizumab for ovarian or pancreatic cancer). In some drug/disease combinations (e.g., imatinib for ALL), a target was always present. Sometimes the target was defined as an eligibility criterion, and sometimes not; for example the alemtuzumab target, CD52, was not a prerequisite for study entry in trials of alemtuzumab for NHL and it was not clearly linked to outcomes. However, in nearly all of the NHL settings where alemtuzumab was used, the presence of CD52 could be confidently assumed; only one study required CD52 positivity.

In this technology assessment, the array of data presented in randomized controlled trials, controlled clinical trials, case series, case reports, abstracts, review articles, and other reports raised the issue of what constitutes "evidence." Disagreements are likely to surround this question, making the process of evidence review susceptible to differences of opinion and subjectivity. Much of the evidence retrieved through this series of systematic reviews would not, generally, be considered "good science;" the identified publications presented results of Phase II trials, were inadequately controlled, had potential conflicts of interest due to funding scenarios, involved double-counting across studies, or did not conform to good clinical practice. Sometimes the remarkably low quality of the reporting obscured any ability to determine the strength of the evidence. The pace of research, combined with clinical urgency, may at times threaten the integrity of the science underlying clinical decisions.

Abstracts, a harbinger of emerging trials, become available at ASCO and could inform decisions supporting the use of an agent before the fully published reports become available (e.g., bevacizumab for renal cell carcinoma). Sometimes referred to as the "June 5 effect," oncologists start applying new data presented in abstract form at the ASCO conference that takes place at the beginning of June, often with a resulting uptick in relevant drug utilization. Because of the nature of evidence available to compendia reviewers as well as clinicians, the use of targeted therapies may not be based on sound or robust scientific evidence.

The timeliness of evidence review and the pace of research are particularly acute issues in oncology. Many cancers are potentially life-limiting diseases, for which there are few if any effective treatment options. Oncologists and patients find themselves in a situation characterized by urgency, fear, and a desperate desire to take action in hopes of a response. Cancer care providers, therefore, may approach the literature from a different perspective than do primary care providers or those in other disciplines where outcomes are not as dire. In the cancer setting, the definition of what constitutes "evidence" may thus be substantially looser than in other disciplines, and providers reviewing the evidence may be more inclined to entertain data derived from lower-quality studies or the "gray" literature. It has been estimated that less than half of all medical care in the United States is based on or supported by adequate evidence about its effectiveness.[8] This may be particularly true in cancer (especially as we question the adequacy of the evidence identified in this review).

The exercise of performing 19 systematic reviews of off-label indications in oncology pointed to clear challenges in the current methods of evidence review; these challenges are likely heightened in areas of medicine where research is advancing rapidly and scientific productivity is high. A different model of evidence generation and evaluation is warranted – but is it possible? What would such a model look like? Much discussion is currently underway in national forums to answer these questions.

Developing consensus holds that the new system must be designed for rapid learning and expedient translation of research results into clinical practice improvements, and must include evaluation of the comparative effectiveness of available treatments in real-world clinical populations. As yet, there is no articulated consensus on the role of comparative effectiveness research [CER] in evaluation of cancer treatments, but national discussion is striving to define the parameters of, and the appropriate context for, CER. In the words of an expert committee convened by the Friends of Cancer Research and comprising leading academic scientists, clinicians, and advocates in the field of cancer, "To ensure that evidence-based information on the effectiveness and comparative effectiveness of medical care keeps pace with the newest diagnostic and therapeutic interventions, the nation's approach to the performance of CER must be structured to ensure continuous learning and the rapid translation of the best available evidence into clinical practice. Ultimately, we need to move closer to the development of a sustainable, 'learning' U.S. health care system that develops research insights as a natural byproduct of the care process and gets the right care to people when they need it and then captures the results for improvement."[9] Two clear foci of this technology assessment that highlight the need for comparative effectiveness research within a learning healthcare system model are: (1) the nature of adverse event data, where the patterns for new/emerging adverse events which we identified were largely case reports; until we can describe a pattern of such events, e.g., through data collected routinely in a rapid learning healthcare model, sporadic reports of adverse events have little clinical utility; and (2) the lack of comparative effectiveness data, where the volume of Phase II studies of targeted therapies serves only to suggest potential benefit but not to describe how each new therapy may compare to other available treatments in terms of relative efficacy or tolerability. It remains unclear, however, whether CER is more appropriate than other types of clinical trial for establishing the efficacy and role of targeted therapies in treating specific cancers, and thus whether and how CER should be integrated into drug discovery trials.

While it is beyond the scope of this technology assessment to discuss rapid learning healthcare or comparative effectiveness research, these topics represent a logical next area of exploration in the effort to understand and improve upon the state of the evidence available to support medical care.

The principal limitation of this technology assessment was the variability in quality and quantity of data which made the drawing of conclusions regarding either the efficacy or the safety of the included drugs and respective indications both difficult, if possible, and inconclusive. At times, the volume of poorly done work was remarkable; for example, with rituxumab for chronic lymphocytic leukemia, despite abstracting 81 reports, we were unable to draw conclusions. Second, with respect to drug efficacy, our review may be skewed by publication bias; the publication of negative results typically lags behind publication of positive results, hence this review may disproportionately weight studies reporting positive findings. Even if negative results were published, our search may not have picked them up if they preceded the less than ten-year window of literature which we examined. A third limitation is that our literature review does not include published reports indexed in MEDLINE® after September 14, 2007.

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Acronyms and Abbreviations

2-CDA	2-chlorodeoxyadenosine (cladribine)
4-DHAP	Dexamethasone, high-dose cytarabine, and cisplatin
AC	Doxorubicin and cyclophosphamide
ADE	Adverse drug event
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AF	Atrial fibrillation
AHFS-DI	American Hospital Formulary Service-Drug Information
ALL	Acute lymphoblastic leukemia
Allo	Allograft
AML	Acute myelocytic leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
AST/ALT	Aspartate aminotransferase/alanine transaminase
ATP	Adenosine triphosphate
AV	Atrioventricular
BC	Blast crisis
BCVA	Best correct visual acuity
BEAM	Bischloroethylnitrosourea, etoposide, cytarabine, and melphalan
Bili	Bilirubin
BID	Twice daily
BIW	Biweekly
BM	Bone marrow
BMN	Bone marrow necrosis
BMT	Bone marrow transplant
BP	Blood pressure
CA125	Cancer antigen 125
CCR	Clinical complete response
CEL	Chronic eosinophilic leukemia
Chemo	Chemotherapy
CHF	Congestive heart failure
CHOP	Cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
CMML	Chronic myelomonocytic leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
COG	Children's Oncology Group
CR	Complete response
CRT	Cathode ray tube
CrCl	Creatinine clearance

CRu	Complete response unconfirmed
CT	Computerized tomography
CTC	Common Toxicity Criteria
CTCL	Cutaneous T-cell lymphoma
CVAD	Cyclophosphamide, vincristine, Adriamycin®, and dexamethasone
CVP	Cyclophosphamide, vincristine, and prednisone
d/c	Discontinued
DCF	Deoxycoformycin
Dexa-BEAM	Dexamethasone, carmustine, etoposide, arabinoside C, and melphalan
DFCI	Dana Farber Consortium Induction
DFS	Disease-free survival
DFSP	Dermatofibrosarcoma protuberans
DHAC	Dexamethasone, cytosine arabinoside, and carboplatin
DHAP	Dexamethasone, high-dose cytarabine, and cisplatin
DIV	Dexamethasone, Imatinib, and vincristine
DLBCL	Diffuse large B-cell lymphoma
DLI	Donor lymphocyte infusion
DVT/PE	Deep vein thrombosis / pulmonary embolism
ECOG	Eastern Collaborative Oncology Group
EGFR	Epidermal growth factor receptor
EOC	Epithelial ovarian cancer
ER	Emergency room
ER	Estrogen receptor
ESHAP	Etoposide, cisplatin, cytarabine, and methylprednisolone
FDA	U.S. Food and Drug Administration
FDG	Fluorodeoxyglucose
FIGO	International Federation of Gynecology and Obstetrics
FMC	Fludarabine phosphate, mitoxantrone, and cyclophosphamide
FP	FIP1L1-PDGFR
GBM	Glioblastoma multiforme
G-CSF	Granulocyte-specific colony-stimulating factor
GGT	Gamma glutamyl transpeptidase
GFLIP	Gemcitabine, irinotecan, fluorouracil followed by leucovorin and cisplatin
GI	Gastrointestinal
GMALL	German Multicenter Study Group for Adult ALL
GVHD	Graft versus host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor
HES	Hyper eosinophilic syndrome
HG	High grade
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
H&N	Head and neck
HNSCC	Head and neck squamous cell cancers
HR-MDS	High-risk myelodysplastic syndrome

HSTCL	Hepatosplenic T-cell non-Hodgkin lymphoma
HSV	Herpes simplex virus
HTN	Hypertension
IBC	Inflammatory breast cancer
ICE	Ifosfamide, carboplatin and etoposide
ICU	Intensive care unit
IFN	Interferon
IgM	Immunoglobulin M
IL	Interleukin
INV	Investigator
IRF	Independent research facility
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRC	International Workshop Response Criteria
JALSG	Japan Adult Leukemia Study Group
JC virus	John Cunningham virus
KM curve	Kaplan Meier curve
KS	Kaposi Sarcoma
LABC	Locally advanced breast cancer
LDAC	Low-dose Ara-C
LFTs	Liver function tests
LVEF	Left ventricular ejection fraction
LyBC	Lymphoid blast crisis
MALT	Mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndrome
MF	Mycosis fungoides or myelofibrosis
MI	Myocardial infarction
MINE	Mesna, ifosfamide, mitoxantrone, and etoposide
MM	Multiple myeloma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MUD	Marrow unrelated donor
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI-WG	National Cancer Institute-sponsored Working Group
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NLPHD	Nodular lymphocyte predominant Hodgkin’s disease
NMST	Nonmyeloablative allogenic stem cell transplantation
NPC	Nasopharyngeal carcinoma
NR	Not reported
NYHA	New York Heart Association
OIC	Oxaliplatin, irinotecan, and cetuximab
OR	Overall response
ORR	Pverall response rate

OS	Overall survival
PCR	Pathological complete response
PD	Progressive disease
PDGFR	Platelet-derived growth factor receptor
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PFI	Progression-free interval
PFS	Progression-free survival
Ph+	Philadelphia chromosome-positive
PLL	Prolymphocytic leukemia
PML	Progressive multifocal leukoencephalopathy
PO	Orally
PR	Partial response
PR+	Progesterone receptor positive
PS	Performance status
PTL (PTCL)	Peripheral T-cell lymphoma
PTLD	Post-transplant lymphoproliferative disorder
PUVA	Photochemotherapy
Q	Every
QoL	Quality of life
RAEB	Refractory anemia with excess blasts
RBC	Red blood cell
RCC	Renal cell carcinoma
R-CHOP	Rituximab, cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), and prednisone
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
RFS	Relapse-free survival
RIC	Reduced intensity conditioning
RI-UCBT	Reduced intensity unrelated cord blood transplantation
RPTD	Recommended phase two dose
RR	Response rate
RSC	Reed-Sternberg cells
RT	Radiation therapy
RT-PCR	Reverse transcription polymerase chain reaction
SC or SQ	Subcutaneous
SCC	Squamous cell carcinoma
SCR	Screen
SCT	Stem cell transplant
SCTCL	Subcutaneous T-cell lymphoma
SD	Stable disease
SLE	Systemic lupus erythematosus
SLL	Small lymphocytic lymphoma
SM	Systemic mastocytosis
SUV	Standardized uptake value
TBIL	Total bilirubin

TID	Thrice daily
TIW	Thrice weekly
TK	Tyrosine kinases
TMP/SMS	Trimethoprim/sulfamethoxazole
T-NHL	T-cell non-Hodgkin lymphoma
T-PLL	T-cell prolymphocytic leukemia
TRM	Transplantation-related mortality
TTP	Time to tumor progression
ULN	Per limit of normal
USP-DI	United States Pharmacopeia Drug Information
VCR	Vincristine
VEGF	Vascular endothelial growth factor
VHL	Von Hippel–Lindau
VZV	Varicella zoster virus
WBC	White blood cell
WHO	World Health Organization
WM	Waldenström's macroglobulinemia
XRT	X-ray therapy
y/o	Year(s) old

Appendix: Results of Systematic Literature Review for Specific Drug/Disease Combinations

Appendix Table of Contents

Alemtuzumab for Cutaneous T-Cell Lymphoma

Background

Drug: Alemtuzumab (Campath®). Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody (Campath-1H) directed against the 21–28 kD cell surface glycoprotein, CD52. Campath-1H is an IgG1 kappa antibody with human variable framework and constant regions, and complementarity-determining regions from a murine monoclonal antibody (Campath-1G). Alemtuzumab binds to CD52, an antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. The proposed mechanism of action is antibody-dependent cellular-mediated lysis following cell surface binding of alemtuzumab to the leukemic cells.

Alemtuzumab was approved in May 2001 under the accelerated approval program for the "Treatment of patients with B-cell chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed fludarabine therapy." In September 2007, the Food and Drug Administration (FDA) expanded the labeling and granted regular approval for single-agent alemtuzumab for the treatment of untreated B-cell chronic lymphocytic leukemia. It has been evaluated for off-label use in cutaneous T-cell lymphoma (CTCL), non-Hodgkin lymphoma (NHL), and T-cell prolymphocytic leukemia (T-PLL).

Disease: Cutaneous T-cell lymphoma. CTCL, generally classified as a type of NHL, represents a spectrum of lymphoproliferative disorders characterized by epidermal localization of malignant T lymphocytes, typically of the CD4+ immunophenotype. Following a neoplastic mutation of T cells, a defensive biological response pushes the noxious material to the surface of the skin, where it appears as a widespread, chronic, cutaneous eruption.[10-12] Because it presents with a wide variety of clinical and histopathologic expressions, diagnosis and treatment remain challenging.

The natural history of CTCL is equally heterogeneous, with survival ranging from months to decades, depending on the stage of the disease.[13,14] Early-stage disease is generally addressed with skin-directed treatments, while patients with more extensive disease may receive a variety of systemic treatments, including chemotherapy and immunotherapy. There is no cure for CTCL, and as no current therapeutic protocol significantly improves overall survival, treatment is largely directed at achieving clinically meaningful remission, managing symptoms, and maintaining quality of life.[13,14]

CTCL largely affects an older population (median age, 50–55 years),[10,12] and its annual incidence has risen dramatically and consistently since the early 1970s, with an overall age-adjusted incidence of 6.4 cases of CTCL per million persons.[15]

Drug/Disease: Alemtuzumab for CTCL. As an anti-CD52 immunoglobulin, alemtuzumab slows the proliferation of leukocytes by binding to the CD52 receptor found in variable levels on most malignant T-cells, including the CD34+ cells characteristic of CTCL. Early research demonstrates that alemtuzumab is well tolerated and exerts promising clinical activity in patients with advanced CTCL.[16] It is currently recognized by the National Cancer Institute (NCI) and the American Cancer Society as an acceptable off-label treatment for relapsed CTCL.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded at total of 18 reports: four full reports of Phase II clinical trials (Table A1), four published abstracts from the American Society of Hematology (ASH) 2006 and 2007 conferences (Table A2), and 10 additional articles considered in the horizon scan (Table A3). Of the four published abstracts, three were Phase II clinical trials and one was a retrospective study, for a total of seven Phase II clinical trials represented in the full reports and abstracts combined.

The earliest publication seen in the literature was a case series published in 1997 that described nine cases of patients with Sézary cell leukemia, two of whom were treated with, and responded to, alemtuzumab. The next publications of alemtuzumab in the treatment of CTCL appeared in 2003. In that year, three full reports of Phase II clinical trials were published.

Sample sizes for the seven clinical trials ranged from 8 to 78, with a total of 153 patients presented in the full reports plus abstract. Eligibility criteria for inclusion in the studies were variable, with several studies enrolling patients with leukemias other than CTCL, and the total number of CTCL patients in these reports is unclear. All of the clinical trials enrolled subjects who had previously been treated, and all involved only adults.

Alemtuzumab was used as monotherapy in all seven clinical trials, in escalating dosages starting as low as 3 mg and ending with dosages as high as 30 mg three times per week. In two of the trials, alemtuzumab was given in escalating dosages, beginning with 3 mg, then increased to 10 mg and ending with 30 mg three times per week for 4 to 12 weeks. Dosages and administration schedules were different in each of the other studies.

Efficacy data were provided in each of the seven studies represented in the full reports. Outcomes assessed differed between studies, although most included skin outcomes. Adverse events were assessed using the NCI's Common Toxicity Criteria (CTC) (Table A4).

Study quality of the full published reports was generally poor. Three of the four studies met three of the five quality criteria; the patients in these studies were not enrolled at similar points in the disease progression, and the followup period was not sufficiently long to adequately assess outcomes. One study met only two of the quality criteria.

Efficacy. The range of complete response (CR) rates was 0 percent to 32 percent among the fully published reports. This range remained unchanged when abstracts from prospective studies were considered in conjunction with the full reports. Several of these response rates included patients with leukemias other than CTCL, which made it difficult to truly determine efficacy; however, the study with the highest CR rate[16] only enrolled patients with CTCL. The range of partial response (PR) rates was 23 percent to 79 percent among the fully published reports. The range remained unchanged when abstracts of prospective studies were considered in conjunction with the full reports, except for one study with a 0 percent PR rate but a 25 percent CR rate.

Survival. Median overall survival was 35 months in a study which included heavily pre-treated patients with CTCL/Sézary syndrome or refractory disease. In another study, six out of eight relapsed/refractory patients died within four months of starting treatment. The abstracts

presented little survival data, but available information was consistent with the information contained in published reports.

Adverse events. Data presented in Table A4 were derived from the four full reports. Hematologic toxicity was the major serious adverse event, with Grade 3 and 4 thrombocytopenia (range, 7 percent to 50 percent) reported in all four studies, and neutropenia/granulocytopenia (range, 23 percent to 63 percent) reported in three studies. Several cases of treatment-associated cytomegalovirus (CMV) infection were reported, especially in the ASH abstracts.

Horizon scan. The horizon scan identified 10 reports published between 1997 and 2006 of alemtuzumab used in the treatment of various leukemias, including CTCL. Some reported clinical response; others reported adverse events. The overall message of the horizon scans was that alemtuzumab may have activity in CTCL, including patients who were heavily pretreated. One report of alemtuzumab with gemcitabine suggested that the drug had activity when used in this combination.

Discussion

There are emerging data for the role of alemtuzumab in the treatment of patients with progressive CTCL. Historically, single and combination chemotherapies for advanced disease (e.g., gemcitabine; methotrexate; cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone [CHOP]) have had variable response rates, high risk of neutropenic infections, and short median survivals. In Phase II reports, alemtuzumab compares favorably to these existing treatment options.

This review identified four published Phase II reports suggesting some efficacy, with PR rates ranging as high as 79 percent and median survival reaching 35 months (though a median survival rate as low as four months was also reported). The ASH abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. Toxicities were predominantly hematological and as expected. Over time, our understanding of the CMV risk with alemtuzumab is improving; this clarity stands out as the main emerging information in the most recently published abstracts.

Table A1: Alemtuzumab for Cutaneous T-Cell Lymphoma/Mycosis Fungoides – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Bernengo, Quaglino, Comessatti, et al., 2007[17]	**Design:** Open **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Sézary syndrome-refractory or progressive following prior treatment - Untreated if high peripheral count - CD52+ - Age > 18 yr - ECOG ≤ 2	**No. in study:** 14 (11 rel/ref, 3 untreated) **Age:** 72 **Previous treatment:** 11/14 **Stage of disease:** Varied **Drug dose/day [followup]:** Pts 1–4: 3, 10, 15 mg alemtuzumab SQ; Pts 5–14: 3, then 10 mg alemtuzumab alternating days (one pt – dwarf – got further reduced dosing) **Outcomes sought:** Efficacy, toxicity	**N:** 14 **CR:** 1 (7%) **PR:** 11 (79%) **Stable disease:** 2 (14%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** 35 mo **1 yr:** 60% (from KM curve) **2 yr:** 60% **3 yr:** NR **Survival (disease-free):** **Median survival:** 12 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A4 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** OR assessed at 4 wk, in f/u, 2 PR pts went to CCR
Ferrajoli, O'Brien, Cortes, et al., 2003[18]	**Design:** Open label **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Age > 16 yr - CD52 > 20% - < 20% predicted probability of response to conventional	**No. in study:** 78 (42 CLL, 6 CTCL) **Age:** 61 **Previous treatment:** Yes (median 3) **Stage of disease:** **Drug dose/day [followup]:** Alemtuzumab 3, 10, 30 mg then 30 mg TIW x 4-	**N:** 78 (6 CTCL) **CR:** Not reported **PR:** 2 (33% of CTCL pts) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** CTCL survival not reported **Survival (disease-free):** **Median survival:** CTCL survival not reported	**Adverse events & tolerability:** See Table A4 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:**

Study	Study Design	Patients	Tumor Response	Survival	Other
	treatment - Any lymphoid leukemia subtype w/ no established frontline treatment - WHO 0–2	12 wk **Outcomes sought:** Efficacy, safety			- Aggregate study of lymphoproliferative disorders with less than 10% CTCL - Individual results not available except as mentioned above.
Kennedy, Seymour, Wolf, et al., 2003[19]	**Design:** Open-label **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Relapsed or refractory CTCL - ECOG ≤ 2 - Symptomatic disease	**No. in study:** 8 **Age:** 48 **Previous treatment:** Yes, heavily pretreated (1–17 treatments) **Stage of disease:** IIb–IV **Drug dose/day [followup]:** Alemtuzumab 3, 10, 30 mg first wk, then 30 mg TIW x up to 12 wk **Outcomes sought:** Efficacy, safety	**N:** 8 **CR:** 0 **PR:** 3 (38%) **Stable disease:** 2 (25%) **Progressive disease:** 3 (38%)	**Survival overall (from start of treatment):** **Median survival:** 6/8 dead at median 4 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 9.5 wk (all progressed w/in 4 mo) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A4 **Quality assessment:** 1) Representative sample from a relevant population?: No (only 8 pts) 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** - Median duration of treatment 6 wk - Prophylactic w/ antibiotic, antifungal, and antiviral - Conclude modest activity w/ significant heme and infectious complications
Lundin, Hagberg, Repp, et al., 2003[16]	**Design:** **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Age > 18 yr - CD52+	**No. in study:** 22 **Age:** 61 **Previous treatment:** Yes, median 3 **Stage of disease:** II–IV (mostly III–IV) **Drug dose/day**	**N:** 22 **CR:** 7 (32%) **PR:** 5 (23%) **Stable disease:** 3 (14%) **Progressive disease:** 7 (32%)	**Survival overall (from start of treatment):** Not reported **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):**	**Adverse events & tolerability:** See Table A4 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes

Study	Study Design	Patients	Tumor Response	Survival	Other
	- Stage II–IV - ≤ 5 prior treatments - WHO ≤ 2 - Life expectancy ≥ 15 wk - Prior PUVA and/or local RT - Chemo or IFN-alpha w/ documented failure - Clinical signs/symptoms	**[followup]:** Alemtuzumab 3, 10, 30 mg then 30 mg TIW x 12 wk **Outcomes sought:** OR, safety, clinical benefit		**Median survival:** Among 12 responders, time to treatment failure: **1 yr:** 40% **2 yr:** 15% **3 yr:** NR **Median PFS:** 12 mo (range 5–32+ months) in responding patients	assessments?: Yes **Comments:** - OR 80% for those w/ 1–2 prior treatments; 33% if more than 3 priors - All received antibiotic and viral prophylaxis - 11/12 completed 12 wk of treatment - Concluded was active with acceptable toxicity

Abbreviations: CCR = clinical complete response; chemo = chemotherapy; CLL = chronic lymphocytic leukemia; CR = complete response; CTCL = cutaneous T-cell lymphoma; ECOG = Eastern Collaborative Oncology Group; IFN = interferon; KM curve = Kaplan Meier curve; NR = not reported; OR = overall response; PFS = progression-free survival; PR = partial response; PUVA = photochemotherapy; RT = radiation therapy; SQ = subcutaneous; TIW = thrice weekly; WHO = World Health Organization.

Table A2: Alemtuzumab & Cutaneous T-Cell Lymphoma: ASH 2006 and 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Beltran-Garate, Huamani-Zavala, Arones-Valdivia, et al., 2006[20] ASH 2006 Abstract #4728	**Disease:** CTCL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Age 18 yr, PS 0–2, no infection, ≤ 3 chemo, HIV negative, normal renal and liver function	**No. in study:** 8 **Age:** 64 (36–72) **Previous treatment:** Median 2 (range, 2–3) **Stage of disease:** **Drug dose/day [followup]:** Alemtuzumab 30 mg IV TIW x 12 wk. Dose later reduced to 30 mg TIW x 4, then 30 mg q wk x 8 wk, 10 mg TIW x 4 wk, 10 mg BIW x 4 wk, and 10 mg q wk x 4 wk. **Outcomes sought:** Response, pruritus score	**N:** 7 **CR:** 2 (29%) **PR:** 2 (29%) **Stable disease:** 0 **Progressive disease:** 3 (43%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 4 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 5/8 CMV reactivation, 1 Kaposi sarcoma, 1 neutropenia, 1 thrombocytopenia, 1 urosepsis (E. Coli) **Comments:** Median Pruritus Analogue Scale reduced from 4 to 1.
Querfeld, Rosen, Guitart, et al., 2006[21] ASH 2006 Abstract #2732	**Disease:** CTCL **Design:** Retrospective **Phase:** N/A **Selection/randomization:** Eligible patients and off-study patients	**No. in study:** 19 **Age:** 63 (39–88) **Previous treatment:** 19 pre-treated, median of 5 treatments **Stage of disease:** III: 8 IVa: 10 IVb: 1 **Drug dose/day [followup]:** Alemtuzumab 30 mg IV TIW x 4 wk, then 30 mg SC TIW x 8 wk	**N:** 19 **CR:** 9 (47%) **PR:** 6 (32%) **Stable disease:** 0 **Progressive disease:** 4 (21%)	**Survival overall (from start of treatment):** **Median survival:** 18 mo (range 1–50) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 7 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 1 aplastic anemia, 4 infections, 1 neutropenic fever, 6 leukopenia, no CMV

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Response, survival			
Beltran-Garate, Gomez, Lopez, et al., 2007[22] ASH 2007 Abstract #3425	**Disease:** CTCL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized; all eligible	**No. in study:** 13 **Age:** 60 (36–72) **Previous treatment:** Yes, median 2.5 treatments (2–7) **Drug dose/day [followup]:** Alemtuzumab 30 mg IV TIW x 8 wk **Outcomes sought:** Response, toxicity	**N:** 12 **CR:** 3 (25%) **PR:** 6 (50%) **Stable disease:** 0 **Progressive disease:** 3 (25%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 50% CMV reactivation, 1 fatal, KS reactivation in 1, HSV in 1
Porcu, Baiocchi, Lin, et al., 2007[23] ASH 2007 Abstract #3417	**Disease:** NHL, CTCL **Design:** Prospective cohort **Phase:** Phase I **Selection/randomization:** Not randomized; all eligible **Eligibility criteria:** T-neoplasm, no HIV, HBV, HCV. Untreated overall, relapsed CTCL only.	**No. in study:** 18 **Age:** 62 median **Previous treatment:** 3/18 patients **Stage of disease:** **Drug dose/day [followup]:** Alemtuzumab SQ loading (3, 10, 30 mg) over 5 days followed by one SQ dose with each cycle of CHOP q 21 days for a total of 8 cycles. All patients received valacyclovir, trimethoprim-sulfamethoxazole prophylaxis and G-CSF. Erythropoietin was given according to published	**N:** 16 **CR:** 4 (25%) **PR:** 0 **Stable disease:** 2 (13%) **Progressive disease:** 1 (6%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 1 neutropenic fever, 2 anemia, 1 grade III CMV, 5 all CMV

Study	Study Design	Patients	Tumor Response	Survival	Other
		guidelines. **Outcomes sought:** Response, toxicity			

Abbreviations: ASH = American Society of Hematology; BIW = biweekly; chemo = chemotherapy; CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone; CMV = cytomegalovirus; CR = complete response; CTCL = cutaneous T-cell lymphoma; G-CSF = granulocyte-specific colony-stimulating factor; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HSV =herpes simplex virus; IV = intravenous; KS = Kaposi Sarcoma; NHL = non-Hodgkin lymphoma; PR = partial response; PS = performance status; q = every; SC = subcutaneous; SQ = subcutaneous; TIW = thrice weekly.

Table A3: Alemtuzumab for Cutaneous T-Cell Lymphoma/Mycosis Fungoides – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Bolli, Di Ianni, Simonetti, et al., 2004[24]	Case report	3, 10, 30 mg wk 1, then 30 mg TIW x 11 wk	1	1 pt; previously received 1 cycle of chlorambucil 25 mg/day x 5 days but stopped due to lung infections, liver toxicity; started alemtuzumab with antibiotic prophylaxis, IVIG q mo; stopped at 4 wk due to CMV pneumonia, 2 wk rest, then resumed; skipped 12th wk due to counts
Capalbo, Delia, Dargenio, et al., 2003[25]	Case reports	3, 10, 30 mg wk 1, then 30 mg TIW	3	3 pts; 12 wk, 3 wk, and 6 wk duration of treatment; all heavily pretreated
Gautschi, Blumenthal, Streit, et al., 2004[26]	Case report	30 mg TIW x 10 wk	1	Stage II HL at age 25; at age 31 diagnosed with CTCL (Sézary); multiple therapies; treatment with alemtuzumab with CR; 12 mo f/u no sign of disease
Goteri, Rupoli, Tassetti, et al., 2006[27]	Case report	3, 10, 30 mg wk 1, then 30 mg TIW x 8 wk	1	1 pt with 2-yr h/o MF treated with multiple therapies; alemtuzumab for 8 wk until developed diarrhea; discontinued drug; endoscopy and biopsy showed degeneration and tissue necrosis with E. coli infection
Gutierrez, Rodriguez, Ramos, et al., 2004[28]	Case report	30 mg TIW x 12 wk	1	32 y/o with large T-cell lymphoma treated with multiple therapies; CR at 3 mo post alemtuzumab; at 9 mo still disease-free
Lenihan, Alencar, Yang, et al., 2004[29]	Retrospective case reports	3, 10, 30 mg wk 1, then 30 mg TIW x 12 wk	8	8 pts with multiple previous chemos (3 doxorubicin); 6 of 8 developed cardiotoxicity (AF, CHF, decreased LVEF)
Lundin, Kennedy, Dearden, et al., 2005[30]	Retrospective case series of 30 pts who participated in European trials	3, 10, 30 mg wk 1, then 30 mg TIW x 12 wk	8	Response to above case report; no cardiotoxicity noted in their pts
Magro, Crowson, Byrd, et al., 2004[31]	Prospective case series	30 mg TIW	12	12 pts with SCTCL; 1 pt received alemtuzumab and obtained CR, maintained at 1 yr
Pawson, Matutes, Brito-Babapulle, et al., 1997[32]	Case reports		9	9 cases with Sézary cell leukemia with no or very late skin involvement; 2 pts treated with alemtuzumab and achieved CR; 1 recurred and achieved 2nd CR with alemtuzumab

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Weder, Anliker, Itin, et al., 2004[33]	Case report	Gemcitabine 1000 mg/m^2 day 1 & 8, alemtuzumab 30 mg TIW	2	Did not reply to gemcitabine or alemtuzumab alone; combination PFS > 1 yr

Abbreviations: AF = atrial fibrillation; chemo = chemotherapy; CHF = congestive heart failure; CMV = cytomegalovirus; CR = complete response; CTCL = cutaneous T-cell lymphoma; h/o = history of; HL = Hodgkin lymphoma; IVIG = intravenous immunoglobulin; LVEF = left ventricular ejection fraction; MF = mycosis fungoides; q = every; PFS = progression-free survival; SCTCL = subcutaneous T-cell lymphoma; TIW = thrice weekly; y/o = year(s) old.

Table A4: Alemtuzumab for Cutaneous T-Cell Lymphoma – Adverse Events (Grade 3/4+ Events Only)

Study	Anemia	Neutropenia/ granulocytopenia	Thrombocytopenia	Nausea	Dyspepsia	Dermatitis or rash	Fatigue	Headache	Pain	Chills/fever	Infection	CMV viral load detectable	Hypotension	Erythema	Bronchospasm
Bernengo et al., 2007[17]	-	-	7%	-	-	-	-	-	-	-	29%	21%	-	-	-
Ferrajoli et al., 2003[18]	0%	35%	41%	0%	9%	0%	-	1%	-	1%	-	-	1%	-	-
Kennedy et al., 2003[19]	37%	63%	50%	-	-	-	-	-	13%	-	-	-	-	13%	-
Lundin et al., 2003[16]	5%	23%	18%	0%	-	0%	9%	-	-	23%	-	-	0%	-	0%

Abbreviation: CMV = cytomegalovirus.

Alemtuzumab for Non-Hodgkin Lymphoma

Background

Drug: Alemtuzumab (Campath®). Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody (Campath-1H) directed against the 21–28 kD cell surface glycoprotein, CD52. Campath-1H is an IgG1 kappa antibody with human variable framework and constant regions, and complementarity-determining regions from a murine monoclonal antibody (Campath-1G). Alemtuzumab binds to CD52, an antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. The proposed mechanism of action is antibody-dependent cellular-mediated lysis following cell surface binding of alemtuzumab to the leukemic cells.

Alemtuzumab was approved in May 2001 under the accelerated approval program for the "Treatment of patients with B-cell chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed fludarabine therapy." In September 2007, the Food and Drug Administration (FDA) expanded the labeling and granted regular approval for single-agent alemtuzumab for the treatment of untreated B-cell chronic lymphocytic leukemia. It has been evaluated for off-label use in cutaneous T-cell lymphoma (CTCL), non-Hodgkin lymphoma (NHL), and T-cell prolymphocytic leukemia (T-PLL).

Disease: Non-Hodgkin lymphoma. NHL encompasses a diverse group of lymphoproliferative neoplasms with equally diverse natural histories, treatments, and prognoses. NHL tends to affect an older population, the median age being 67, and is the sixth most deadly form of cancer, with 19,160 patients predicted to die of the disease in 2008. Once a relatively rare condition, it is now the fifth most common cancer, with more than 63,000 new cases diagnosed each year and an annual incidence rate of 19.5 per 100,000 persons.[34,35]

The long-term survival and cure rates for these diseases are influenced by a number of prognostic factors, the most significant being the relative aggressiveness of the lymphomas, which fall into two prognostic categories: indolent and aggressive. Indolent NHL progresses slowly but is typically incurable; although it initially responds to radiation therapy and chemotherapy, time to relapse usually shortens with each successive therapy regimen. Patients with aggressive and highly aggressive NHLs have a 30 percent to 60 percent cure rate with intensive chemotherapy regimens. Other available treatments include hematopoietic stem cell transplantation and immunotherapy, with individual regimens being determined by disease stage and other prognostic considerations.[36,37]

Drug/Disease: Alemtuzumab for NHL. As an anti-CD52 immunoglobulin, alemtuzumab slows the proliferation of leukocytes by binding to the CD52 receptor found in variable levels on most malignant T-cells. Therefore, it may prove promising for patients with lymphomas that involve cells expressing the CD52 antigen. Recent preclinical evidence also suggests that alemtuzumab may reverse acquired resistance to rituximab, an immunotherapy approved for treating some forms of NHL.[38]

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded a total of 35 reports: 11 full reports of Phase II clinical trials (Table A5), 13 published abstracts from the American Society of Clinical Oncology **(**ASCO) and American Society of Hematology (ASH) conferences (Table A6), and 12 additional articles considered in the horizon scan (Table A7). Of the 13 published abstracts, 10 were Phase II clinical trials and three were retrospective studies, for a total of 20 non-randomized Phase II clinical trials represented in the full reports and abstracts combined. Several of the clinical trials included patients with other malignancies.

The earliest publication seen in the literature was a full report of a Phase II clinical trial involving seven patients, published in 1996. The next study was published in 1998; this trial involved 50 patients with relapsed or refractory NHL. At least one full report has been published every year beginning in 2000.

Sample sizes for the 11 clinical trials published as full reports ranged from 5 to 88, with a total of 346 patients. When both full reports and abstracts are considered, the total number of patients enrolled in prospective trials is 658. This figure does not include, however, patients enrolled in studies presented only in abstracts prior to 2006, and it includes patients with other malignancies that were included in some of the Phase II clinical trials summarized in this report (since it All of the studies involved adults. Importantly, some of the patients had sub-types of NHL represented in other sections of this report, (i.e., CTCL, PLL), or had diseases for which there was already FDA-approval for alemtuzumab.

Clinical indication for use of alemtuzumab varied. Four of the 11 published reports included alemtuzumab as a part of a stem cell transplant conditioning regimen, to reduce toxicity from donor lymphocyte infusion, or some other aspect of transplantation therapy. Similarly, transplant was frequently the indication in the abstracts and the horizon scan. The rest of study participants generally had relapsed or refractory NHL, or minimal residual disease after other standard therapies. Two abstracts presented the choice of alemtuzumab as first-line therapy in NHL, both involving patients with peripheral T cell lymphoma as their NHL subtype.

Only one published study specifically required evidence of CD-52+ tumor in the eligibility criteria. Other studies specified NHL sub-types known to be CD-52+ such as T-cell lymphomas.

Approximately half of the 11 full reports used alemtuzumab as monotherapy, in escalating dosages starting as low as 3 mg and ending with dosages as high as 30 mg three times per week. Dosages and administration schedules varied between studies. Efficacy data were provided in each of the 11 studies represented in the full reports. Outcomes assessed differed between studies. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

Study quality of the full published reports was generally poor. Three of the 11 studies met four of the five quality criteria, seven met three criteria, and one met only two quality criteria. The criteria most commonly not met were: patients entering the study at a similar point in disease progression, and adequate followup period.

Efficacy. The range of complete response (CR) rates was 4 percent to 80 percent among the fully published reports and 25 percent to 80 percent among the abstracts. Some of these response rates include patients with malignancies other than NHL, however, and also NHL-subtypes with an established FDA indication for alemtuzumab (e.g., chronic lymphocytic leukemia [CLL]). CR rates also reflect the full spectrum of uses for alemtuzumab in the context

of NHL, from single-agent therapy to transplantation. The range of partial response (PR) rates was 8 percent to 22 percent among the fully published reports and 0 percent to 56 percent among the abstracts. The same caveats as for CR data apply for PR data.

Survival. One-year overall survival was 44 percent, 50 percent and 70 percent in the three full reports that clearly provided these data, which were two monotherapy and one transplantation study, respectively. Median overall survival was 12 and 21 months in the full reports that clearly provided these data. Median disease-free survival was variably reported from 3.5 to 8.5 months.

Adverse events. Data in Table A8 were derived from the eight full reports that provided these data. Nausea (range: 6 percent to 22 percent) and chills or fever (range: 1 percent to 24 percent) are the only two adverse events that reached Grade III/IV severity reported in at least three of the eight studies. One study that enrolled 20 patients and administered alemtuzumab in combination with cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone (CHOP) chemotherapy reported a 90 percent incidence of both neutropenia/granulocytopenia and thrombocytopenia. Infectious complications with cytomegalovirus (CMV) were frequently described.

Horizon scan. The horizon scan identified nine case reports, one cohort study, and one retrospective study involving the use of alemtuzumab in the treatment of NHL. Five of these reports described good clinical response to alemtuzumab, and four reported adverse events. Adverse events included: seven cases of CMV reactivation; one case of fever, chills, chest pain, nausea, vomiting, and hypotension one hour after initiation of alemtuzumab; and one case of aplasia. CMV reactivation was the emerging finding in the adverse event reports in the abstracts as well.

Discussion

These are some of the most mature and disparate data reflecting the efficacy of alemtuzumab for the treatment of patients with progressive lymphoma, most notably because this dataset encompasses the mix of studies from both before and after the FDA-approval of alemtuzumab for one NHL sub-type, CLL. Further, these data reflect the use of alemtuzumab in a variety of settings; e.g., as monotherapy for relapsed/refractory NHL and as a conditioning regimen for stem cell transplantation. As a result, the efficacy results are divergent and difficult to interpret.

Key messages of the published dataset are the following: 1) alemtuzumab may have a place in the therapy of general NHL for heavily pre-treated patients who can tolerate the adverse event profile (e.g., patients with good performance status) and for whom there are no other established options; 2) alemtuzumab may have a significant role in the preparatory management for stem cell transplantation; 3) new NHL sub-classifications particularly responsive to alemtuzumab, such as monotherapy for newly diagnosed peripheral T-cell lymphoma, are likely to emerge; and, 4) adverse events for alemtuzumab are as expected (i.e., predominantly hematological), with data supporting the importance of CMV reactivation as a major concern with alemtuzumab. Demonstration of the alemtuzumab target, CD52, was not a requisite for study entry and not clearly linked to outcomes, although in nearly all of the NHL settings where alemtuzumab was used, the presence of CD52 could be confidently assumed.

Table A5: Alemtuzumab for Non-Hodgkin Lymphoma – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Cull, Haynes, Byrne, et al., 2000[39]	**Design:** Pilot **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 12 NHL = 9 HD = 2 CLL = 1 **Age:** 26 (23–54) **Previous treatment:** Yes **Stage of disease:** PR = 8 Residual or progressive = 8 **Drug dose/day [followup]:** BEAM conditioning regimen for all transplant with alemtuzumab 10 mg days -5 to 1 **Outcomes sought:** Not reported	**N:** 12 **CR:** 1 CR died at 6 mo due to pneumonia, 9 CCR **PR:** 1 died at 6 mo due to relapse **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** 70% **2 yr:** 70% **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** 60% **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: No 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes (6–32 mo) 5) Objective outcomes assessments?: Yes (no blinding) **Comments:** - Median f/u 12 mo (6–32) - Concluded this was a well-tolerated conditioning regimen
Enblad, Hagberg, Erlanson, et al., 2004[40]	**Design:** Pilot, multi-center, open label **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Age 18–75 yr - PTL Not otherwise specified - Angioimmunoblastic T-cell	**No. in study:** 14 **Age:** Range 57–79 **Previous treatment:** Yes **Stage of disease:** III or IV **Drug dose/day [followup]:** 3, 10, 30 mg alemtuzumab first wk, then 30 mg alemtuzumab TIW x 12 wk	**N:** 14 **CR:** 3 (overall RR 36%) **PR:** 2 (14%) **Stable disease:** 4 (29%) **Progressive disease:** 5 (36%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** Duration of responses = 2, 6, & 12 mo **Median survival:** **1 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** - Effective but toxic regimens

Study	Study Design	Patients	Tumor Response	Survival	Other
	- Extranodal t-cell - Enteropathy-type T-cell - Anaplastic T-cell - Failed or relapsed post anthracycline-containing regimen - Not eligible for high-dose chemo - SCR & TBIL </+ 2x ULN, - WHO ≤ 2 - Life expectancy ≥ 3 mo - ≤ 3 prior regimens	**Outcomes sought:** RR, safety, DFS, OS		**2 yr:** NR **3 yr:** NR	- Authors do not recommend use in poor-prognosis PTL unless a carefully controlled clinical trial
Ferrajoli, O'Brien, Cortes, et al., 2003[18]	**Design:** Open **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Age 16 yr - CD52 on > 20% cells - < 20% predicted response to conventional chemo - Any subtype of leukemia w/ no frontline chemo - PLL w/ at least one treatment failure - WHO 0–2 - Cr & conj. Bili < 2x ULN	**No. in study:** 78 42 CLL 18 T-cell leukemia **Age:** 61 **Previous treatment:** Yes, 3 (0–9) **Stage of disease:** Not reported **Drug dose/day [followup]:** 3, 10, 30 mg alemtuzumab first wk, then 30 mg alemtuzumab TIW x 4–12 wk **Outcomes sought:** Efficacy and safety	**N:** 78 **CR:** 10 (13%) **PR:** 17 (22%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** 25 mo in responders 12 mo in whole population **1 yr:** 50% **2 yr:** 35% **3 yr:** NR **Survival (disease-free):** **Median survival:** Median duration of response 18 mo (CR) and 7 mo (PR) **1 yr:** 75% **2 yr:** 65% **3 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** - CLL pts comprised majority of pts (2 CR, 11 PR, of which 2 CR & 5 PR in Fludara® sensitive and 6 PR were in Fludara® refractory pts) - Majority of pts received at least 4 wk of treatment, 12 received 8 wk & 10 received 12 wk - All pts received TMP/SMS and Valtrex® prophylaxis - 84% of pts achieved normalized lymphocyte count and 49% resolution on BM involvement

Study	Study Design	Patients	Tumor Response	Survival	Other
Khorana, Bunn, McLaughlin, et al., 2001[41]	**Design:** Open label, multi-center **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Non-bulky NHL protocol: - Indolent, aggressive NHL - 1st-, 2nd-, or 3rd-line chemo w/ or w/o SCT, - Measurable dx - Age 18 yr - WHO 0–1 - 12-wk life expectancy Min resid. dx protocol: - Follicular or diffuse NHL - Complete remission - Residual dx having t14:18 translocation detectable by PCR - Age 18 yr - WHO PS 0–1	**No. in study:** 18 16 bulky 2 min residual dx **Age:** 22–77 **Previous treatment:** Yes **Stage of disease:** Various; 10 had Stage III–IV **Drug dose/day [followup]:** 10 mg alemtuzumab q day until acceptable tox then up to 30 mg alemtuzumab at investigators' discretion Then changed to 30 mg alemtuzumab TIW x 6 wk After 6 wk CR could d/c on at least 4 more wk; PR got at least 4 more wk; PD stopped; no response could d/c or continue at investigators' discretion **Outcomes sought:** Safety, efficacy	**N:** 16 = bulky 2 = min residual dx **CR:** Bulky: 2 – one lasted 7 mo, one lasted > 4.5 yr, both low-grade lymph; Min res. dx: one molecular response duration > 5 yr **PR:** Bulky NHL – follicular large cell; duration 5 mo **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Terminated early due to infectious complications
Kim, Sohn, Chae, et al., 2007[42]	**Design:** Open, pilot **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:**	**No. in study:** 20 (of planned 43) **Age:** 50.5 **Previous treatment:** No **Stage of disease:** Newly diagnosed	**N:** 20 **CR:** 13 (65%) **PR:** 3 (15%) **Stable disease:** 1 (5%) **Progressive disease:** 3	**Survival overall (from start of treatment):** **Median survival:** 265 days **1 yr:** 44.3% **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No

Study	Study Design	Patients	Tumor Response	Survival	Other
	- PTCL except for cutaneous T-cell lymphoma and anaplastic lymph kinase-positive anaplastic, - Large cell lymphoma - Age 17–65 yr - ECOG ≤ 2 - ≥ 1 measurable lesion - Adequate bone marrow - Adequate cardiac, organ function	**Drug dose/day [followup]:** CHOP plus alemtuzumab (10 mg day 1, 20 mg day 2 cycle #1, 30 mg IV cycles 2-6) q 3 wk **Outcomes sought:** Safety and efficacy	(15%)	**Survival (disease-free):** **Median survival:** 255 days **1 yr:** 43.3% **2 yr:** NR **3 yr:** NR	4) Adequate followup period?: Only 219 days 5) Objective outcomes assessments?: Yes **Comments:** - All pts received TMP.SMX prophylaxis - No growth factors allowed in cycle #1 - 11 pts completed planned 6 cycles (low or low-int IPI), 4 went on to SCT ((high IPI) - 9 pts withdrawn due to toxicity or progression on chemo - Study terminated after 20 pts due to AEs and heme toxicity - 5 of 7 pts who completed treatment and then relapsed received salvage (4-DHAP, 1 ICE followed by auto SCT) - 9 pts at time of evaluation
Lundin, Osterborg, Brittinger, et al., 1998[43]	**Design:** Open, multi-center **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Low-grade NHL, stage II, II, or IV - Age ≥ 18 yr - WHO 0–1 - Refractory or relapsed from CR, or PR to 1st line conventional chemo - 12-wk life expectancy	**No. in study:** 50 25 relapse 25 refractory **Age:** Not reported **Previous treatment:** Yes (range 1 to > 4 prior treatments) **Stage of disease:** Stage II, III, or IV **Drug dose/day [followup]:** 3 mg or 10 mg	**N:** 50 **CR:** 2 (4%) – mycoses fungoides **PR:** 8 (16%) **Stable disease:** 24 (48%) **Progressive disease:** 16 (32%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 4 mo, 10 mo for mycoses fungoides **1 yr:** 30% **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** - Lymph nodes responded poorly; blood, bone marrow and skin lesions most pronounced effects - No specifics reported, but noted that no difference in RR between refractory and relapsed pts or

Study	Study Design	Patients	Tumor Response	Survival	Other
		alemtuzumab per investigator, escalated up to 30 mg alemtuzumab IV TIW x 12 wk (9 received all 12 wk, rest 2–11, median 8 wk) **Outcomes sought:** Safety, efficacy			heavily vs. non-heavily pre-treated pts
Tang, Hewitt, Reis, et al., 1996[44]	**Design:** Open **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Refractory or relapse from CR or PR - Low-grade NHL - Age >18 yr - WHO 0, 1, or 2 - Stage 2b, 3, or 4 - Life expectancy ≥ 12 wk	**No. in study:** 7 **Age:** 52.9 **Previous treatment:** Yes for 6 **Stage of disease:** 2b, 3, or 4 **Drug dose/day [followup]:** Initial dose of 8 mg alemtuzumab escalating up to 25 mg alemtuzumab TIW x max 12 wk **Outcomes sought:** Not reported	**N:** 7 **CR:** 2 (29%) **PR:** Not reported **Stable disease:** 1 (14%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Of 3 responses, durations of 4 mo, 12+ mo, and 8.5 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: No - lymph node index, size of splenomegaly, tumor as measured by PE or CT **Comments:** Only 7 pts
Uppenkamp, Engert, Diehl, et al., 2002[45]	**Design:** Open; 2 studies, A & B combined results **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:**	**No. in study:** 18 2 = dose finding 16 = fixed dose **Age:** 61 **Previous treatment:** Yes (1–4 prior treatments) **Stage of disease:**	**N:** 18 **CR:** 6 (33%) limited Dz improvement, 2 (11%) Dz improvement **PR:** Not reported **Stable disease:** 2 (11%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):**	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No

Study	Study Design	Patients	Tumor Response	Survival	Other
	- Relapsed or refractory low-grade or high-grade NHL - Age >18 yr - Ann Arbor stage IIb, III or IV; Rai stage I-IV; or Binet stage A, B, or C	Not reported **Drug dose/day [followup]:** Dose finding- Alemtuzumab 7.5, 24, 75 to 240 mg x 4 weeks Fixed dose- 30 mg TIW x 6 weeks, repeat x 6 weeks if response. **Outcomes sought:** Safety and efficacy	**Progressive disease:** 5 (28%)	**Median survival:** 3.5 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	5) Objective outcomes assessments?: Yes **Comments:** Sub-groups: CLL, PLL, IC, CB-CL, CC, CB
Ho, Devereux, Mufti, et al., 2003[46] Study of alemtuzumab in transplant conditioning	**Design:** Open **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** CD20+ follicular, refractory lymphoma after 1st or 2nd complete remission	**No. in study:** 5 **Age:** 50.9 **Previous treatment:** Yes **Stage of disease:** All IPI 2 **Drug dose/day [followup]:** Reduced intensity conditioning w/ rituximab 375 mg/m^2 wkly x 4 wk (within 12 wk of SCT) Alemtuzumab 20 mg IV day -5 to 1 BCNU 300 mg/m^2 day -6 Cytarabine 200 mg/m^2 q 12 hr day -5 to -2 Etoposide 200 mg/m^2 day -5 to -2 Melphalan 140 mg/m^2 day -1 **Outcomes sought:** Safety and efficacy	**N:** 5 **CR:** 4 (80%) **PR:** 1 (20%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Median f/u 521 days, 4/5 alive and 3 still in CR **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** - Appears to be safe and effective conditioning regimen - More f/u needed, as small study

Study	Study Design	Patients	Tumor Response	Survival	Other
Morris and Mackinnon, 2005[47] Study of alemtuzumab in transplant conditioning	**Design:** Open **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - NHL - Age 18–75 yr - HLA-identical sibling donor or HLA-compatible unrelated donor	**No. in study:** 88 **Age:** 48 **Previous treatment:** 37 prior autograft HG: median 4 prior treatments LG/MCL: median 3 **Stage of disease:** 21 CR 57 PR 10 refractory or PD 41 indolent/LG 37 aggressive/HG 10 mantle cell **Drug dose/day [followup]:** Alemtuzumab 20 mg/d on days -8 to -4 Fludarabine 30 mg/m^2 on days -7 to -3 Melphalan 140 mg/m^2 on day -2 **Outcomes sought:** PFS, OS	**N:** 74 **CR:** 42 at 6 mo; Of 21 in CR at transplant, 13 CR at median 38 mo **PR:** 17 at 6 mo; Of 57 PR at transplant, 27 PR and 17 CR at median 37 mo, 6 PD by 6 mo, all dead by 10 mo **Stable disease:** Not reported **Progressive disease:** 17 at 6 mo 1 CR at 31 mo post-DLI 1 PR at 6 mo (died of viral encephalitis)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** 34% - HG 60% - MCL 73% - LG **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** 65% - LG 50% - MCL 34% HG (includes pt who received PLI) Actual PFS: 49% - LG 30% - HG 40% - MCL	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes (median 36 mo) 5) Objective outcomes assessments?: Yes
Pegg, Thomson, Hart, et al., 2004[48] Study of alemtuzumab in transplant conditioning	**Design:** **Phase:** Phase II **Selection/ randomization:** Non-randomized	**No. in study:** 36 **Age:** 46 **Previous treatment:** Yes **Stage of disease:** Various Dz and stages	**N:** 3 **CR:** Indicated some response in the 3 evaluable LG-NHL pts; too small to make any further comments	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A8 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: No 3) Patients entered at similar point

Study	Study Design	Patients	Tumor Response	Survival	Other
	Eligibility criteria: Heme malignancy receiving transplant conditioning regimen of alemtuzumab, fludarabine, melphalan	**Drug dose/day [followup]:** Alemtuzumab 20 mg/d for days -8 to -4 Fludarabine 30 mg/m^2 on days -7 to -3 Melphalan 140 mg/m^2 on day -2 **Outcomes sought:** Efficacy of DLI post transplant on chimerism and disease response	**PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	in disease progression?: No – different disease and stages 4) Adequate followup period?: Yes – median f/u 765 days from first DLI 5) Objective outcomes assessments?: Yes **Comments:** - Subgroups: 19 MM; 13 HD; 7 LG-NHL; 2 CLL; 1 PLL; 1 CML; 3 HG-NHL - Too few NHL pts to make any comments

Abbreviations: 4-DHAP = Dexamethasone, high-dose cytarabine, and cisplatin; AE(s) = adverse event(s); BEAM = bischloroethylnitrosourea, etoposide, cytarabine, and melphalan; bili = bilirubin; BM = bone marrow; CCR = complete clinical response; chemo = chemotherapy; CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin® (vincristine), and prednisone; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; CR = complete response; CT = computerized tomography; d/c = discontinued; DFS = disease-free survival; DLI = donor lymphocyte infusion; Dz = disease; ECOG = Eastern Collaborative Oncology Group; graft-versus-host disease; heme = hematology; HG = high grade; HLA = human leukocyte antigenICE = ifosfamide, carboplatin and etoposideIPI = International Prognostic Index; IV = intravenous; LG = low grade; MCL = mantle cell lymphoma ; MM = multiple myeloma; NHL = Non-Hodgkin lymphoma; OS = overall survival; PCR: polymerase chain reaction; PD = progressive disease; PFS = progression-free survival; PLL = prolymphocytic leukemia; PR = partial response; PS = performance status; PTL = peripheral T-cell lymphoma; PTCL = peripheral T-cell lymphoma; q = every;; resid = residual; RR = response rate; SCR = screen; SCT = stem cell transplant; TBIL = total bilirubin; TIW = three times a week; TMP/SMS = trimethoprim/sulfamethoxazole; tox = toxicity; ULN = upper limit of normal; WHO = World Health Organization.

Table A6: Alemtuzumab & Non-Hodgkin Lymphoma: ASH 2006, ASH 2007, and ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Bigelow, Elkins, Herrin, et al., 2006[49] ASH 2006 Abstract #5253	**Disease:** NHL **Design:** Retrospective **Phase:** NR **Selection/randomization:** Not reported **Eligibility criteria:** Not reported	**No. in study:** 29 **Age:** 53 (24–66) **Previous treatment:** Yes **Stage of disease:** **Drug dose/day [followup]:** Alemtuzumab 20 mg/d x 3 d (n = 10 patients); Alemtuzumab 20 mg/d x 2 d (n = 19 patients) **Outcomes sought:** TRM at 100 days, OS, GVHD, relapse	**N:** 29 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** 11 (38%)	**Survival overall (from start of treatment):** 41% overall (no time provided) **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** TRM at d100 = 21%
Chang, Lau, Chew, et al., 2006[50] ASH 2006 Abstract #4684	**Disease:** NHL **Design:** Retrospective **Phase:** NR **Selection/randomization:** Not reported **Eligibility criteria:** Not reported	**No. in study:** 5 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab 30 mg on day 1 of HyperCVAD/MTX and ARA C **Outcomes sought:** Response	**N:** 4 **CR:** 3 (75%; one with transplant) **PR:** 0 **Stable disease:** 0 **Progressive disease:** 1 (25%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported

Study	Study Design	Patients	Tumor Response	Survival	Other
Gallamini, Campidelli, Zaja, et al., 2006[51] ASH 2006 Abstract #4732	**Disease:** NHL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized; newly diagnosed PTCL **Eligibility criteria:** PTCL	**No. in study:** 25 **Age:** 51.2 (28–69) **Previous treatment:** None **Stage of disease:** III or IV in 22 (88%) **Drug dose/day [followup]:** All with CHOP; Alemtuzumab 30 mg SC x 1 x 4 cycles (n = 4 patients); Alemtuzumab 30 mg SC x 1 x 8 cycles (n = 21 patients) **Outcomes sought:** CR, OS, PFS	**N:** 25 **CR:** 17 (68%) **PR:** 1 (4%) **Stable disease:** 1 (4%) **Progressive disease:** 6 (24%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** 45% **3 yr:** NR **Survival (disease-free):** **Median survival:** 9 mo **1 yr:** NR **2 yr:** 50% **3 yr:** NR	**Adverse events & tolerability:** Not reported
Intragumtorn-chai, Bunworasate, Na Nakorn, et al., 2006[52] ASH 2006 Abstract #4740	**Disease:** NHL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized; newly diagnosed PTCL **Eligibility criteria:** PTCL	**No. in study:** 13 **Age:** 44 (21–56) **Previous treatment:** None **Stage of disease:** III or IV in 7 (54%) **Drug dose/day [followup]:** Alemtuzumab 30 mg SC days 1–3 q 28 days of cycles 1-5, CHOP day 1 of cycles 1, 3, & 5, ESHAP day 1 of cycles 2, 4, & 6 **Outcomes sought:** OS, CR, AEs	**N:** 10 **CR:** 8 (80%) **PR:** 1 (10%) **Stable disease:** 0 **Progressive disease:** 1 (10%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** 75% **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** 48% **3 yr:** NR	**Adverse events & tolerability:** CMV react in 54%, neutropenic fever 54%, tuberculosis 15%

Study	Study Design	Patients	Tumor Response	Survival	Other
Ravandi-Kashani, Kantarjian, Faderl, et al., 2006[53] ASH 2006 Abstract #4971	**Disease:** T-PLL, NHL **Design:** Retrospective **Phase:** NR **Selection/randomization:** Not reported **Eligibility criteria:** Not reported	**No. in study:** 17 **Age:** 57 (22–79) **Previous treatment:** Yes: 11 No: 6 **Stage of disease:** **Drug dose/day [followup]:** Alemtuzumab 30 mg IV TIW x 12; pentostatin 4 mg/m^2 QW x 4 then QOW x 6 mo **Outcomes sought:** Response, toxicity	**N:** 17 **CR:** 8 (47%) **PR:** 3 (18%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** CMV 6/17, HSV 1/17, pneumonia 3/17, pancytopenia 2/17 **Comments:** This is the same patient cohort as ASCO 2007 Alemtuzumab Abstract #7037
Weidmann, Hess, Krause, et al., 2006[54] ASH 2006 Abstract #2721	**Disease:** NHL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized; all eligible **Eligibility criteria:** First diagnosis, first relapse, or primary refractory; CTCL excluded	**No. in study:** 37 (30 evaluable) **Age:** 56 (21–77) **Previous treatment:** 11/30 **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab 3 mg, 10 mg, 30 mg, 30 mg days 1–4 of FCD chemo regimen **Outcomes sought:** Response, toxicity	**N:** 30 **CR:** 14 (47%) **PR:** 3 (10%) **Stable disease:** 0 **Progressive disease:** 13 (43%)	**Survival overall (from start of treatment):** **Median survival:** Median not reached **Survival (disease-free):** **Median survival:** Median not reached	**Adverse events & tolerability:** 65% leucopenia, 40% CMV reactivation, 17% anemia, 35% thrombocytopenia, 16% infections, 11% pruritus/skin reactions, 6% nausea/emesis, 4% mucositis, 4% cardiac toxicity (2 patients with relapsed disease after pre-treatment with CHOP-like regimens developed severe heart failure and died) **Comments:** Trial closed for relapse and refractory disease due to toxicity

Study	Study Design	Patients	Tumor Response	Survival	Other
Binder, Ziepert, Loeffler, et al., 2007[55] ASH 2007 Abstract #3431	**Disease:** NHL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** T neoplasm, age < 70, PS 0–3	**No. in study:** 41 **Age:** 55 median **Previous treatment:** Not reported **Stage of disease:** III/IV: 63.4% **Drug dose/day [followup]:** CHOP or CHOEP-14 x 6, CAM 133 mg over 4 wk consolidation **Outcomes sought:** Response, toxicity, TRM, OS, EFS	**N:** 29 **CR:** 17 (58%) **PR:** 1 (2.4%) **Stable disease:** 3 (9.8%) **Progressive disease:** 8 (29.3%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** 13 (44%) **3 yr:** NR	**Adverse events & tolerability:** 14% infection, 11% leukopenia
Porcu, Baiocchi, Lin, et al., 2007[23] ASH 2007 Abstract #3417	**Disease:** NHL, CTCL **Design:** Prospective cohort **Phase:** Phase I **Selection/randomization:** Not randomized; all eligible **Eligibility criteria:** T-neoplasm, no HIV, HBV, HCV. Untreated overall, relapsed CTCL only.	**No. in study:** 18 **Age:** 62 median **Previous treatment:** 3/18 patients **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab SQ loading (3, 10, 30 mg) over 5 days followed by one SQ dose with each cycle of CHOP q 21 days for a total of 8 cycles. All patients received valacyclovir, trimethoprim-sulfamethoxazole prophylaxis and G-CSF. Erythropoietin was given	**N:** 16 **CR:** 4 (25%) **PR:** 0 **Stable disease:** 2 (13%) **Progressive disease:** 1 (6%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 1 neutropenic fever, 2 anemia, 1 grade III CMV, 5 all CMV

Study	Study Design	Patients	Tumor Response	Survival	Other
		according to published guidelines. **Outcomes sought:** Response, toxicity			
Thomson, Morris, Bloor, et al., 2007[56] ASH 2007 Abstract #1661	**Disease:** NHL/transplant **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** DLBCL in relapse	**No. in study:** 54 **Age:** 44 (18–64) **Previous treatment:** 4 (1–7) **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab 20–100 mg conditioning **Outcomes sought:** GVHD, survival	**N:** 54 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **5 yr:** 24 (45%) **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **5 yr:** 25 (46%)	**Adverse events & tolerability:** Not reported
Thomson, Morris, Milligan, et al., 2007[57] ASH 2007 Abstract #1666	**Disease:** NHL/transplant **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Follicular lymphoma, relapse	**No. in study:** 64 **Age:** 44 (26–65) **Previous treatment:** 3 (1–8) **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab 20–100 mg conditioning **Outcomes sought:** GVHD, survival	**N:** 64 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** 51 (80%) **2 yr:** NR **3 yr:** NR **5 yr:** 49 (76%) **Survival (disease-free):** **Median survival:** **1 yr:** 51 (79%) **2 yr:** NR **3 yr:** NR **5 yr:** 49 (77%)	**Adverse events & tolerability:** Not reported

Study	Study Design	Patients	Tumor Response	Survival	Other
Aribi, Kantarjian, O'Brien, et al., 2007[58] ASCO 2007 Abstract #7037	**Disease:** NHL, T-PLL **Design:** Retrospective **Phase:** NR **Selection/randomization:** Not reported **Eligibility criteria:** T-cell lymphoma	**No. in study:** 20 **Age:** 57 (22–79) **Previous treatment:** 13 Yes, median 2 **Stage of disease:** Not reported **Drug dose/day [followup]:** Pentostatin and alemtuzumab 30 mg TIW x 12, then QOW x 6 **Outcomes sought:** Not reported	**N:** 20 **CR:** 10 (50%) **PR:** 2 (10%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 35% CMV reactivation, 5% HSV, 15% pneumonia **Comments:** This is the same patient cohort as ASH 2006 Alemtuzumab Abstract #4971
Moon, Kim, Sohn, et al., 2007[59] ASCO 2007 Abstract #8069	**Disease:** NHL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Not reported	**No. in study:** 20 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** 10 mg/m^2 IV day 1 of CHOP, and 20 mg/m^2 IV on day 2 of 1st cycle, then 30 mg/m^2 IV on in the subsequent cycles based on 3-wk intervals **Outcomes sought:** Response, AEs	**N:** 20 **CR:** 13 (65%) **PR:** 3 (15%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** 43.3% **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 90% Grade 4 neutropenia, 55% febrile neutropenia, 25% CMV

Study	Study Design	Patients	Tumor Response	Survival	Other
Sharma, Wilson, Dunleavy, et al., 2007[60] ASCO 2007 Abstract #3033	**Disease:** NHL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** T or NK cell lymphoma	**No. in study:** 20 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab with EPOCH chemotherapy **Outcomes sought:** AEs	**N:** Not reported **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 4 patients with BK virus reactivation out of 20 given alemtuzumab with EPOCH developed hemorrhagic cystitis

Abbreviations: AE(s) = adverse event(s); ASH = American Society of Hematology; ASCO = American Society of Clinical Oncology; chemo = chemotherapy; CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin® (vincristine), and prednisone; CML = chronic myelogenous leukemia; CMV = cytomegalovirus; CR = complete response; CT = computerized tomography; CTCL = cutaneous T-cell lymphoma; CVAD = cyclophosphamide, vincristine, Adriamycin®, and dexamethasone; DLBCL = diffuse large B-cell lymphoma; ESHAP = etoposide, cisplatin, cytarabine, and methylprednisolone; G-CSF = granulocyte-specific colony stimulating factor; GVHD = graft versus host disease; HCV = hepatitis C virus; HG = high grade; HIV = human immunodeficiency virus; HSV = herpes simplex virus; IV = intravenous; MTX = methotrexate; NHL = non-Hodgkin lymphoma; NK = natural killer; NR = not reported; OS = overall survival; PFS = progression-free survival; PLL = prolymphocytic leukemia; PR = partial response; PS = performance status; q = every; QOW = every other week; QW = every week; react =reaction; SC = subcutaneous; SQ = subcutaneous; TIW = three times a week; T-PLL = T-cell prolymphocytic leukemia; TRM = transplantation-related mortality ; WHO = World Health Organization.

Table A7: Alemtuzumab for Non-Hodgkin Lymphoma – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Chanan-Khan, Islam, Alam, et al., 2004[61]	Case report	3, 10, and 30 mg escalating doses	1	26 y/o male diagnosed w/ stage IV α/β HSTCL. Pt received CHOP, and PD was recorded after 2 cycles. Pt switched to DHAC showing PR, w/ resolution of lymphadenopathy and hepatomegaly (although residual splenomegaly was observed) after 2 cycles. Splenectomy revealed no residual disease, so pt considered in CR. 2 mo later, pt relapsed. Pentostatin, oral VP-16, and high-dose cytosine arabinoside and methotrexate all failed. Alemtuzumab was initiated. Response was immediate. Decrease in total WBC count was achieved w/ first dose. Slowly increasing lymphocytosis observed at day 181. Pt given DLI on day 216, and considered to be in CR. At day 655, pt remains in clinical and molecular remission w/ limited cutaneous chronic GVHD. Pt is no longer receiving immunosuppressive treatment.
Damaj, Rubio, Audard, et al., 2002[62]	Case report	10 mg over 2 h in association w/ Polaramin® and aceta-minophin	1	52 y/o male w/o h/o cardiac problems diagnosed w/ localized peripheral T-cell lymphoma. CR was achieved after 3 cycles of CHOP and inguinal radiotherapy. 3 yr later a refractory relapse occurred. Alemtuzumab was considered after failure of CHOP, DHAP, DexaBEAM, and 2CDA. 1 hr after initiation of alemtuzumab, pt experienced fever, chills, and sweats, followed by severe chest pain, nausea, vomiting, and hypotension. Symptoms resolved progressively after symptomatic treatment.
Halene, Zieska, and Berliner, 2006[63]	Case report	30 mg SC TIW x 7.5 wk	1	73 y/o female presented w/ lower back pain, fever, chills, and arthralgia. Diagnosed w/ angioimmunoblastic T-cell lymphoma. After repeated episodes of symptoms and temporary responses, pt experienced sudden clinical deterioration. Alemtuzumab was started w/ slow improvement. Pt had aplasia attributed to alemtuzumab.
Magro, Crowson, Byrd, et al., 2004[31]	Prospective case study	30 mg TIW x 12 wk	12	Pts presented w/ lymphocytic panniculitis accompanied by lymphoid atypia. 5 males, 6 women, and one male child had symptoms compatible with lupus erythematosus or aggressive SCTCL. While some response w/ prednisone, lesions relapsed. In 1 pt treated w/ alemtuzumab there was complete lesional resolution w/ no recurrence.
Martin, Marty, Fiumara, et al., 2006[64]	Retrospective evaluation	3, 10, 30 mg escalating doses TIW	27 (21 w/ CLL and 6 w/ plasma cell disorders)	Overall mortality was 37%, w/ 7/10 deaths related to infection. Significant opportunistic infections occurred in 9 (43%) pts w/ CLL. Alemtuzumab recipients had incidence of cytomegalovirus reactivation of 66.7% (6/8 pts). Non-alemtuzumab group had 37% (10/27 pts).
Mittal, Milner, Johnston, et al., 2006[65]	Case report	Alemtuzumab 30 mg/m^2 TIW and fludarabine 40 mg/m^2 PO 3d q 4 wk for total of 12 wk	1	18 y/o male presented w/ pancytopenia w/ swinging fevers and hepatosplenomegaly, but no lymphadenopathy. IVE and ESHAP gave PR, but pt became refractory. Alemtuzumab treatment produced dramatic response evidenced by weight gain, resolution of fevers, complete regression of hepatomegaly and achievement of normal blood counts. 6 wk post-transplant pt developed pyrexia and cervical lymphadenopathy. Test confirmed aggressive B-cell post-transplant lymphoproliferative disease from which pt died.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Robinson, Goldstone, Mackinnon, et al., 2002[66]			188	Median age = 40; median number of prior treatment courses = 3; 48% of pts had prior autologous transplantation. 84% received conditioning w/ fludarabine-based regimens and 10% w/ BEAM protocol. Full donor chimerism confirmed in 71% of 100 pts assessed. Acute GVDH developed in 37% of pts, and chronic GVHD in 17%. W/ median f/u of 283 days, OS at 1 yr and 2 yr was 62% and 50%, respectively. 100-day and 1-yr TRM rates were 12.8% and 25.5%, respectively, and were significantly worse in older pts. PFS at 1 yr was 46%.
Snyder, Stenzel, Buckley, et al., 2004[67]	Case reports	Pts received alemtuzumab as part of conditioning regimen	2	These 2 cases were retrieved from the Department of Pathology archives. Pt 1: 37 y/o female w/ low-grade B-cell lymphoma of the liver. Several courses of chemo and radiation offered no response. Pt received NMST, which was well tolerated, CR and full donor engraftment. Pt 2: 48 y/o female w/ poorly differentiated infiltrating ductal adenocarcinoma of the breast. 19 mo later, pt received Adriamycin® and cyclophosphamide for metastatic carcinoma w/ CR. 7 yr after initial diagnosis, myelodysplastic syndrome was diagnosed and 2 mo later pt had NMST resulting in remission and full donor engraftment. 6 mo later, test revealed relapse. Further aggressive treatment was not given and pt died a few weeks later from progressive PTLD.
Vivas, Ruiz de Morales, Ramos, et al., 2006[68]	Case report	30 mg 2 x wk for 12 consecutive wk	1	56 y/o female had 2-yr h/o refractory celiac disease. Pt opted for alemtuzumab treatment, given according to conventional therapeutic schedule. After 9 mo of treatment, pt remained asymptomatic. Duodenal biopsy showed total recovery.
Wong, de Lima, Couriel, et al., 2003[69]	Case report		1	31 y/o male with diffuse large-cell lymphoma in first refractory relapse received BMT using alemtuzumab as part of conditioning regimen. Transplant was complicated by grade II skin acute GVHD. Lymphoma relapse occurred 4 mo post-transplant. Immunosuppression withdrawal plus rituximab induced CR. Pt remains in CR 11 mo post-immunosuppression withdrawal and 15 mo post-transplant.
Wulf, Hasenkamp, Jung, et al., 2005[70]	Consecutive cases	3, 10, 30 mg q 48 hr in 1st wk, followed by 30 mg q 48 hr up to maximal response	10	Pts had relapsed or primary progressive T-NHL. Pts given alemtuzumab as single agent (2 pts) and in combination chemo (8 pts). Following alemtuzumab treatment, all pts judged eligible for allogeneic stem cell transplantation after RIC. One pt died on day 12 from cardiac arrest. One pt experienced grade III acute GVHD, 3 pts grade II, and 1 pt grade I, whereas 4 pts developed no signs of GVHD. Chronic GVHD was either extensive in 5 pts, including two fatal complications or completely absent (4 pts). W/ median f/u time of 7 mo (4-16) after SCT, 7 pts are alive, 6 pts are in CR, and 1 pt had cerebral relapse 4 mo after SCT.
Zeitlinger, Schmidinger, Zielinski, et al., 2005[71]	Case report	30 mg q 3rd day	1	74 y/o male w/ disseminated Lennert's lymphoma. Pt underwent CHOP and ICE w/ no response. Alemtuzumab treatment was initiated. Leukocytopenia with reactivation of cytomegalovirus infection was observed and alemtuzumab was temporarily stopped. 5 wk after start of alemtuzumab, reassessment disclosed significant reduction of all thoracic and abdominal lesions, and treatment was continued after normalization of the number of CMV copies and is currently ongoing.

Abbreviations: 2-CDA = 2-chlorodeoxyadenosine (cladribine); AE(s) = adverse event(s); BMT = bone marrow transplant; chemo = chemotherapy; CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin® (vincristine), and prednisone; CMV = cytomegalovirus; CR = complete response; CT = computerized tomography; CTCL = cutaneous T-cell lymphoma; Dexa-BEAM = dexamethasone, carmustine, etoposide, arabinoside C, and melphalan; DHAC = dexamethasone, cytosine arabinoside, and carboplatin; DHAP = dexamethasone, high-dose cytarabine, and cisplatin; ESHAP = etoposide, cisplatin, cytarabine, and methylprednisolone; GVHD = graft versus host disease; h/o = history of; HSTCL = hepatosplenic T-cell non-Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; NMST = nonmyeloablative allogenic stem cell transplantation; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PO = orally; PR = partial response; PTLD = post-transplant lymphoproliferative disorder; q = every; RIC = reduced intensity conditioning; SC = subcutaneous; SCTCL = subcutaneous T-cell lymphoma; SQ = subcutaneous; TIW = three times a week; T-NHL = T-cell non-Hodgkin lymphoma; TRM = transplantation-related mortality; WBC = white blood cell.

Table A8.1: Alemtuzumab for Non-Hodgkin Lymphoma - Adverse Events (Grade 3/4+ Events Only) – Part 1

Study	Anemia	Neutropenia/ granulocytopenia	Leukopenia	Thrombocytopenia	Diarrhea	Nausea	Vomiting	Dyspepsia	Constipation	Dermatitis or rash	Fatigue	Headache	Pain	Chills/fever	Dyspnea
Ferrajoli et al., 2003[18]	0%	35%	-	41%	-	0%	-	9%	-	0%	-	1%	-	1%	-
Khorana et al., 2001[41]	-	-	-	-	-	22%	-	-	-	11%	11%	-	-	22%	-
Kim et al., 2007[42]	30%	90%	90%	30%	0%	0%	0%	-	0%	-	-	-	-	-	-
Lundin et al., 1998[43]	-	-	-	-	0%	12%	-	-	-	0%	-	-	-	24%	-
Morris et al., 2004[72]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Peggs et al., 2004[48]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tang et al., 1996[44]	-	-	-	-	0%	-	0%	-	-	-	0%	-	-	0%	-
Uppen-kamp et al., 2002[45]	-	-	-	-	-	6%	6%	-	-	-	-	6%	6%	22%	6%

Table A8.2: Alemtuzumab for Non-Hodgkin Lymphoma - Adverse Events (Grade 3/4+ Events Only) – Part 2

Study	Infection	Neutropenic fever	Hypotension	Rhythm disturbance	Lymphopenia	Stomatitis	Neuropathy	AST/ALT elevation	Bilirubinemia	Febrile neutropenia	GVHD	Flushing	Hives/urticaria	Wheezing/ bronchospasm	Muscle ache	Mucositis
Ferrajoli et al., 2003[18]	-	-	1%	-	-	-	-	-	-	-	-	-	-	-	-	
Khorana et al., 2001[41]	-	-	11%	0%	-	-	-	-	-	-	-	-	-	-	-	-
Kim et al., 2007[42]	-	-	-	-	95%	5%	5%	10%	5%	55%	-	-	-	-	-	-
Lundin et al., 1998[43]	32%	36%	0%	-	-	-	-	-	-	-	-	-	-	-	-	-
Morris et al., 2004[72]	-	-	-	-	-	-	-	-	-	-	5%	-	-	-	-	% NR
Peggs et al., 2004[48]	-	-	-	-	-	-	-	-	-	-	11%	-	-	-	-	-
Tang et al., 1996[44]	-	-	0%	-	-	-	-	-	-	-	-	0%	0%	0%	0%	-
Uppen-kamp et al., 2002[45]	6%	-	0%	-	-	-	-	-	-	-	-	-	6%	22%	-	-

Abbreviations: AST/ALT = aspartate aminotransferase/alanine transaminase; GVHD = graft versus host disease.

Alemtuzumab for T-Cell Prolymphocytic Leukemia

Background

Drug: Alemtuzumab (Campath®). Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody (Campath-1H) directed against the 21–28 kD cell surface glycoprotein, CD52. Campath-1H is an IgG1 kappa antibody with human variable framework and constant regions, and complementarity-determining regions from a murine monoclonal antibody (Campath-1G). Alemtuzumab binds to CD52, an antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. The proposed mechanism of action is antibody-dependent cellular-mediated lysis following cell surface binding of alemtuzumab to the leukemic cells.

Alemtuzumab was approved in May 2001 under the accelerated approval program for the "treatment of patients with B-cell chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed fludarabine therapy." In September 2007, the Food and Drug Administration (FDA) expanded the labeling and granted regular approval for single-agent alemtuzumab for the treatment of untreated B-cell chronic lymphocytic leukemia. It has been evaluated for off-label use in cutaneous T-cell lymphoma (CTCL), non-Hodgkin lymphoma (NHL), and T-cell prolymphocytic leukemia (T-PLL).

Disease: T-cell prolymphocytic leukemia. T-PLL is a postthymic lymphoproliferative malignancy with a poor prognosis. Primarily affecting individuals over the age of 30, T-PLL is rare, representing only 2 percent of all adult occurrences of small lymphocytic leukemia.[73] However, it has an extremely aggressive clinical course, with a median survival of 7.5 months.[74,75] Although T-PLL patients may present with a leukemic profile of B-cell chronic lymphocytic leukemia, T-PLL is a distinct disease entity with specific clinical, morphological, and cytogenetic markers.[76] Characterized by splenomegaly, lymphadenopathy, hepatomegaly, and skin lesions, T-PLL is largely resistant to conventional chemotherapy regimens, with partial or short-lived responses. Treatment with the purine analog 2'-deoxycoformycin as a single agent has resulted in partial or complete responses in 45 percent of patients, with median survival increasing to 17.5 months.[75] Even among patients who respond to treatment, remission is usually partial and short-lived. Recurrence is universal.[74,75]

Drug/Disease: Alemtuzumab for T-PLL. As an anti-CD52 immunoglobulin, alemtuzumab slows the proliferation of leukocytes by binding to the CD52 receptor found in variable levels on most malignant T-cells. T-prolymphocytes, in particular, express a higher density of the CD52 marker than do normal T-cells.[77] Given the poor response of T-PLL to standard therapies, as well as evidence that patients with higher expressions of the CD52 antigen are especially responsive to alemtuzumab, researchers have in the last decade investigated alemtuzumab for T-PLL, with promising results.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded a total of 18 reports: Four full reports of Phase II clinical trials (Table A9), three published abstracts from the American Society of Hematology (ASH) or American Society of Clinical Oncology (ASCO) conferences (Table A10), and 11 additional articles considered in the horizon scan (Table A11). Of the three published abstracts, one was a Phase II clinical trial, while the other two were retrospective studies for a total of 5 Phase II trials between the full reports and abstracts combined.

The first description of alemtuzumab activity in T-PLL was a Phase II clinical trial with 15 patients published in 1997. In that trial, 11 of 15 patients who were refractory to treatment with pentostatin achieved either a complete or partial response to alemtuzumab. A total of three additional Phase II trials were published in 2001, 2002, and 2003.

Sample sizes in the five clinical trials ranged from 15 to 38 with a total of 103 patients presented in the published trials and abstract. Eligibility criteria varied, with some trials requiring failure of previous treatment and others permitting alemtuzumab as a first treatment. In addition, some studies enrolled patients with diseases other than T-PLL, preventing disease-specific interpretation of progression-free and overall survival statistics.

Alemtuzumab monotherapy was used in all of the published clinical trials, typically at starting doses of 3 mg, escalating to 30 mg three times weekly. One trial did allow dose escalation up to 80 mg in patients refractory to the 30 mg dose. The duration of therapy varied between trials, but did not exceed 12 weeks. In the one clinical trial available only in abstract form, alemtuzumab was used immediately following a multi-agent chemotherapy regimen (fludarabine, mitoxantrone, cyclophosphamide).

Efficacy data were provided in each of the four studies represented in the full reports. Outcomes assessed differed between studies, and disease-specific survival data were not provided in those studies that evaluated T-PLL along with other diseases. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

Study quality of the full published reports was generally poor. Three of the four published studies met only two of the five quality criteria. One study met four of the five criteria, though this study was limited by the inclusion of numerous heterogeneous diseases, such that interpretation of disease-specific outcomes was not possible.

Efficacy. The range of complete response (CR) rates was 31 percent to 60 percent among the fully published reports. This range remained unchanged when abstracts from prospective studies were considered in conjunction with the full reports. Two published studies found a response rate of 60 percent. Nearly all of the patients in those two studies had received previous treatment for T-PLL. The range of partial response (PR) rates was 11 percent to 19 percent among the fully published reports. The range did change when the abstract of one prospective study was considered in conjunction with the full reports, with an observed PR rate of 56 percent on that study. That study involved alemtuzumab following chemotherapy.

Survival: Median disease-free survival ranged from six to 10 months in three studies, and overall survival was 10 and 19 months in two studies. Disease-specific survival statistics were not available from one study, which provided aggregate survival information for all patients treated with alemtuzumab for lymphoproliferative disorders.[18]

Adverse events. Data presented in Table A12 were derived from the four full reports. Hematologic toxicity was the major serious adverse event, with Grade 3 and 4 thrombocytopenia

(range, 13 percent to 41 percent) reported in three of four studies, and neutropenia/granulocytopenia of 35 percent reported in two studies. Several cases of treatment-associated cytomegalovirus (CMV) infection were reported, especially in the ASH/ASCO abstracts.

Horizon scan. The horizon scan identified 11 reports published between 1997 and 2007 of alemtuzumab used in the treatment of various leukemias, including T-PLL. Some reported clinical response, others reported adverse events, and others reported on the use of alemtuzumab as part of a conditioning regimen before hematopoietic stem cell transplant. The overall message of the horizon scans was that alemtuzumab may have activity in T-PLL, though infectious complications may be significant.

Discussion

There are emerging data for the role of alemtuzumab in the treatment of patients with T-PLL. Historically, single-agent pentostatin therapy has resulted in reasonable response rates, though response duration is often short and disease progression and death occur relatively quickly. Second-line therapies remain unsatisfactory for this disease in most cases. In Phase II reports, alemtuzumab appears to be active in the second-line therapy of this disease, though disease-free and overall survival outcomes are were not adequately reported. A role for alemtuzumab as front-line therapy for T-PLL was not evaluated in the trials identified during this review.

This review identified four published Phase II reports suggesting significant efficacy, with CR rates as high as 60 percent and median overall survival reaching 19 months in one report. The ASH/ASCO abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. As expected, toxicities were predominantly hematological and infectious. Over time, our understanding of the risk of CMV and other opportunistic infections with alemtuzumab is improving, resulting in appropriate prophylactic strategies and early detection and treatment of infectious complications.

Table A9: Alemtuzumab for T-Cell Promyelocytic Leukemia – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Dearden, Matutes, Cazin, et al., 2001[74]	**Design:** Multi-center **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 39 **Age:** 57 **Previous treatment:** Yes, all but 2 **Stage of disease:** Not reported **Drug dose/day [followup]:** 3 mg, 10 mg, 30 mg alemtuzumab IV until maximum response **Outcomes sought:** Not reported	**N:** 38 **CR:** 60% **PR:** 16% **Stable disease:** Not reported **Progressive disease:** 24%	**Survival overall (from start of treatment):** **Median survival:** 10 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 7 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A12 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: No 3) Patients entered at similar point in disease progression?: Unknown 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** - None of the pts had history of CR w/ prior treatment - 24 were PR or resistant - 12 pts were treated w/ 2nd course following relapse, 5 achieved 2nd CR, 1 PR - 7 pts went on to auto SCT, 4 allo and 1 MUD
Ferrajoli, O'Brien, Cortes, et al., 2003[18]	**Design:** Open label **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - Age >16 yr - CD52 >20% - < 20% predicted probability of response to conventional treatment - Any leukemia sub-type	**No. in study:** 78 **Age:** 61 **Previous treatment:** Yes, median 3 **Stage of disease:** Not reported **Drug dose/day [followup]:** 3 mg, 10 mg, 30 mg alemtuzumab then 30 mg alemtuzumab TIW x 4–12 wk	**N:** 78 (18 PLL pts) **CR:** 13% (44% for PLL pts) **PR:** 22% (11% for PLL pts) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** T-PLL survival not reported **Survival (disease-free):** **Median survival:** T-PLL survival not reported	**Adverse events & tolerability:** See Table A12 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** At time of writing, 5 pts w/ T-cell PLL still in CR @ 9, 10, 11, 12, &

Study	Study Design	Patients	Tumor Response	Survival	Other
	w/ no established frontline treatment - WHO 0–2	**Outcomes sought:** Efficacy and safety			15 mo
Nguyen, Cao, Dugan, et al., 2002[78]	**Design:** Compassionate-use, open label **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** - CLL or PLL - Failure of at least one prior treatment	**No. in study:** 34 (18-CLL, 16-PLL) **Age:** 67 **Previous treatment:** Yes **Stage of disease:** Not reported **Drug dose/day [followup]:** 3 mg 10 mg, 30 mg alemtuzumab, then 30 mg alemtuzumab TIW x 6 wk **Outcomes sought:** Efficacy and safety	**N:** 34 **CR:** 5 PLL, 3 CLL **PR:** 3 PLL, 7 CLL **Stable disease:** 1PLL, 3 CLL **Progressive disease:** 6 PLL, 4 CLL	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A12 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: No 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Unknown 5) Objective outcomes assessments?: Yes **Comments:** Main purpose of report was CMV incidence, which was 15%
Pawson, Dyer, Barge, et al., 1997[79]	**Design:** Open label, compared to historical controls **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 15 **Age:** 59 **Previous treatment:** Yes, 12 w/ pentostatin **Stage of disease:** Relapsed or refractory (none achieved CR, 8 refractory) **Drug dose/day [followup]:** 10-80 mg alemtuzumab x 6 wk **Outcomes sought:**	**N:** 15 **CR:** 9 (60%) **PR:** 2 (13%) **Stable disease:** 2 (13%) **Progressive disease:** 2 (13%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 6 mo in CR group **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A12 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: No 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Unknown 5) Objective outcomes assessments?: Yes **Comments:** - Compared to historical control of 25 pts who had received DCF - 6 pts retreated: 3 achieved 2nd

Study	Study Design	Patients	Tumor Response	Survival	Other
		Not reported			CR, 2 went on to auto SCT

Abbreviations: allo = allograft; auto = autologous; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CR = complete response; DCF = deoxycoformycin; IV = intravenous; MUD = marrow unrelated donor; PLL = prolymphocytic leukemia; PR = partial response; SCT = stem cell transplantation; TIW = thrice weekly; T-PLL = T-cell prolymphocytic leukemia; WHO = World Health Organization.

Table A10: Alemtuzumab & T-Cell Promyelocytic Leukemia: ASH 2006, ASH 2007, and ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Ravandi-Kashani, Kantarjian, Faderl, et al., 2006[53] ASH 2006 Abstract #4971	**Disease:** T-PLL, NHL **Design:** Retrospective **Phase:** N/A **Selection/randomization:** **Eligibility criteria:**	**No. in study:** 17 **Age:** 57 (22–79) **Previous Treatment:** Yes: 11 No: 6 **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab 30 mg IV TIW x 12; pentostatin 4 mg/m^2 QW x 4 then QOW x 6 mo **Outcomes sought:** Response, toxicity	**N:** 17 **CR:** 8 (47%) **PR:** 3 (18%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** CMV 6/17, HSV 1/17, pneumonia 3/17, pancytopenia 2/17 **Comments:** This is the same patient cohort as ASCO 2007 Alemtuzumab Abstract #7037
Hopfinger, Busch, Eichhorst, et al., 2007[80] ASH 2007 Abstract #2039	**Disease:** T-PLL **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized; all eligible **Eligibility criteria:**	**No. in study:** 18 **Age:** 71 (46–76) **Previous Treatment:** No: 12 Yes: 6 **Stage of disease:** Not reported **Drug dose/day [followup]:** FMC x 2 or 4 followed by alemtuzumab 30 mg TIW x 12 wk **Outcomes sought:** Response, OS, PFS	**N:** 16 **CR:** 5 (31%) **PR:** 9 (56%) **Stable disease:** 0 **Progressive disease:** 2 (13%)	**Survival overall (from start of treatment):** **Median survival:** 19.2 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 10.2 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 1 death due to MI

Study	Study Design	Patients	Tumor Response	Survival	Other
Aribi, Kantarjian, O'Brien, et al., 2007[58] ASCO 2007 Abstract #7037	**Disease:** NHL, T-PLL **Design:** Retrospective **Phase:** N/A **Selection/randomization:** **Eligibility criteria:** T-cell lymphoma	**No. in study:** 20 **Age:** 57 (22–79) **Previous treatment:** 13 Yes, median 2 **Stage of disease:** Not reported **Drug dose/day [followup]:** Pentostatin and alemtuzumab 30 mg TIW x 12, then QOW x 6 **Outcomes sought:** Not reported	**N:** 20 **CR:** 10 (50%) **PR:** 2 (10%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 35% CMV reactivation, 5% HSV, 15% pneumonia **Comments:** This is the same patient cohort as ASH 2006 Alemtuzumab Abstract #4971

Abbreviations: ASH = American Society of Hematology; ASCO = American Society of Clinical Oncology; CMV = cytomegalovirus; CR = complete response; FMC = fludarabine phosphate, mitoxantrone, and cyclophosphamide; HSV = herpes simplex virus; IV = intravenous; MI = myocardial infarction; NHL = non-Hodgkin lymphoma; OS = overall survival; PFS = progression-free survival; PR = partial response; QOW = every other week; QW = every week; T-PLL = T-cell prolymphocytic leukemia; TIW = thrice weekly.

Table A11: Alemtuzumab for T-Cell Promyelocytic Leukemia - Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Birhiray, Shaw, Guldan, et al., 2002[81]	Case reports	Pt 1: Test dose of 3 mg, followed by 10 mg 2 days later, and beginning on day 5, 30 mg TIW for 9 wk Pt 2: Dosage NR	2	This report discusses use of alemtuzumab as initial treatment in pts w/ T-PLL. One of these demonstrated the emergence of a CD52-negative clone resistant and, as a consequence, was refractory to alemtuzumab treatment. Use of alemtuzumab has resulted in CD52-negative populations merging in rheumatoid arthritis and non-Hodgkin lymphoma pts. This is the first reported case of phenotypic conversion of leukemic cells from CD52-positive to CD52-negative during alemtuzumab treatment in T-PLL. Aspects of the case provide insight into mechanisms of treatment failure. Pt 1: 62 y/o female given alemtuzumab which was discontinued at wk 7 because of AEs. Pt 2: 83 y/o male was given alemtuzumab for 12 wk in conjunction w/ combined androgen blockade.
Crowley and Woodcock, 2002[82]	Case report	3 mg on days 1 & 2. 10 mg on day 3, and 30 mg on day 4, thereafter 30 mg TIW for 4 wk	1	73 y/o female presented w/ unsteady gait and poor balance and was diagnosed w/ Parvovirus B19 induced red cell aplasia. Treatment w/ alemtuzumab was started 14 mo after initial diagnosis. Pt entered complete remission. Following treatment, pt became progressively anemic and required transfusion. Pt was diagnosed w/ Parvovirus B19 and treated successfully w/ immunoglobulin. Hematological markers have remained normal since.
Dhar-Munshi, Alton, and Ayliffe, 2001[83]	Case report	30 mg TIW for 6 wk and 4 intrathecal injections of methotrexate	1	46 y/o female presented w/ pain and blurred vision in right eye. Diagnosed as panuveitis w/ a central exudative retinal detachment. Further investigation revealed T-cell prolymphocytic leukemia. Both systemic and ocular manifestations of the disease resolved after chemotherapy w/ Campath-IH antigen, as she went into complete remission. Exudative detachment settled, and visual acuity recovered to 20/20. Authors state leukemias can present with primarily ocular findings, and the sudden appearance of a serious retinal detachment w/ inflammatory signs in an otherwise healthy person warrants a thorough systemic screening for an underlying malignancy.
Dybjer, Hellquist, Johansson, et al., 2000[84]	Case report	30 mg IV TIW	1	47 y/o male presented w/ swelling and severe pain in multiple joints. Pt also presented several blue-reddish papular, partly confluent, skin lesions on both trunk and extremities, but not in the face except for an intense auricular painful swelling. Treatment w/ 2 cycles of cladribine was ineffective, whereas a 6-wk course of alemtuzumab led to resolution of the skin infiltrations and synovitis. 5 mo after diagnosis, bilateral face palsies and impaired hearing developed due to meningeal leukemia. Pt developed chest pain and was diagnosed w/ leukemic myocardial infarction. Pt died 10 mo after diagnosis w/ signs of rapidly progressive involvement of the CNS.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Ingram, Howman, Leahy, et al., 2007[85]	Case report	TIW dose	1	55 y/o male diagnosed w/ T-PLL. Sequential treatment w/ fludarabine and cyclophosphamide failed to achieve disease remission. 26 of a planned 36 doses of TIW alemtuzumab were administered together w/ prophylactic cotrimoxazole and valacyclovir. Profound lymphopenia and neutropenia ensued. Pt developed acute renal, respiratory, and circulatory failure requiring treatment in ICU. Symptoms gradually resolved and 6 mo later, pt remained well, receiving fluconazole 200 mg daily.
Lee, Robinson, Morris, et al., 2004[86]	Case report	30 mg TIW	1	Reports the clinical and histopathologic findings of conjunctival involvement by T-PLL. 53 y/o male presented w/ 2 wk h/o low-grade fever, fatigue, and cough, diagnosed w/ T-PLL. Pt received a 12-wk course of alemtuzumab and achieved a CR w/ no clinical manifestations or molecular evidence of tumor in the bone marrow aspirate. Pt relapsed and received 2nd course of alemtuzumab. 3rd course of alemtuzumab achieved minimal response. Pt died of *Aspergillus* pneumonia.
Pawson, Matutes, Brito-Babapulle, et al., 1997[32]	Case reports		9	All pts presented w/ lymphocytosis, bone marrow infiltration, splenomegaly, and lymphadenopathy. Skin involvement was absent at presentation, but developed as a terminal event in 2 pts. Pts were treated w/ various chemotherapy regimens but w/ poor outcome (median survival being 13 mo). 2/9 pts received alemtuzumab. 1 pt survived 24 mo, while the other is alive at 35 mo.
Ravandi, O'Brien, Jones, et al., 2005[87]	Prospective observation		57	The clinical, pathologic and molecular features of 57 pts w/ T-PLL were evaluated. 19 of these pts received alemtuzumab. 8/19 (42%) achieved CR, while 9/19 (47%) achieved overall response This report followed pts w/ no intervention.
Tuset, Matutes, Brito-Babapulle, et al., 2001[88]	Case reports	Pt 1: 30 mg TIW for 4 wk Pt 2: 30 mg TIW for 6 wk	2	Pt 1: 61 y/o male diagnosed w/ T-PLL, treated w/o response w/ pentostatin IV. Pt had significant response, but treatment was stopped because of cytomegalovirus reactivation which responded to ganciclovir. Pt remained stable for 4 yr. Disease progressed, was treated w/ alemtuzumab w/ no response. Pt died within 2 wk (5.5 yr after diagnosis). Pt 2: 38 y/o male diagnosed w/ T-PLL, treated w/ pentostatin and subsequently w/ CHOP w/o response. Started on alemtuzumab and achiever CR. 2 mo later, pt became pancytopenic requiring hematopoietic growth factors and blood transfusions. Disease progressed and pt died 3 yr from diagnosis.
Vivas, Ruiz de Morales, Ramos, et al., 2006[68]	Case report	30 mg 2 x wk for 12 consecutive wk	1	56 y/o female decided to undergo immunotherapy w/ alemtuzumab, which was administered according to the conventional therapeutic schedule used in CLL. Cytomegalovirus developed after first mo of treatment and was treated successfully w/ ganciclovir. After 9 mo of treatment, pt remained asymptomatic. Pt had celiac disease and was at risk for T-cell. Pt was treated w/ imatinib

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Wulf, Hasenkamp, Jung, et al., 2005[70]	Case report series	3, 10, 30 mg q 48 hr, then 30 mg q 48 hr	10 consecu-tive pts	About 10 pts who received chemotherapy/alemtuzumab prior to all SCT; at median 7 mo f/u, 7 were alive, 6 w/ CR.

Abbreviations: AE(s) = adverse event(s); CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CR = complete response; h/o = history of; ICU = intensive care unit; IV = intravenous; NR = not reported; q = every; SCT = stem cell transplantation; T-PLL = T-cell prolymphocytic leukemia; TIW = thrice weekly.

Table A12: Alemtuzumab for T-Cell Promyelocytic Leukemia - Adverse Events (Grade 3/4+ Events Only)

Study	Anemia	Neutropenia/ granulocytopenia	Thrombocytopenia	Nausea	Dyspepsia	Dermatitis or rash	Headache	Chills/fever	Prolonged pancytopenia	Hypotension	Hematologic toxicity	Severe bone marrow aplasia
Dearden et al., 2001[74]	-	-	13%	-	-	-	-	-	5%	-	3%	-
Ferrajoli et al., 2003[18]	0%	35%	41%	0%	9%	0%	1%	3%	-	1%	-	-
Nguyen et al., 2002[78]	-	35%	37%	-	-	-	-	-	-	-	-	-
Pawson et al., 1997[79]	-	-	-	-	-	-	-	-	-	-	13%	13%

Bevacizumab for Breast Cancer

Background

Drug: Bevacizumab (Avastin®). Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab was approved in February 2004 as a first-line treatment for patients with metastatic colorectal cancer. In June 2006, the Food and Drug Administration (FDA) granted approval for a labeling extension for bevacizumab, in combination with intravenous 5-fluorouracil-based chemotherapy, as a second-line treatment of patients with metastatic carcinoma of the colon or rectum. The FDA granted another labeling extension in October 2006 for bevacizumab administered with carboplatin and paclitaxel. It is indicated for the initial systemic treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer. In February 2008, the FDA granted accelerated approval for bevacizumab in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer; approval for renal cell carcinoma (RCC) and glioblastoma followed. It has been evaluated for off-label use in pancreatic adenocarcinoma and epithelial ovarian cancer (EOC). At the time this review was initiated, the breast and renal cell indications had not been approved.

Disease: Breast cancer. Breast cancer is the second most common cancer worldwide and is by far the most common cancer among women. Incidence is generally higher in more developed countries, with North American women being at highest risk. In the United States, where women have a 12.5 percent (1 in 8) lifetime chance of developing the disease, it is estimated that more than 180,000 cases of invasive breast cancer will be diagnosed and more than 40,000 breast-cancer-related deaths will occur among women in 2008. The median age at diagnosis is 61, and the median age at death is 69.

Although it has an excellent overall five-year survival rate of 88.7 percent, breast cancer is the second leading cause of cancer death among women. Individual prognosis is linked primarily to disease stage, but also to tumor size and location, grading, metastatic involvement, recurrence, and patient age. Fortunately, more than 60 percent of breast cancer cases are diagnosed during the localized stage of the disease. For localized tumors, surgical resection is the primary treatment, but adjuvant hormonal therapy, chemotherapy, and radiotherapy may also be indicated, depending on the clinical criteria. For late-stage disease, systemic therapy is the main approach. Metastatic spread occurs most often to the bones; metastatic breast cancer is generally (but not always) incurable although patients can live for years after the metastatic spread depending upon patient and and tumor characteristics.

Like most cancers, breast cancer is likely the result of multiple environmental and hereditary factors, and although the cause of any individual breast cancer is usually hard to specify, many epidemiological risk factors have been identified, including sex, age, childbearing, hormones, and obesity. Approximately 5 percent of breast cancers can be attributed to hereditary factors.[35,89,90]

Drug/Disease: Bevacizumab for breast cancer. Over the past few years, clinical research initiatives attempting to improve the efficacy and minimize the toxicity of breast cancer therapy have examined the development of new strategies for drugs approved for other malignant

conditions, including bevacizumab. According to research, bevacizumab is well tolerated and has demonstrated promising efficacy in refractory metastatic breast cancer.[91] This may be due to its activity against vascular endothelial growth factor (VEGF), a central agent in angiogenesis, which is critical to tumor growth and metastasis.[92] Invasive ductal carcinomas, which account for 80 percent of all breast cancers, express a high degree of VEGF,[93] an upregulation that appears to be linked to the overexpression of the HER2 oncogene in breast cancer cells.[91,94] Research has linked high rates of the VEGF biomarker to worse recurrence-free progression and diminished overall survival rates among early-stage breast cancer patients.[95] Furthermore, elevated tumor levels of VEGF increase the disease's ability to resist chemotherapy and hormonal therapy.[96]

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded a total of 13 reports; of these, four were full reports of clinical trials (Table A13), six were published abstracts from the American Society of Clinical Oncology (ASCO) 2007 conference (Table A14), and three were additional articles considered in the horizon scan (Table A15). Study designs included one Phase III randomized clinical trial, nine Phase I/II non-controlled trials, and three case reports. The first report, published in 2003, was a Phase I/II dose-escalation trial involving 75 patients. The next report, published in 2005, was a Phase III clinical trial that began enrolling patients in 2000.

Sample sizes for the clinical trials ranged from 21 to 462, with a total of 585 patients presented in the full reports, and 846 patients presented in the full reports plus abstracts.

Eligibility criteria for inclusion in the studies were not well described in the abstracts. Metastatic breast cancer was an eligibility criterion in all four full reports. All four of these studies included patients who had had prior chemotherapy or surgery or both, but some patients had not been previously treated. All of the studies involved adults. Patient age across the full reports ranged from 29 to 78.

Bevacizumab was used as monotherapy in the dose-escalation trial, in dosages of 3 mg/kg to 20 mg/kg. Bevacizumab was used in combination with capecitabine in one study, and with either docetaxel alone or docetaxel and doxorubicin in the other two studies. Dosages of bevacizumab varied across the four full report studies. The most frequently used dosage of bevacizumab among the six Phase II studies published as abstracts was 15 mg/kg every 21 days for seven to 17 doses.

Efficacy was reported in three of the four studies represented in the full reports. Primary outcomes assessed varied across the studies. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

Study quality of the fully published reports was generally good. Eighty percent of the studies met four of five quality criteria, and 20 percent met three of five criteria. None of the studies had an adequate followup period.

Efficacy. The Phase III clinical trial that compared capecitabine alone to capecitabine plus bevacizumab demonstrated higher response rates in the combination group, but the primary outcome of progression-free survival was essentially unchanged at about 4.5 months. Of the 121 patients enrolled in the three fully published reports for which a complete response (CR) was defined and reported, only a single patient (< 1 percent) had a CR. The range of CR rates among the studies published as abstracts was 0 percent to 2 percent. PR rates ranged from 5 percent to 67 percent among the fully published reports, and from 33 percent to 66 percent among the studies published as abstracts.

Survival. Median overall survival was 4.8 months in the Phase III clinical trial (versus 4.2 months for patients randomized to capecitabine without bevacizumab), and 10 months in one of the Phase II fully published reports. Median disease-free survival ranged from 2.4 months in the dose-escalation study to 25 months in the trial in which bevacizumab, doxorubicin, and docetaxel were administered. In the latter study, the one-year probability of overall survival was 90 percent.

Adverse events. Data in Table A16 were derived from three of the four full reports. Hypertension (range, 4 percent to 19 percent) was the only Grade 3/4 adverse event that was reported in all three studies. The trial that used both bevacizumab and docetaxel reported an incidence of 26 percent and 19 percent of leucopenia and neutropenia, respectively.

Horizon scan. The horizon scan (Table A15) identified three case reports of four patients. One report described reduction in the size of metastatic tumors to the bones and lung. The other two reports described two cases of new-onset hypertension and one case of nasal septum perforation attributed to bevacizumab.

Discussion

Because multiple treatment regimens are available to patients with metastatic breast cancer, and patients with no visceral involvement will sometimes live for years with their disease, demonstration of survival benefit from the addition of a VEGF inhibitor to the treatment regimen will be difficult. This review identified a single clinical trial that assessed the marginal benefits and harms associated with bevacizumab as adjunctive therapy in the treatment of breast cancer. That trial compared capecitabine alone to capecitabine with bevacizumab among patients with previously treated metastatic breast cancer. Bevacizumab contributed to improved response rates but not progression-free survival.

The existing literature suggests that bevacizumab is relatively well tolerated at doses of 10 to 15 mg/kg every two to three weeks. Leukopenia and hypertension were the two most common serious adverse events. The ASCO 2007 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. Additional research is needed to determine whether the addition of a VEGF antibody, which has clearly been shown to be effective in the treatment of some cancers, and for which there is biological plausibility for the treatment of breast cancer, adds significantly to the current treatment options for metastatic breast cancer in terms of survival benefit.

The FDA approved the use of bevacizumab for breast cancer in 2008 based upon emerging data, some of which were not available at the time of the most recent literature search presented in this report.

Table A13: Bevacizumab for Breast Cancer – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Cobleigh, Langmuir, Sledge, et al., 2003[97]	**Design:** Open, dose-escalation study **Phase:** Phase I/II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Metastatic breast cancer following at least one prior chemo for metastatic disease - Measurable or unmeasurable disease - ECOG 0–1 - Life expectancy at least 6 mo - No pleural effusions or blastic bone disease only - No prior bevacizumab - Any other prior antibody OK if at least 6 mo prior - No anticoagulation	**No. in study:** 75 **Age:** 48.1 (range 29-78) **Previous treatment:** Required to have ≥ 1 prior chemo for metastatic disease; 4 pts did NOT meet this criterion **Stage of disease:** Metastatic **Drug dose/day [followup]:** 3 mg/kg bevacizumab (18 pts); received 8 mg/kg bevacizumab load on day 1 10 mg/kg bevacizumab (41 pts) 20 mg/kg bevacizumab (16 pts) **Outcomes sought:** Primary: Safety and efficacy Secondary: TTP and 1-yr survival	**N:** 75 **OR:** 7 pts, 9.3% (confirmed 5 pts or 6.7%); 5 responses seen at 70-day evaluation, 2 at 154-day evaluation **CR:** 1 (1.3%) **PR:** 6 (8%) (2 [2.6%] unconfirmed) **Stable disease:** 12 (16%) **Progressive disease:** Median duration of response: 5.5 mo (2.3-13.7) At 154 days (end of study), 12 of 75 (16%) had SD or ongoing response	**Survival overall (from start of treatment):** **Median survival:** 10.2 Mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 2.4 Mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A16 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No (154 days) 5) Objective outcomes assessments?: Yes **Comments:** Majority infiltrating ductal cancer; 47 (63%) HER2-, 24% prior Herceptin

Study	Study Design	Patients	Tumor Response	Survival	Other
Miller, Chap, Holmes, et al., 2005[98]	**Design:** RCT Arm A = capecitabine Arm B = capecitabine + bevacizumab **Phase:** Phase III **Selection/ randomization:** Randomized **Eligibility criteria:** - Metastatic breast cancer - Prior chemo with both taxane and anthracycline - ≥ 1 but < 3 prior chemo for metastatic disease - If relapse within ≤ 12 mo, no prior chemo required - HER2+ must have progressed following Herceptin - No CNS disease - ECOG 0-1 - Normal hepatic, renal and hematologic function - Bidimentionally measurable disease with at least one lesion ≥ 2 cm	**No. in study:** 462 Arm A = 230 Arm B = 232 **Age:** Arm A = 52 (30–77) Arm B = 51 (29–78) **Previous treatment:** Yes **Stage of disease:** Metastatic **Drug dose/day [followup]:** Capecitabine 2500 mg/m^2/d on days 1–14 +/- bevacizumab 15 mg/kg q 3 wk **Outcomes sought:** Primary: PFS based on IRF Secondary: PFS based on INV assess, obj RR & duration of response based on IRF & INV, QoL, survival	**N:** 462 **Obj. RR:** Independent review (IRF): 19.8% (14.7–25%) vs. 9.1% (5.4–12.9%); p = 0.001 Investigator review (INV): 30.2% (24.3–36.1%) vs. 19.1% (14.1–24.2%); p = 0.006 IRF median duration of response: 7.6 mo (Arm A) vs. 5 mo (Arm B) **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Overall median survival 14.5 mo (Arm A) vs. 15.1 mo (Arm B) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** IRF: 4.17 mo (Arm A) vs. 4.8 mo (Arm B) (0.98 HR) **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A16 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No (93 did not meet entry criteria) 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes-independent review facility used **Comments:** - 18 pts never received therapy so are not included in safety analysis - 93 pts enrolled were NOT actually eligible for various reasons but are included in results (excluding them did not alter results) - Max 35 cycles - Combo arm could continue on to bevacizumab alone or with other chemo upon progression, but capecitabine-only arm could NOT receive bevacizumab at any time - 70 pts continued bevacizumab after PD - 38% of pts dead at data cutoff (95% die to PD) - INV: Data not included, but authors reported no improvement.

Study	Study Design	Patients	Tumor Response	Survival	Other
Ramaswamy, Elias, Kelbick, et al., 2006[99]	**Design:** Prospective cohort **Phase:** II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Age > 18 yr - One or more measurable metastatic sites measurable by RECIST criteria - ECOG ≤ 2 - Normal labs - ≤ 1 prior chemo for metastatic breast cancer - If chemo contained taxane, ≥ 6 mo elapsed	**No. in study:** 27 **Age:** 51 (range 39-68) **Previous treatment:** No –21 (78%) **Stage of disease:** Metastatic **Drug dose/day [followup]:** Bevacizumab 10 mg/kg on days 1 & 15 Docetaxel 35 mg/m^2 days 1, 8 & 15 q 28 days **Outcomes sought:** Primary: Toxicity, efficacy-ORR & PFS Secondary: Relationship between plasma endothelial and adhesion cell markers and RR & PFS	**N:** 25 **CR:** 0 **PR:** 14 (52%; CI 32–71%) **Stable disease:** 9 (33%) **Progressive disease:** 2 (7%) Median duration of response 6 mo (4.6–6.5) 2 were non-evaluable	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 7.5 mo (6.2–8.3) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A16 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comment:** 13 (48%) received all 6 planned cycles, 11 (41%) went on to receive median of 2 cycles of bevacizumab alone

Study	Study Design	Patients	Tumor Response	Survival	Other
Wedam, Low, Yang, et al., 2006[100]	**Design:** Prospective cohort **Phase:** Pilot **Selection/ randomization:** Not randomized **Eligibility criteria:** - Age ≥ 18 yr - Untreated stage III or IV IBC or LABC - ECOG 0–2 - LVEF ≥ 50% - Normal organ function	**No. in study:** 21 **Age:** 50 (range 35-73) **Previous treatment:** No **Stage of disease:** III or IV **Drug dose/day [followup]:** Cycle 1: Bevacizumab 15 mg/kg q 3 wk Cycles 2–7: Bevacizumab 15 mg/kg q 3 wk, doxorubicin 50 mg/m^2, and docetaxel 75 mg/m^2 q 3 wk Followed by surgery, XRT and additional 8 cycles of bevacizumab 15 mg/kg & hormonal treatment if indicated **Outcomes sought:** Response	**N:** 21 **CR:** 0 **PR:** 14 clinical (67%, 95% CI 43% to 85%) **Stable disease:** 5 (24%) **Progressive disease:** 2 (10%)	**Survival overall (from start of treatment):** **Median survival:** Not reached (median follow-up 26.9 mo) **1 yr:** Probability 90.5% **2 yr:** Probability 80% **3 yr:** NR **Survival (disease-free):** **Median survival:** Median PFS 25.3 mo **1 yr:** Probability 77.5% **2 yr:** Probability 53.3% **3 yr:** NR	**Adverse events & tolerability:** See Table A16 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** - 16 completed all 7 neo-adjuvant chemo cycles - 13 had surgery (8 who did not were taken off therapy in neo-adjuvant phase) - 15 did NOT complete all 7 cycles of therapy

Abbreviations: chemo = chemotherapy; CI = confidence interval; CNS = central nervous system; CR = complete response; ECOG = Eastern Collaborative Oncology Group; HER2 = human epidermal growth factor receptor; IBC = inflammatory breast cancer; INV = investigator; IRF = independent research facility; LABC = locally advanced breast cancer; LVEF = left ventricular ejection fraction; OR = overall response; ORR = overall response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; q = every; QoL = quality of life; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria In Solid Tumors; RR = response rate(s); SD = stable disease; TTP = time to tumor progression; XRT = x-ray therapy.

Table A14: Bevacizumab for Breast Cancer – ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Dickler, Traina, Panageas, et al., 2007[101] ASCO 2007 Abstract #567	**Disease:** Breast cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Resected breast cancer, HER2-, normal LVEF	**No. in study:** 44 **Age:** 46.5 (33–67) **Previous treatment:** Surgery **Stage of disease:** No evidence of disease, adjuvant study **Drug dose/day [followup]:** Dose dense AC q2 wk x 4; Paclitaxel q 2 wk x 4; *plus* Abraxane x 4 with Pegfilgrastim on day 2; *plus* Bevacizumab 10 mg/kg IV q 2 wk x 8 with chemo, then 15 mg/kg q 3 wk. **Outcomes sought:** Toxicity, specifically cardiac	**N:** 28 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** No decrease in LV function seen in 28 patients Grade 3–4 toxicities: Neutropenia: 6.8% Diarrhea: 2.3% HTN: 2.3% Neuropathy: 2.3% Fatigue: 2.3% Mucositis: 2.3%
Ferrero-Torres, Percent, Galleshaw, et al., 2007[102] ASCO 2007 Abstract #11020	**Disease:** Breast cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Postmenopausal, ER/PR+, HER2-, operable disease	**No. in study:** 27 **Age:** 63 (56–79) **Previous treatment:** None **Stage of disease:** Stage II/III **Drug dose/day [followup]:** Letrozole 2.5 mg daily; *plus* Bevacizumab 15 mg/kg q 3 wk x 24 wk.	**N:** 12 **CR:** 2 (17%) **PR:** 8 (66%) **Stable disease:** 0 **Progressive disease:** 2 (17%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 HTN = 1

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Toxicity, response			
Mayer, Miller, Rugo, et al., 2007[103] ASCO 2007 Abstract #561	**Disease:** Breast cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Stage II or III breast cancer with residual disease at time of surgical resection, after neoadjuvant anthracycline chemotherapy	**No. in study:** 40 **Age:** 50 (median) **Previous treatment:** Anthracycline neoadjuvant **Stage of disease:** 45% stage III **Drug dose/day [followup]:** Bevacizumab 15 mg/kg q 3 wks x 17 doses **Outcomes sought:** Toxicity	**N:** 40 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Arthralgia: 50% Headache: 50% Epistaxis: 20% HTN: 23% Reversible encephalopathy syndrome in 1 patient (related to HTN) GI Bleed in 1 patient No cardiac dysfunction
Rocca, Dellapasqua, Pietri, et al., 2007[104] ASCO 2007 Abstract #11501	**Disease:** Breast cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Metastatic breast cancer, after 2 or 3 previous lines of therapy	**No. in study:** 26 **Age:** Not reported **Previous treatment:** Endocrine/chemo/ trastuzumab 13/21/1 patients **Stage of disease:** Advanced disease **Drug dose/day [followup]:** Capecitabine 500 mg TID; *plus* Cytoxan 50 mg q day; *plus* Bevacizumab 10 mg/kg q 2 wk.	**N:** 23 **CR:** 1 (4 %) **PR:** 10 (43%) **Stable disease:** 6 (26%) **Progressive disease:** 6 (26%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** PFS 6 Mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 HTN: 6 Grade 3 leukopenia: 1 Grade 3 neutropenia: 2 Grade 3 transaminitis: 2

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Efficacy, toxicity			
Sledge, Miller, Moisa, et al., 2007[105] ASCO 2007 Abstract #1013	**Disease:** Breast cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Untreated metastatic breast cancer. HER-2 negative, ECOG PS 1, no prior anti-angiogenic or oral fluoropyrimidine therapy	**No. in study:** 103 **Age:** Not reported **Previous treatment:** None **Stage of disease:** IV **Drug dose/day [followup]:** Capecitabine 1000 mg/m^2 BID days 1–15, q 21 days; *plus* Bevacizumab 15 mg/kg q 21 days. **Outcomes sought:** Toxicity, response	**N:** 91 **CR:** 5 (5.5%) **PR:** 30 (33%) **Stable disease:** 39/91 (42.9%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Not Reached **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Not Reached **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 hand/foot syndrome: 13% Pain: 10% Grade 4 pulmonary embolism: 2%
Swain, Steinberg, Modrusan, et al., 2007[106] ASCO 2007 Abstract #509	**Disease:** Breast cancer **Design:** Prospective cohort, open label **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Inflammatory or locally advanced breast cancer, biopsied, not resected	**No. in study:** 21 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Before surgery, with inflammatory or locally advanced breast cancer **Drug dose/day [followup]:** Bevacizumab 15 mg/kg x 7 cycles; *plus*	**N:** 21 **CR:** 0 **PR:** 14 (67%) **Stable disease:** 5 (24%) **Progressive disease:** 2 (10%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported

Study	Study Design	Patients	Tumor Response	Survival	Other
		Doxorubicin 50 mg/m^2 x 6 cycles; *plus* Docetaxel 75 mg/m^2 x 6 cycles. **Outcomes sought:** Efficacy, laboratory outcomes			

Abbreviations: AC = Doxorubicin and cyclophosphamide; ASCO = American Society of Clinical Oncology; BID = twice daily; chemo = chemotherapy; CR = complete response; ECOG = Eastern Collaborative Oncology Group; ER = estrogen receptor; GI = gastrointestinal; HER2 = human epidermal growth factor receptor; HTN = hypertension; IV = intravenous; LV = left ventricular; PFS = progression-free survival; PR = partial response; PR+ = progesterone receptor positive; q = every; TID = thrice daily.

Table A15: Bevacizumab for Breast Cancer – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Amselem, Cervera, Diaz-Llopis, et al., 2007[107]	Case report	Single injection bevacizumab 4 mg	1	57 y/o female with stage IV non-estrogen-sensitive breast carcinoma with bone and lung metastasis. Vision was 10/200 in right eye. Three weeks after intravitreal injection of bevacizumab, BCVA improved to 20/60. B-mode ultrasonography demonstrated dramatic reduction of the tumor size. No ocular or systemic complications observed at end of followup.
Handler, 2006[108]	Case reports		2	Pt 1: 64 y/o female presented with rectal carcinoma. Initiation of capecitabine/ bevacizumab led to development of hypertension. Discontinuation of bevacizumab led to lower BP. Pt 2: 60 y/o female with stage T2 N1, estrogen receptor positive human epidermal growth factor receptor 2 negative, right breast cancer. Bevacizumab/paclitaxel chemotherapy was initiated. BP increased. Bevacizumab was discontinued, and BP returned to normal levels. Both cases involved new-onset hypertension closely associated with the initiation of bevacizumab, which resolved when the drug was discontinued.
Traina, Norton, Drucker, et al., 2006[109]	Case report	Bevacizumab 10 mg/kg q 2 wk	1	54 y/o female with hormone-sensitive, HER2/*neu*-normal, metastatic breast cancer. After 2–4 cycles of bevacizumab, pt developed rhinorrhea, nasal irritation, and alopecia of the nasal passages. After 6th cycle, she incidentally noted a "hole in her nose." This case is the second report of nasal septum perforation. Bevacizumab was discontinued and pt is slowly improving.

Abbreviations: BCVA = best correct visual acuity; BP = blood pressure; HER2 = human epidermal growth factor receptor 2; q = every; y/o = year-old.

Table A16.1: Bevacizumab for Breast Cancer – Adverse Events (Grade 3/4+ Events Only) – Part 1

Study	Superficial edema	Neutropenia	Anemia	Leukopenia	Thrombocytopenia	Diarrhea	Nausea	Vomiting	Constipation	Photosensitivity	Fatigue	Headache	Arthralgia	Neuropathy	Pain	Chills/fever	Increased lacrimation
Cobleigh et al., 2003[97]	-	-	-	-	-	1%	0%	0%	-	0%	-	7%	4%	-	5%	-	-
Miller et al., 2005[98]	-	-	2%	3%	2%	-	3%	-	0%	-	-	2%	-	-	3%	0%	-
Ramasamy et al., 2006[99]	0%	19%	0%	26%	0%	-	-	4%	-	-	15%	-	7%	8%	-	-	0%
Wedam, Low, Yang, et al., 2006[100]	-	-	-	-	-	19%	-	-	-	-	19%	5%	-	-	-	-	-

Table A16.2: Bevacizumab for Breast Cancer – Adverse Events (Grade 3/4+ Events Only) – Part 2

Study	Cough	Dyspnea	Myalgia or musculoskeletal pain	Infection	Hypertension	Paresthesia	Sinusitis	Proteinuria	Bleeding	Pulmonary embolism	Thrombotic event	Congestive heart failure	Pleural effusion	Stomatitis	Cardiomyopathy	Febrile neutropenia	Nail Changes	Other
Cobleigh et al., 2003[97]	1%	11%	4%	0%	19%	0%	0%	-	-	-	-	-	-	-	-	-	-	9%
Miller et al., 2005[98]	-	-	-	1%	18%	-	-	1%	0%	1%	6%	2%	-	-	1%	-	-	8%
Ramasamy et al., 2006[99]	-	4%	4%	4%	4%	-	-	0%	0%	-	7%	-	4%	7%	-	-	-	-
Wedam, Low, Yang, et al., 2006[100]	-	-	-	-	38%	-	-	-	-	-	5%	-	-	-	-	86%	0%	10%

Bevacizumab for Epithelial Ovarian Cancer

Background

Drug: Bevacizumab (Avastin®). Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab was approved in February 2004 as a first-line treatment for patients with metastatic colorectal cancer. In June 2006, the Food and Drug Administration (FDA) granted approval for a labeling extension for bevacizumab, in combination with intravenous 5-fluorouracil-based chemotherapy, as a second-line treatment of patients with metastatic carcinoma of the colon or rectum. The FDA granted another labeling extension in October 2006 for bevacizumab administered with carboplatin and paclitaxel. It is indicated for the initial systemic treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer. In February 2008, the FDA granted accelerated approval for bevacizumab in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer; approval for renal cell carcinoma (RCC) and glioblastoma followed. It has been evaluated for off-label use in pancreatic adenocarcinoma and epithelial ovarian cancer (EOC). At the time this review was initiated, the breast and renal cell indications had not been approved.

Disease: Epithelial ovarian cancer. In EOC, the ovarian epithelium undergoes malignant transformation. Little is known about EOC's process of neoplastic evolution, its invasive mechanisms, or its metastatic spread.[110] Its cause also remains unknown, but a number of risk factors, primarily a family history of the disease, have been identified.[111]

Currently accounting for more deaths than any other female reproductive cancer, EOC is the fifth deadliest cancer among women, with more than 21,000 new cases and more than 15,000 deaths predicted for 2008. Affecting primarily an older population, with a median age at diagnosis of 63, EOC has a five-year survival rate of 45 percent. If found before metastasis, its five-year survival rate improves to 92 percent.[35,111] However, because early-stage EOC is often not associated with clinical symptoms, fewer than 20 percent of all ovarian cancers are detected prior to metastatic spread.[112]

Prognosis and treatment options are determined by the stage of the cancer, tumor size, the patient's age and health, and whether the tumor represents a recurrence.[35] Treatment almost always involves surgery, followed by adjuvant chemotherapy. Despite the responsiveness of EOC to these treatments, the five-year survival of late-stage patients drops to below 30 percent. Recurrent disease occurs in the majority of patients with advanced EOC and is generally incurable, so palliation of symptoms and prevention of complications are indicated at this stage.[112]

Drug/Disease: Bevacizumab for EOC. Over the past few years, clinical research initiatives attempting to improve the efficacy and minimize the toxicity of EOC therapy have examined the development of new strategies for drugs approved for other malignant conditions, including bevacizumab. According to preliminary research, bevacizumab has demonstrated activity in recurrent EOC.[113] This may be due to its activity against VEGF, a central agent in angiogenesis, which is critical to tumor growth and metastasis.[92] Indeed, neovascularization appears to be central to the development and clinical behavior of EOC,[114] with VEGF expressing

in the majority of EOC tumors and being correlated with poor survival among EOC patients.[115,116]

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

The search strategy yielded at total of six reports, one of which was a published abstract from the American Society of Clinical Oncology (ASCO) 2007 conference (Table A17), and five of which were articles considered in the horizon scan (Table A18). No published full reports of clinical trials were identified. Among the horizon scan articles, there were three retrospective studies and two case reports.

The ASCO abstract summarized the results of a Phase II non-randomized clinical trial that evaluated the efficacy and toxicity of bevacizumab 15 mg/kg every 21 days for one year in combination with carboplatin AUC 5 plus paclitaxel 175 mg/m^2 in the treatment of 58 chemotherapy-naïve patients with ovarian cancer. Eighty percent of the patients had previously undergone debulking surgery. Ages ranged from 18 to 77, with a median age of 58. Sixty-two percent and 19 percent of the patients had Stage III and Stage IV disease, respectively, at time of enrollment into the study. Of the 28 evaluable patients, 11 (39 percent) had a complete response (CR) and 10 (36 percent) had a partial response (PR). Median progression-free survival (PFS) was 11 months. Adverse events included two cases of pulmonary embolism and two cases of gastrointestinal perforation, all of which occurred during the induction phase. During the maintenance phase, there were 13 Grade 3 toxicities reported and no Grade 4 toxicities.

Among the articles considered in the horizon scan, one of the retrospective studies reported the clinical outcomes of 10 patients with advanced, refractory ovarian cancer who had been treated biweekly with bevacizumab 10 mg/kg and weekly with taxane chemotherapy. All nine of the evaluable patients demonstrated a reduction in CA125. All symptomatic patients experienced palliation of pain, nausea, and ascites. Adverse events were mild, with no Grade 3/4 toxicities noted.

Another retrospective study reported the clinical outcomes of 32 patients with advanced ovarian cancer who had failed multiple prior cytotoxic chemotherapies. Among the 23 (72 percent) patients who received bevacizumab as monotherapy, 16 percent demonstrated a clinical response. Grade 3 adverse events included hypertension, proteinuria, and an enterocutaneous fistula.

The third retrospective study reported the clinical outcomes of 23 patients with ovarian cancer who received bevacizumab in combination with chemotherapeutic agents. Overall best response rate was a PR of 35 percent. Grade 4/5 adverse events were reported in 17 percent of patients.

One of the horizon scan articles reported on three patients, all of whom had a clinical response to bevacizumab. Adverse events included myalgias, bone pain, fatigue, and worsening of osteoarthritis.

The final horizon scan article reported on four patients with end-stage ovarian cancer with symptomatic ascites treated with bevacizumab for palliation. All four patients reported a reduction in abdominal distention.

Discussion

There are compelling reasons to evaluate the use of monoclonal antibodies to VEGF in the treatment of epithelial ovarian cancer, especially in light of ovarian cancer's high mortality rate and the proven efficacy of this class of targeted therapies in the treatment of colon, rectal, non-small cell lung, and breast cancers, and glioma.. However, to date there are limited data that support the use of bevacizumab in the treatment of epithelial ovarian cancer. The published case series and case reports suggest that bevacizumab may contribute to clinical response, including reduction in CA125 levels. These studies were not designed to directly evaluate the efficacy of bevacizumab, however, and there is inherent bias in relying on case reports or retrospective case series to assess either efficacy or safety of interventions, especially those typically used in combination with other treatments.

The ASCO abstract and horizon scan articles did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. There were insufficient data identified in this review to comment on toxicities potentially associated with bevacizumab in the treatment of ovarian cancer.

Table A17: Bevacizumab for Epithelial Ovarian Cancer – ASCO 2007 Abstract

Study	Study Design	Patients	Tumor Response	Survival	Other
Campos, Dizon, Cannistra, et al., 2007[117] ASCO 2007 Abstract #5517	**Disease:** Ovarian cancer and Müllerian cancer **Design:** Prospective cohort, open label **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Chemo naïve ovarian cancer, ECOG status ≤ 2	**No. in study:** 58 **Age:** 58 (18–77) **Previous treatment:** Optimal debulking surgery in 80% **Stage of disease:** III: 62% IV: 19% **Drug dose/day [followup]:** Bevacizumab 15 mg/kg q 21 days x 1 yr; *plus* Carboplatin AUC 5; *plus* Paclitaxel 175 mg/m^2 q 21 days x 6–8 cycles. **Outcomes sought:** Toxicity, response	**N:** 28 **CR:** 11 (39%) **PR:** 10 (36%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** PFS 11 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Pulmonary embolism: 2 GI perforation: 2 Both AEs occurred during induction phase During maintenance: 13 Grade 3 toxicities No Grade 4 toxicities

Abbreviations: AE(s) = adverse event(s); CR = complete response; ECOG = Eastern Collaborative Oncology Group; GI = gastrointestinal; PFS = progression-free survival; PR = partial response; q = every.

Table A18: Bevacizumab for Epithelial Ovarian Cancer – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Bidus, Webb, Seidman, et al., 2006[118]	Case reports	Pt 1: 15 mg/m^2 IV q 3 wk Pt 2: 15 mg/m^2 IV q 3 wk Pt 3: 15 mg/m^2 IV q 3 wk	3	Pt 1: 58 y/o female diagnosed with invasive FIGO stage IIIB micropapillary serous ovarian carcinoma. Was treated with 6 cycles of combination paclitaxel and cisplatin given q 3 wk, followed by multiple cycles of intraperitoneal cisplatin. Was clinically free of disease for over 2 yr. Disease progressed and exam revealed a tumor in left upper quadrant of the abdominal wall and multiple nodules at the vaginal apex. She was treated with bevacizumab and obtained a complete clinical response by 15 mo of starting treatment. To date, she has received 20 cycles (over 15 mo), experiencing side effects of severe myalgias, bone pain, and fatigue. Pt 2: 39 y/o female diagnosed with invasive FIGO stage IIB micropapillary serous primary peritoneal carcinoma. Treated unsuccessfully with regimens of paclitaxel, cisplatin, carboxymido-triazole, imatinib, anastrozole, panzem, and liposomal doxorubicin. Exam revealed multiple subcutaneous nodules at the vaginal apex, a pararectal mass, and a tumor at the colostomy site. She was then treated with bevacizumab, receiving 20 cycles over 15 mo, which stabilized her disease on the abdominal wall and the vaginal apex, while eradicating the tumor growing at the colostomy site and adjacent to the rectum. Notable side effects included myalgia, fatigue, and worsening of her osteoarthritis. Pt 3: 62 y/o female diagnosed with invasive FIGO stage IIB grade 1 mixed serous-endometrioid ovarian carcinoma. After surgery for recurrent disease, pt was given paclitaxel and carboplatin with a complete clinical response. Was treated with tamoxifen and megace for disease recurrence. Progression was treated with 6 cycles of docetaxel and carboplatin with a PR. Again disease progressed, pt was treated with bevacizumab with complete resolution of mass within 2 mo of starting treatment. To date, pt has received 29 cycles over 22 mo and has complete resolution of her disease. Notable side effects were myalgias, fatigue, and a worsening of her osteoarthritis.
Cohn, Valmadre, Resnick, et al., 2006[119]	Retro-spective study	10 mg/kg	10	10 pts with advanced, recurrent, and refractory ovarian cancer were treated biweekly with bevacizumab and weekly with taxane chemotherapy on days 1, 8, 15, & 22 q 28 days. All pts were followed with serial CA125 measurements prior to each cycle of treatment. Toxicities were assessed prior to each cycle of treatment. Nine pts were evaluable and all had decrease in CA125. Five pts have had an increase in CA125 after treatment after a median of 3 cycles, while 3 pts experienced normalization of CA125 and another with continued improvement of CA125. All symptomatic pts experienced rapid palliation of pain, nausea, and ascites. Side effects have been mild, with no Grade 3/4 toxicities noted. No treatment delays or discontinuations have been necessary. Concluded significant, temporary improvement in symptoms, requiring further study.
Monk, Han, Josephs-Cowan, et al., 2006[120]	Retro-spective chart review	15 mg/kg IV q 3 wk	32	Median pt age was 57 (35–80), FIGO stages included 80% stage III and 10% stage IV. All pts had failed multiple cytotoxic chemotherapies prior to bevacizumab. Median duration of followup was 4.8 mo (0.4–16.3). 23 pts were treated with bevacizumab alone, 2 received bevacizumab with another chemotherapy regimen, and 8 initially received bevacizumab alone followed by bevacizumab with capecitabine, cyclophosphamide, docetaxel, carboplatin, or weekly paclitaxel. One pt was lost to followup after cycle 1. There was a 16% response rate (all in those treated with bevacizumab alone), with 62.5% of pts demonstrating SD. Median OS was 6.9 mo, and the median PFS was 5.5 mo.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
				Grade 3 AEs included hypertension, proteinuria, and enterocutaneous fistula.
Numnum, Rocconi, Whitworth, et al., 2006[121]	Case reports	15 mg/kg IV q 3 wk	4	4 pts had end-stage ovarian carcinoma with symptomatic ascites treated with bevacizumab with intent of palliation. All had been heavily pretreated and had progressive disease on therapy. Pt 1: 55 y/o female. After 6 wk of bevacizumab treatment, pt noticed reduction in abdominal distention and required no further paracenteses. CT confirmed SD and no ascites. Pt ultimately succumbed to disease and died 6 mo after initiation of bevacizumab treatment. Pt 2: 44 y/o female, after 3 courses of bevacizumab treatment, pt noted an improvement in abdominal distention and required no further paracenteses. Pt is currently alive with SD and minimal abdominal distention after 6 mo treatment. Pt 3: 36 y/o female, had previous treatment but all produced short-term PR with symptomatic ascites. After 2 cycles of bevacizumab treatment, pt noted an improvement in symptomatology and required no further paracenteses. She also had no treatment-induced toxicities. She is presently alive with SD 6 mo after initiation of treatment. Pt 4: 58 y/o female had prior multiple treatments with PR and progression of disease. After 3 mo of bevacizumab treatment, pt has experienced sustained improvement in abdominal distention without necessity of a therapeutic paracentesis.
Wright, Hageman, Rader, et al., 2006[122]	Retro-spective study	5 mg/kg with 15 receiving weekly and 8 receiving every other wk	23	Combination treatment with bevacizumab included cyclophosphamide in 15 (65%), docetaxel in 1 (4%), 5-fluorouracil in 6 (26%), and gemcitabine/liposomal doxorubicin in 1 (4%). 2 (9%) developed chylous ascites, Grade 4–5 toxicities occurred in 4 (17%), GI perforation occurred in 2 (9%), measurable disease was present in 22. Overall best response rate was 8 PR (35%). SD was found in a further 10 (44%), whereas progressive disease was observed in 5 (22%). Median time to progression was 5.6 mo in pts with PR, and 2.3 mo in subjects with SD. 3 (13%) experienced a PFI of > 6 mo. At last followup, 8 (35%) had died of disease, whereas 15 (65%) were alive with disease.

Abbreviations: AE(s) = adverse event(s); CA125 = cancer antigen 125; CT = computed tomography; FIGO = International Federation of Gynecology and Obstetrics; GI = gastrointestinal; IV = intravenous; OS = overall survival; PFI = progression-free interval; PFS = progression-free survival; PR = partial response; q = every; SD = stable disease; y/o = year-old.

Bevacizumab for Pancreatic Adenocarcinoma

Background

Drug: Bevacizumab (Avastin®). Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab was approved in February 2004 as a first-line treatment for patients with metastatic colorectal cancer. In June 2006, the Food and Drug Administration (FDA) granted approval for a labeling extension for bevacizumab, in combination with intravenous 5-fluorouracil-based chemotherapy, as a second-line treatment of patients with metastatic carcinoma of the colon or rectum. The FDA granted another labeling extension in October 2006 for bevacizumab administered with carboplatin and paclitaxel. It is indicated for the initial systemic treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer. In February 2008, the FDA granted accelerated approval for bevacizumab in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer; approval for renal cell carcinoma (RCC) and glioblastoma followed. It has been evaluated for off-label use in pancreatic adenocarcinoma and epithelial ovarian cancer (EOC). At the time this review was initiated, the breast and renal cell indications had not been approved.

Disease: Pancreatic adenocarcinoma. Pancreatic adenocarcinoma can affect both the exocrine and endocrine portions of the pancreas, although 95 percent of pancreatic tumors develop in the exocrine portion, including the ductal epithelium, acinar cells, connective tissue, and lymphatic tissue.[123,124] In the United States, the annual overall incidence is eight to 10 cases per 100,000 persons, with more than 35,000 new cases diagnosed each year and an almost identical number of deaths[35] due to the aggressiveness of the disease and the inherent difficulties of early diagnosis. There has been a marked increase in the incidence of pancreatic cancer during the last few decades, and it is currently the fourth leading cause of death from cancer in the United States.[123]

Its prognosis is dismal, with an average median survival of four to six months and an overall five-year survival rate of less than 4 percent. Patients with endocrine and cystic neoplasms fare better, but even among those who undergo successful curative resection, the median survival improves only to 12 to 19 months, with a 15 percent to 20 percent five-year survival rate.[123,124] Pancreaticoduodenectomy remains the only therapy that definitively improves survival. However, it is indicated only for patients with tumors affecting the head of the pancreas, and the procedure itself has been associated with significant mortality and morbidity. For patients with unresectable disease, palliative therapies are indicated.[124]

Although chronic inflammation and hereditary factors are common predisposing factors, the cause of pancreatic cancer is heterogeneous and remains elusive.[124] However, its underlying genetic and molecular abnormalities have been well documented, which may eventually help clarify causality and improve strategies for screening and treatment. Research suggests that alterations to oncogenes, tumor suppressor genes, and the expression of regulatory proteins play critical roles in the development of pancreatic cancer. In addition, a number of growth factors, including VEGF, are expressed at higher levels in chronic pancreatitis and pancreatic cancer, and may contribute to metastatic disease.[125-127]

Drug/Disease: Bevacizumab for pancreatic adenocarcinoma. Over the past few years, clinical research initiatives attempting to improve the efficacy and minimize the toxicity of pancreatic cancer therapy have examined the development of new strategies for drugs approved for other malignant conditions. Given the overexpression of VEGF that is associated with pancreatic adenocarcinoma, researchers have turned their attention to therapies that target the VEGF pathway.[126] The growth factor VEGF appears to be a central factor in angiogenesis and is thus critical to tumor growth and metastasis.[92] Early investigations of bevacizumab, a recombinant humanized antibody to VEGF, have suggested that it may prove useful as a targeted therapy for patients with advanced pancreatic adenocarcinoma.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded a total of 10 reports describing eight studies. Study designs included one Phase III randomized clinical trial (partially described in three publications, including a review article, a published comment, and a published abstract), four Phase II non-randomized trials, two Phase I trials, and one case report. Two studies (including the Phase III trial) were published as full reports (Table A19), four were published abstracts from the American Society of Clinical Oncology (ASCO) 2007 conference (Table A20), and two were additional articles considered in the horizon scan (Table A21). The first publication to appear in the literature in 2005 was a case report of a 75 year-old male with pancreatic adenocarcinoma that was refractory to prior treatment who demonstrated a marked clinical response to bevacizumab without significant side effects. This report was followed by a Phase I dose-escalating study published in 2006. The Phase III randomized, double-blind, placebo-controlled trial randomized 602 patients with advanced pancreatic adenocarcinoma not previously treated to either gemcitabine plus placebo or to gemcitabine plus bevacizumab 10 mg/kg. The single fully published Phase II trial enrolled 52 patients with pancreatic cancer not amenable to surgery.

Sample sizes for the six Phase I/II trials ranged from 12 to 82, with a total of 195 patients presented in the full report plus abstracts. Eligibility criteria for inclusion in the studies were not well described in the abstracts, but generally included metastatic disease not previously treated. All of studies involved adults. Patient age across these trials ranged from 32 to 86 years.

Bevacizumab was used as monotherapy in one study, and in combination with gemcitabine, oxaliplatin, or docetaxel in the other trials. Dosages of bevacizumab ranged from 5 mg/kg to 15 mg/kg, with the most frequently used dosage being 10 mg/kg.

Efficacy data were provided in all the included publications. Primary outcomes assessed were not clearly defined. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

Both clinical trials published as full reports met five of five quality criteria.

Efficacy. The complete response (CR) rate among patients who received bevacizumab ranged from 0 percent to 2.8 percent. Partial response (PR) rates ranged from 0 percent to 21 percent.

Survival. Median overall survival ranged from 5.7 to 8.8 months in the four trials that provided these data. In the Phase III trial that compared gemcitabine plus bevacizumab 10 mg/kg to gemcitabine plus placebo, median survival was 5.7 months in the bevacizumab group and 6.0 months in the placebo group.

Adverse events. Data on adverse events are summarized in Table A22. Grade 3/4 adverse events were: neutropenia/granulocytopenia (range, 35 percent to 50 percent); hypertension (range, 10 percent to 19 percent); venous thrombosis (range, 14 percent to 18 percent); gastrointestinal bleed (range, 2 percent to 5 percent); and anemia (range, 4 percent to 13 percent).

Horizon scan. The two articles identified as horizon scans included a Phase I dosing study and a case report of a 75 year-old male who responded well to treatment with bevacizumab.

Discussion

The findings from the Phase II studies suggest that bevacizumab does little to improve clinical outcomes in the treatment of pancreatic adenocarcinoma. Complete responses ranged from 0 percent to 1 percent in these studies. The single Phase III trial, which enrolled 602 patients and compared gemcitabine plus bevacizumab 10 mg/kg to gemcitabine plus placebo, did not demonstrate a survival benefit associated with bevacizumab. These findings are consistent with recently published expert opinion that there is no consensus about second-line therapy after pancreatic cancer progression after gemcitabine failure.[128,129]

Table A19: Bevacizumab for Pancreatic Adenocarcinoma – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Kindler, Friberg, Singh, et al., 2005[130]	**Design:** Open label **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Confirmed pancreatic cancer not amenable to surgery - Measurable disease - ECOG 0–2 - No prior chemo for metastatic disease - Adjuvant chemo as radiosensitizer OK if NOT gemcitabine or bevacizumab and completed ≥ 4 wk prior - Prior XRT OK only if sites of measurable disease not included in radiation field	**No. in study:** 52 **Age:** 63 **Previous treatment:** 41-no, 11-yes (adjuvant chemorad) **Stage of disease:** Metastatic **Drug dose/day [followup]:** Gemcitabine 1000 mg/m^2 d1, 8, &15 q 28 days Bevacizumab 10 mg/kg d 1 & 15 q 28 days **Outcomes sought:** ORR	**N:** 52 **CR:** 0 **PR:** 11 (21%); median duration of response 10 mo **Stable disease:** 24 (46%); median duration of response 6.3 mo **Progressive disease:** 13 (25%)	**Survival overall (from start of treatment):** **Median survival:** 8.8 mo (7.4–9.7) **6 mo:** 77% (63–83%) **1 yr:** 29% (17–42%) **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 5.4 mo (3.7–6.2) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A22. **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** - At time of analysis, all patients off therapy and 45 (87%) dead - Median f/u 8 mo
Saif, 2007[131] AND Anonymous, 2007[132] AND Kindler, Niedzwiecki, Hollis, et al., 2007[133]	**Design:** RCT, double-blind, placebo-controlled **Phase:** Phase III **Selection/ randomization:** Randomized **Eligibility criteria:** - No prior treatment - ECOG 0–2 - No tumor invasion of	**No. in study:** 602 **Age:** 63.8 G+B; 65 G **Previous treatment:** None **Stage of disease:** Loc. advanced or metastatic **Drug dose/day [followup]:** Gemcitabine 1000 mg/m^2	**N:** 602 **OR:** 13.5 vs. 10.3% (from article-breakdown below from ASCO abstract) **CR:** 1.1% vs. 2.8% (G + B/G) **PR:** 12.4% vs. 7.7% (G + B/G) **Stable disease:** 40.9%	**Survival overall (from start of treatment):** **Median survival:** 5.7 (G+B) vs. 6 mo (G) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 4.8	**Adverse events & tolerability:** See Table A22. **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
	adjuvant organs - No bleeding risk	d 1, 8, &15 q 28 days; *plus* Bevacizumab 10 mg/kg *or* placebo d 1 & 15, q 28 days **Outcomes sought:** binOS stratified by ECOG, disease (loc. advanced or metastatic) and prior external beam XRT (yes/no)	vs. 33.6% **Progressive disease:** Not reported	(G+B) vs. 4.3 mo (G) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Comments:** - Median f/u 8.4 mo (G+B) and 8.1 mo (G) - Info released in 6/06 because futility criteria reached. - As of 8/06 377 dead - No improvement in survival with addition of bevacizumab to gemcitabine

Abbreviationschemo = chemotherapy; chemorad = chemotherapy and radiation; CR = complete response; ECOG = Eastern Collaborative Oncology Group; OR = overall response; OS = overall survival; PR = partial response; q = every; RCT = randomized controlled trial; XRT = x-ray therapy.

Table A20: Bevacizumab for Pancreatic Adenocarcinoma – ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Astsaturov, Meropol, Alpaugh, et al., 2007[134] ASCO 2007 Abstract #4556	**Disease:** Pancreatic cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Randomized **Eligibility criteria:** Metastatic disease, previous gemcitabine, PS 0 or 1, no thrombosis or bleeding	**No. in study:** 30 **Age:** 61.5 (38–81) **Previous treatment:** One prior gemcitabine regimen **Stage of disease:** IV **Drug dose/day [followup]:** Group A: Bevacizumab 10mg/kg q 2 wk *versus* Group B: Bevacizumab 10 mg/kg q 2 wk + docetaxel 35 mg/m^2 day 1, 8, and 15 q 28 days **Outcomes sought:** Toxicity, response	**N:** Group A: 15 Group B: 15 **CR:** 0 **PR:** Group B: 1(7%) **Stable disease:** Group A: 4 (27%) Group B: 5 (33%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Group A: 181 days Group B: 123 days **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Group A: 43 days Group B: 45 days **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Bowel perforation: Group A: 1 Group B: 1 DVT/PE: Group A: 3 Group B: 2 **Comments:** Study terminated due to lack of PFS benefit in both arms
Gomez-Martin, Camara, Cortes, et al., 2007[135] ASCO 2007 Abstract #4611	**Disease:** Pancreatic cancer **Design:** Prospective cohort **Phase:** Phase I **Selection/randomization:** Not randomized (2 patient "cohorts") **Eligibility criteria:** Advanced disease	**No. in study:** 12 **Age:** 62 (38–71) **Previous treatment:** Not reported **Stage of disease:** IV **Drug dose/day [followup]:** Erlotinib 150 mg q day, *plus* Bevacizumab 5 mg/kg days 1 and 15 q 28 days; *plus either* Gemcitabine 850 mg/m^2 days 1 and 15 (Cohort 1) *or*	**N:** 12 **CR:** 0 **PR:** 2 (17%) **Stable disease:** 7 (58%) **Progressive disease:** 3 (25%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Cohort 1 (850 mg/m^2): Grade 3 asthenia: 3/6 Grade 3 neutropenia: 2/6 Grade 3 leukopenia: 1/6 Grade 3 skin rash: 1/6 Cohort 2 (1000 mg/m^2): Grade 4 GGT elevation: 1/6 Grade 3 rash: 1/6 Grade 3 asthenia: 1/6

Study	Study Design	Patients	Tumor Response	Survival	Other
		1000 mg/m^2 days 1, 15 (Cohort 2) **Outcomes sought:** Toxicity, response			
Kim, Oberg, Foster, et al., 2007[136] ASCO 2007 Abstract #4553	**Disease:** Pancreatic cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Metastatic pancreatic cancer, untreated, ECOG PS 0-2	**No. in study:** 82 **Age:** 63 (32–86) **Previous treatment:** Not reported **Stage of disease:** IV **Drug dose/day [followup]:** Gemcitabine 1000 mg/m^2 over 100 min q 28 days; *plus* Bevacizumab 10 mg/kg day 1 and 15 q 28 days; *plus* Oxaliplatin 100 mg/m^2 day 2, 16 q 28 days. **Outcomes sought:** Toxicity, response	**N:** 80 **CR:** 1 (1%) **PR:** 8 (10%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** 8.1 mo **1 yr:** 6 mo (65%) **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 4 toxicity in 29% Grade 5 (death) in 3 patients
Small, Mulcahy, Benson, et al., 2007[137] ASCO 2007 Abstract #15043	**Disease:** Pancreatic cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Non-metastatic, PS 0 or 1,	**No. in study:** 19 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Non-metastatic disease **Drug dose/day [followup]:**	**N:** 12 **CR:** 0 **PR:** 0 **Stable disease:** 10 (83%) **Progressive disease:** 2 (17%)	**Survival overall (from start of treatment):** **Median survival:** Not reached **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Not	**Adverse events & tolerability:** No Grade 4 or 5 toxicity 10 (83%) with Grade 3 toxicity (mostly hematologic); Grade 3 cytopenia: 9 Grade 3 DVT: 2

Study	Study Design	Patients	Tumor Response	Survival	Other
	adequate organ function	3 cycles of gemcitabine 1000 mg/m^2 *plus* bevacizumab 10 mg/kg with 36Gy in 2.4Gy fractions in cycle 2 Cycle 1 (21d): Gemcitabine days 1 & 8 Bevacizumab days 1 & 15 Cycle 2 (28d): Gemcitabine days 1, 8, & 15 Bevacizumab days 8 & 22 Cycle 3 (21d): Gemcitabine days 1 & 8 Bevacizumab day 8 **Outcomes sought:** Toxicity, response		reached **1 yr:** NR **2 yr:** NR **3 yr:** NR	

Abbreviations: ASCO = American Society of Clinical Oncology; CR = complete response; DVT/PE = deep vein thrombosis / pulmonary embolism; GGT = Gamma glutamyl transpeptidase; OS = overall survival; PR = partial response; PS = performance status; q = every.

Table A21: Bevacizumab for Pancreatic Adenocarcinoma – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Bruckner, Hrehorovich, and Sawhney, 2005[138]	Case report	5 mg/kg day 2 following cisplatin	1	75 y/o male was treated unsuccessfully with low-dose GFLIP for 6 cycles using the 24-hr schedule. Failure was documented by evidence of large new liver lesions. Bevacizumab was added to the low-dose GFLIP given in an identical dose and schedule. After 6 cycles, tumor markers significantly decreased. After 11 cycles, objective response was seen in the liver lesions, one lesion having completely resolved and the remaining two decreasing in size. Pt remained clinically well and continued with no significant side effects after 9 mo of treatment.
Crane, Ellis, Abbruzzese, et al., 2006[139]	Phase I, dose-escalating trial	First 6 pts dosed at 625 mg/m^2, rest at 825 mg/m^2 capecitabine	48	Primary end point of this study was the safety of the combination of bevacizumab, radiotherapy, and capecitabine. Secondary end points were radiographic evidence of local tumor response and median survival duration. Bevacizumab was started 2 wk prior to chemoradiation and given concurrently with chemoradiation q 2 wk for a total of 4 doses. The concurrent bevacizumab dose was escalated from 2.5-10 mg/kg every 2 weeks with capecitabine and radiotherapy. The 4th and final dose of bevacizumab during radiotherapy was dropped in the final 18 pts. The first 6 pts received 650 mg/m^2 of capecitabine bid q day during radiotherapy including weekends. Pts with stable or responding disease were continued on bevacizumab treatment. Nine of 46 assessable patients (20%) had confirmed partial responses for median of 6.2 months. Median overall survival was 11.6 months. Three patients developed Grade 4 neutropenia and five patients developed Grade 3 or worse ulceration with bleeding or perforation.

Abbreviations: bid = twice per day; GFLIP = gemcitabine, irinotecan, fluorouracil followed by leucovorin and cisplatin; q = every; y/o = year-old.

Table A22.1: Bevacizumab for Pancreatic Adenocarcinoma – Adverse Events (Grade 3/4+ Events Only) – Part 1

Study	Anemia	Neutropenia/ granulocytopenia	Leukopenia	Thrombocytopenia	Nausea	Vomiting	Fatigue	Headache	Chills/fever	Anorexia	Dyspnea	Infection
Kindler et al., 2007[133]	13%	50%	-	23%	-	-	-	-	-	-	-	-
Kindler et al., 2005[130]	4%	35%	31%	8%	6%	6%	17%	2%	2%	4%	8%	4%
Saif 2007[131]	5%	31%	-	12%	-	-	-	-	-	-	-	-

Table A22.2: Bevacizumab for Pancreatic Adenocarcinoma – Adverse Events (Grade 3/4+ Events Only) – Part 2

Study	Neutropenic fever	Hypertension	Perforation	Gastrointestinal bleed	CVA	Proteinuria	Venous thrombosis	Hyperglycemia	Elevated AST	Elevated ALT	Elevated alkaline phosphatase	Bilirubin
Kindler et al., 2007[133]	-	10%	0%	5%	3%	3%	18%	-	-	-	-	-
Kindler et al., 2005[130]	0%	19%	8%	2%	-	2%	14%	14%	8%	10%	8%	6%
Saif 2007[131]	-	8%	0%	3%	1%	2%	9%	-	-	-	-	-

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; CVA = cardiovascular accident.

Bevacizumab for Renal Cell Carcinoma

Background

Drug: Bevacizumab (Avastin®). Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Bevacizumab was approved in February 2004 as a first-line treatment for patients with metastatic colorectal cancer. In June 2006, the Food and Drug Administration (FDA) granted approval for a labeling extension for bevacizumab, in combination with intravenous 5-fluorouracil-based chemotherapy, as a second-line treatment of patients with metastatic carcinoma of the colon or rectum. The FDA granted another labeling extension in October 2006 for bevacizumab administered with carboplatin and paclitaxel. It is indicated for the initial systemic treatment of patients with unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer. In February 2008, the FDA granted accelerated approval for bevacizumab in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer; approval for renal cell carcinoma (RCC) and glioblastoma followed. It has been evaluated for off-label use in pancreatic adenocarcinoma and epithelial ovarian cancer (EOC). At the time this review was initiated, the breast and renal cell indications had not been approved.

Disease: Renal cell carcinoma. Renal cell carcinoma (RCC) is a type of cancer in which neoplastic cells proliferate in the proximal renal epithelium, the lining of very small tubes in the kidney that filter the blood and remove waste products. Because it is characterized by a lack of early symptoms, diverse clinical manifestations, and resistance to radiation and chemotherapy, diagnosis and treatment remain challenging.[140]

RCC is the most common form of kidney cancer, accounting for nine out of 10 of all solid renal masses, as well as 3 percent of all solid neoplasms.[141,142] More than 30,000 individuals are diagnosed with RCC and more than 12,000 RCC patients die every year, making RCC the tenth most fatal cancer.[141] The median age at death is approximately 70 years of age.[35] Although its overall 5-year survival rate is 66.5 percent, treatment, outcome, and prognosis vary according to disease stage.[35] When detected early, RCC is often successfully treated by radical nephrectomy. Nevertheless, up to 30 percent of surgical patients go on to develop metastatic disease. Furthermore, up to half of RCC patients initially present with advanced disease.[143] Prognosis for late-stage RCC is poor, with a median survival of 10 months and a 5-year survival rate of less than 2 percent.[143,144]

Classic cytotoxic chemotherapy and radiotherapy demonstrate little antitumor activity in RCC, and immunotherapy —the current standard of care for advanced disease—improves median survival by only 3 to 7 months and is attended by severe, sometimes fatal toxicities.[145] In recent years, the FDA has approved a number of targeted drugs for use against advanced kidney cancer, including agents that interrupt angiogenesis and some that target other important cell growth factors. Whether these drugs can lead to complete remission is not yet clear.[142]

Drug/Disease: Bevacizumab for RCC. Although metastatic RCC continues to be among the most treatment-resistant malignancies, recent clarifications of its biological mechanisms point toward promising new therapeutic agents.[146,147] RCC has been shown to involve a mutated version of the von Hippel–Lindau tumor suppressor gene, which upregulates vascular endothelial

growth factor (VEGF). VEGF appears to be a central factor in angiogenesis, which is critical to tumor growth and metastasis.[92] Indeed, VEGF has been correlated with an increased risk of metastatic disease and poor prognosis in numerous cancers, and animal research demonstrates that its inhibition is associated with stabilization of established tumors.[148] VEGF is thus a logical therapeutic target.[146,147] Because bevacizumab neutralizes circulating VEGF, researchers have begun to investigate it as a targeted therapy for RCC patients. In recent studies, it performed well and was well tolerated, and clinicians can prescribe it for RCC, although it has yet to receive FDA approval for that indication.[142,148]

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded at total of 11 reports. Three of these were full reports of clinical trials (Table A23), four were published abstracts from the American Society of Clinical Oncology (ASCO) 2007 conference (Table A24), and four were additional articles considered in the horizon scan (Table A25). Study designs included eight clinical trials and three case reports. One of the trials was a Phase I crossover trial, five were uncontrolled Phase II studies, and two were Phase III, placebo-controlled, randomized clinical trials. The first report to appear in the published literature was a Phase III, three-arm, double-blind, randomized clinical trial published in 2003. This study involved 116 patients with metastatic renal cancer randomized either to placebo or to low-dose (3 mg/kg) or high-dose (10 mg/kg) bevacizumab every 2 weeks. The next report, published in 2004, was a crossover study that compared bevacizumab plus thalidomide to bevacizumab only. The second Phase III trial involved 649 patients who were randomized either to bevacizumab 10 mg/kg every 2 weeks or to placebo. Patients in both arms were also treated with interferon (IFN) alpha2. Results of this trial were presented at the 2007 ASCO conference and were published only in abstract form when our literature search was conducted.

Sample sizes for the clinical trials ranged from 15 to 649, with a total of 201 patients presented in the full reports and 897 patients presented in the full reports plus abstracts.

Eligibility criteria for inclusion in the studies were generally uniform and consistent with what would be expected from studies of metastatic renal carcinoma. Most of the studies included patients who had had prior surgery, interleukin-2 (IL-2) therapy, or other treatments, but some patients had not had previously undergone treatment. All of the studies involved adults.

Bevacizumab was used in combination with other treatments in the majority of studies, and in all but 105 (12 percent) of patients. Treatments used in combination with bevacizumab include IL-2, thalidomide, erlotinib, sunitinib, and IFN alpha2a. Except for two studies that administered bevacizumab at a dosage of 3 mg/kg, all of the trials use the dosage of 10 mg/kg, usually every 2 weeks.

Efficacy data were reported in seven of the eight clinical trials. Outcomes assessed were generally clinical response and toxicity. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

Study quality of the three fully published reports was generally good. Two studies met five of five quality criteria and one met four of five criteria. The only quality criteria that was not met was an adequate followup period in the crossover trial.

Efficacy. Among the 201 patients enrolled in the three fully published reports, only a single patient (< 1 percent) had a complete response (CR). None of the studies published as abstracts that provided CR rates reported a CR rate greater than 0 percent.

Partial response (PR) rates ranged from 10 to 25 percent among the fully published reports and from 9 to 31 percent among the studies published as abstracts.

Survival. Median progression-free survival ranged from 3 to 11 months among the three fully published reports, and was 10 months (vs. 5 months in the placebo arm) in the only study published in abstract form that provided survival data.

Adverse events. Data in Table A26 were derived from the three full reports. No single Grade 3/4 adverse event was reported in all three studies. Hypertension (range, 8 to 21 percent) and proteinuria (range, 6 to 13 percent) were reported in two studies.

Horizon scan. The horizon scan identified three case reports, each of which described adverse events (e.g., elevation in blood pressure, reversible posterior leukoencephalopathy, or proteinuria) attributed to bevacizumab. The fourth horizon scan publication was a retrospective review of patients who had received interferon-alpha therapy plus bevacizumab. An objective response was reported in 18 of 42 evaluable patients (42 percent).

Discussion

Given the upregulation of VEGF associated with the mutated version of the von Hippel–Lindau tumor suppressor gene in the majority of renal cell cancers, drugs that target the inhibition of angiogenesis are logical therapeutic agents. The findings from this review support the use of bevacizumab in the treatment of renal cell cancer. The three fully published trials as well as the published abstracts demonstrated that bevacizumab appears to be both well tolerated and efficacious. The Phase III clinical trial published in abstract form demonstrated a 30.6 percent complete response associated with bevacizumab, compared to 12.4 percent associated with placebo when administered along with interferon therapy. Hypertension and proteinuria are among the more common adverse events associated with bevacizumab therapy.

Table A23: Bevacizumab for Renal Cell Carcinoma – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Elaraj, White, Steinberg, et al., 2004[149]	**Design:** Crossover **Phase:** Phase II (pilot study) **Selection/ randomization:** Not randomized **Eligibility criteria:** Pts who had progressed on placebo arm of the Yang study (see below)	**No. in study:** 22 **Age:** 52 bevacizumab (B) only; 56 bevacizumab + thalidomide (Th) **Previous treatment**: IL-2 or contra to IL-2 **Stage of disease:** Metastatic **Drug dose/day [followup]:** Bevacizumab 4.5 mg/kg load, then 3 mg/kg q 2 wk Bevacizumab + thalidomide: same bevacizumab dose plus thalidomide 200 mg/day escalated by 100 mg/day q 2 wk to 800 mg/day max **Outcomes sought:** Toxicity, objective response, and TTP	**N:** 22 **CR:** 0 **PR:** 0 **Stable disease:** 0 **Progressive disease:** 22	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** PFS for B: 2.4 mo PFS for B+Th: 3 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A26 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes
Hainsworth, Sosman, Spigel, et al., 2005[150]	**Design:** Multicenter **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Progressive, biopsy proven metastatic or	**No. in study:** 63 **Age:** 61 **Previous treatment:** 68% none; 26% IFN +/- IL2; 6% IL-2. **Stage of disease:** Metastatic or local recurrent	**N:** 59 **CR:** 1 **PR:** 14 (ORR 25%; 95% CI 16–37%) **Stable disease:** 36 (61%; 95% CI 48 to 72%) **Progressive disease:** 8	**Survival overall (from start of treatment):** **Median survival:** Not reached **1 yr:** 78% **1 ½ yr:** 60% **3 yr:** NR **Survival (disease-free):**	**Adverse events & tolerability:** See Table A26 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes

Study	Study Design	Patients	Tumor Response	Survival	Other
	locally recurrent, unresectable clear cell renal cancer - No previous EGFR or thalidomide - Only 1 previous regimen - Nephrectomy > 30 days prior unless medically not an option to have - < 3 brain metastases treated with surgery - XRT ≥ 8 wk prior with no residual neurological symptoms or dexamethasone - ECOG 0–1 - Measurable disease - Normal labs - No prior DVT, bleeding disorders, or thrombosis issues - No hemoptysis or hematemesis	**Drug dose/day [followup]:** Bevacizumab 10 mg/kg q 2 wks Erlotinib 150 mg/day **Outcomes sought:** Efficacy and toxicity of combo; looking for 20% ORR		**Median survival:** 11mo **1 yr:** 43% **1 ½ yr:** 26% **3 yr:** NR	assessments?: Yes
Yang, Haworth, Sherry, et al., 2003[92]	**Design:** Randomized, double-blind **Phase:** Phase II **Selection/ randomization:** Randomized, stratified based on prior IL2 treatment **Eligibility criteria:** - Metastatic clear cell renal cancer - Documented progressive disease - ECOG ≤ 2 - Previous IL2 or contraindication to IL2	**No. in study:** 116 **Age:** 54 low-dose arm; 53 high-dose arm; 53 placebo arm **Previous treatment:** IL2 or contraindicated **Stage of disease:** Metastatic **Drug dose/day [followup]:** Placebo or PK modeled loading dose followed by 3 mg/kg bevacizumab (low-dose) or 10 mg/kg bevacizumab (high-dose)	**N:** 39 high, 37 low, 40 placebo **CR:** 0 **PR:** 4 (10%), all in high-dose arm (95%CI 2.9–24.2%) **Stable disease:** Not reported **Progressive disease:** 108	**Survival overall (from start of treatment):** **Median survival:** (19 patients alive in Feb 2003 – study from 10/98–9/01) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** PFS: 4.8 mo vs. 3.0 mo. vs. 2.5 mo (high-dose vs. low-dose vs. placebo) **Median survival:** PFS: 4.8 mo vs. 2.5 mo (high-	**Adverse events & tolerability:** See Table A26 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** - Closed at 2nd planned interim analysis (based on 110 pts) - Pts were allowed to cross over, no SS difference in survival with placebo (not a primary end point)

Study	Study Design	Patients	Tumor Response	Survival	Other
	treatment	or placebo q 2 wk **Outcomes sought:** TTP, response, and toxicity		vs. low-dose) **1 yr:** NR **2 yr:** NR **3 yr:** NR	- 1 pt PR x 2 yr on treatment and 1 pt minor response x 2 yr on treatment stopped treatment, relapsed and were retreated with same response

Abbreviations: CI =confidence interval; CR = complete response; DVT = deep vein thrombosis; ECOG = Eastern Collaborative Oncology Group; EGFR = epidermal growth factor receptor; IFN = interferon; IL = interleukin; ORR = overall response rate; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; q = every; TTP = time to tumor progression; XRT = radiation therapy.

Table A24: Bevacizumab for Renal Cell Carcinoma – ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Ernstoff, Regan, McDermott, et al., 2007[151] ASCO 2007 Abstract #15524	**Disease:** Renal cell carcinoma **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Met RCC, clear cell, Karnofsky 80% or better, adequate end organ, no coagulopathy or thrombotic event	**No. in study:** 15 **Age:** 54 (40–73) **Previous treatment:** Not reported **Stage of disease:** IV **Drug dose/day [followup]:** Bevacizumab 10 mg/kg q 2 wk x 7 doses; *plus* IL-2 600K units q 8 hrs x 5 days x 2 as part of an 84-day cycle up to 28 doses **Outcomes sought:** Toxicity	**N:** 15 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 1 episode of fatal hypotension related to IL-2 administration
Escudier, Koralewski, Pluzanska, et al., 2007[152] ASCO 2007 Abstract #3	**Disease:** Renal cell carcinoma **Design:** Prospective, double-blind, placebo-controlled RCT **Phase:** Phase III **Selection/randomization:** Randomized and stratified by county and Motzer score **Eligibility criteria:** Metastatic clear cell renal cancer, Karnofsky > 70%, no CNS disease, adequate organ function	**No. in study:** 649 **Age:** 61 (range 18-82) **Previous treatment:** Not reported **Stage of disease:** IV **Drug dose/day [followup]:** IFN alpha2a 9 MIU TIW up to 1 yr; *plus/minus* Bevacizumab 10 mg/kg q 2 wk until disease progression **Outcomes sought:** Toxicity, response	**N:** 641 **CR:** Overall response: Bevacizumab: 30.6% Placebo: 12.4% **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** 505/641 "progression events"	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Progression-free survival: Bevacizumab: 10.2 mo Placebo: 5.4 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 or 4 proteinuria, fatigue, and asthenia were ≥ 3% more common in bevacizumab arm

Study	Study Design	Patients	Tumor Response	Survival	Other
Feldman, Kondagunta, Ronnen, et al., 2007[153] ASCO 2007 Abstract #5099	**Disease:** Renal cell carcinoma **Design:** Prospective cohort **Phase:** Phase I **Selection/randomization:** Not randomized **Eligibility criteria:** Metastatic renal cell carcinoma	**No. in study:** 16 **Age:** 57 **Previous treatment:** Not reported **Stage of disease:** IV **Drug dose/day [followup]:** Sunitinib 25, 37.5, and 50 mg q day x 4 wk on, 2 wk off; *plus* Bevacizumab 10 mg/kg q 2 wk continuous **Outcomes sought:** Toxicity, response	**N:** 13 **CR:** 0 **PR:** 4 (31%) **Stable disease:** 7 (54%) **Progressive disease:** 2 (15%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** HTN grade 3: 4 Abdominal pain grade 3: 2 Proteinuria grade 3: 2 Hemorrhage grade 4: 1 Hand/foot syndrome grade 3: 1
Garcia, Rini, Mekhail, et al., 2007[154] ASCO 2007 Abstract #5103	**Disease:** Renal cell carcinoma **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Not randomized **Eligibility criteria:** Untreated, good and intermediate risk metastatic RCC with clear cell histology, prior nephrectomy, normal organ function	**No. in study:** 16 **Age:** 59 (44–67) **Previous treatment:** None **Stage of disease:** IV **Drug dose/day [followup]:** IL-2 250K U/day, days 1–5 of wk 1; 125K U/day days 1–5 of wk 2–6; *plus* Bevacizumab 10 mg/kg until disease progression **Outcomes sought:** Response, toxicity	**N:** 11 **CR:** 0 **PR:** 1 (9%) **Stable disease:** 3 (27%) **Progressive disease:** 5 (45%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Fatigue, nausea, diarrhea, fever

Abbreviations: ASCO = American Society of Clinical Oncology; CNS = central nervous system; CR = complete response; HTN = hypertension; IFN = interferon; IL = interleukin; PR = partial response; q = every; RCC = renal cell carcinoma; RCT = randomized controlled trial; TIW = thrice weekly;.

Table A25: Bevacizumab for Renal Cell Carcinoma – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Frangie, Lefaucheur, Medioni, et al., 2007[155]	Case report	10 mg/kg q 2 wk	1	70 y/o male had undergone a left total nephrectomy for a clear-cell renal carcinoma. Pt was diagnosed with pulmonary metastasis, and treatment with interferon-alpha was started. Renal function remained stable with no proteinuria, but treatment stopped after 7 mo because of increasingly severe hypertension. Treatment with bevacizumab was started. Renal status changed abruptly and treatment was stopped. Response to stopping bevacizumab was favorable, with normalizing BP, disappearance of the stigmata of haemolysis, and return of renal function to previous baseline levels.
Glusker, Recht, and Lane, 2006[156]	Case report		1	59 y/o female received 7 infusions of bevacizumab at 2-wk intervals for treatment of metastatic renal cancer, during which time her BP remained within her usual range. Eight days after her last infusion, she presented to ER with severe lethargy. Pt was admitted following a tonic-clonic seizure in ER. Pt made a rapid recovery. After day 4, pt was alert and able to read regular newsprint at 18 inches. BP also returned to normal without treatment. F/u MRI 6 wk later showed complete resolution of the leukoencephalopathy. Since bevacizumab has a 20-day half-life, authors believe this pt's reversible posterior leukoencephalopathy was attributable to bevacizumab, resulting from effects of this VEGF inhibitor on the blood-brain barrier.
Rini, Jaeger, Weinberg, et al., 2006[157]	Retrospective review		43/53 evaluable	All pts received treatment with interferon-α plus bevacizumab. Clinical features were collected and activation status of the VHL gene was determined. Tumor response, TTP, and overall survival were recorded. There was an objective response in 18 pts (43%). Median TTP for entire cohort was 8.1 mo. 26 pts (60%) had evidence of VHL mutation or promoter methylation; such pts had an objective response rate of 48% vs. 35% in pts with no VHL mutation or methylation. Pts with VHL methylation or a mutation predicted to truncate or shift the VHL reading frame had a median TTP of 13.3 mo vs. 7.4 mo in pts with none of these features.
Roncone, Satoskar, Nadasdy, et al., 2007[158]	Case report	10 mg/kg q 2 wk	1	59 y/o male had undergone a left nephrectomy for renal cell carcinoma and was found to have metastatic disease during a restaging examination. Pt was started on treatment with interferon α2b plus bevacizumab. After 9 mo of this treatment the pt developed proteinuria which gradually increased. Bevacizumab was stopped after 15.5 mo as a result of the proteinuria and elevated serum creatinine level. Pt achieved complete remission of metastatic renal cell carcinoma and remains disease-free 25 mo after treatment was started.

Abbreviations: BP = blood pressure; ER = emergency room; MRI = magnetic resonance imaging; q = every; TTP = time to progression; VEGF = vascular endothelial growth factor; VHL = von Hippel–Lindau; y/o = year-old.

Table A26: Bevacizumab for Renal Cell Carcinoma – Adverse Events (Grade 3/4+ Events Only)

Study	Superficial edema	Diarrhea	Nausea/vomiting	Pruritus	Dermatitis or rash	Hand weakness	Hypertension	Bleeding	Proteinuria	Neuropathy	Chest pain
Elaraj et al., 2004[149]	-	-	-	-	-	18%	-	-	-	-	-
Hainsworth et al., 2005[150]	2%	13%	10%	3%	13%	-	8%	8%	6%	3%	-
Yang et al., 2003[92]	-	-	-	-	-	-	21%	-	7%	-	5%

Bortezomib for Non-Hodgkin Lymphoma

Background

Drug: Bortezomib (Velcade®). Bortezomib is a modified dipeptidyl boronic acid that acts as a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. By blocking the targeted proteolysis normally performed by the proteasome, bortezomib disrupts various cell signaling pathways, leading to cell cycle arrest, apoptosis, and inhibition of angiogenesis.

In May 2003, under accelerated approval provisions that were based on response rate and durability, bortezomib received Food and Drug Administration (FDA) approval for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. In March 2005, the FDA approved bortezomib for the treatment of patients with multiple myeloma who have received at least one prior therapy. In December 2006, the FDA granted approval to bortezomib for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. It has also been evaluated for off-label use in other types of non-Hodgkin lymphoma (NHL).

Disease: Non-Hodgkin lymphoma. NHL encompasses a diverse group of lymphoproliferative neoplasms with equally diverse natural histories, treatments, and prognoses. NHL tends to affect an older population, the median age being 67, and is the sixth most deadly form of cancer, with 19,160 patients predicted to die of the disease in 2008. Once a relatively rare condition, it is now the fifth most common cancer, with more than 63,000 new cases diagnosed each year and an annual incidence rate of 19.5 per 100,000 persons.[34,35]

The long-term survival and cure rates for these diseases are influenced by a number of prognostic factors, the most significant being the relative aggressiveness of the lymphomas, which fall into two prognostic categories: indolent and aggressive. Indolent NHL tends to progress slowly but is typically incurable; although it initially responds to radiation therapy and chemotherapy, relapses are often frequent in its advanced stages. Patients with aggressive and highly aggressive NHLs have a 30 to 60 percent cure rate with intensive chemotherapy regimens, depending upon the type of lymphoma and treatment. Other available treatments include hematopoietic stem cell transplantation and immunotherapy, with individual regimens being determined by disease stage and other prognostic considerations.[36,37] Prognostic indicators—including performance status, age, serum lactate dehydrogenase level, and extent of disease—provide insight into the individual patient's risk of death from NHL.

Drug/disease: Bortezomib for NHL. Over the past few years, clinical research initiatives seeking to improve the efficacy and minimize the toxicity of NHL therapy have examined the potential of proteasome inhibitors, including bortezomib. Preclinical evidence shows that inhibition of the ubiquitin-proteasome pathway arrests tumor growth, induces cell death, and downregulates tumor metastasis and angiogenesis.[159] As part of this process, the important transcription factor NF-κB is inactivated, which may render cells more sensitive to cytotoxic agents. A number of lymphoproliferative malignancies, including NHL, may be particularly vulnerable to NF-κB inhibition.[160] Phase I and II studies suggest that bortezomib has significant single-agent activity in certain NHL subtypes and that it is generally well tolerated.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded at total of 21 reports. Two of these were full reports of clinical trials (Table A27); 14 were published abstracts from the American Society of Hematology (ASH) 2006, ASH 2007, and American Society of Clinical Oncology (ASCO) 2007 conferences (Table A28); and five were additional articles considered in the horizon scan (Table A29). Study designs included 12 uncontrolled clinical trials, three trials randomized by dose or dosing schedule for bortezomib, and six case reports or case series. Both full reports of clinical trials were uncontrolled Phase II studies. The earliest publication is from 2005; this was a full report of a Phase II study.

Sample sizes for the clinical trials ranged from seven to 81, with a total of 84 patients presented in the full reports, and 415 patients presented in the full reports plus abstracts. Of these, 175 patients were enrolled in randomized Phase II studies. Eligibility criteria for inclusion in the studies were generally uniform and consistent with what would be expected from studies of NHL and other B-cell lymphomas.

Most of the trials enrolled subjects who had previously been treated for NHL, representing 84 (100 percent) patients presented in the full reports. Only 49 (12 percent) of patients presented in the full reports plus abstracts were identified as not having had prior treatment for NHL. Patient age across the studies ranged from 21 to 89.

Bortezomib was used as monotherapy in both clinical trials presented in the full reports. The dosages most commonly studied were 1.3 to 1.8 mg/m^2.

Both full reports reported efficacy and adverse event outcomes. Efficacy was evaluated using disease response according to the International Workshop Response Criteria (IWRC) in both studies. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

Study quality of the two full published reports was poor. The reports met only three of five quality criteria; these studies did not have an adequate followup period, and the patients enrolled were not at a similar point in the disease progression.

Efficacy. The range of complete response (CR) rates in the full reports and abstracts was 0 to 90 percent across different NHL subtypes. When only published full reports and only non-mantle cell patients were considered, CR rates ranged from 7 to 14 percent across different NHL subtypes. The range of partial response (PR) rates in the full reports and abstracts was 0 to 90 percent. When only published full reports and only non-mantle cell patients were considered, the PR rates ranged from 7 to 50 percent.

Adverse events. Data in Table A30 were derived from the two clinical trials that were published in full reports (total n = 85 evaluated for adverse events). Thrombocytopenia was the most common adverse event that reached Grade 3 or higher (range, 29 to 49 percent). Thrombocytopenia, granulocytopenia (range, 4 to 15 percent), and fatigue (range, 4 to 15

percent) were reported in both trials. In one study, 58 percent of subjects experienced Grade 3 or higher lymphopenia.

Horizon scan. The horizon scan identified case reports of cardiologic, dermatologic, and neurologic adverse events associated with bortezomib. One report suggested that bortezomib may be associated with beneficial effects when used in combination with doxorubicin and dexamethasone. Another report presented data that suggest that prophylactic antiviral medication may be indicated for patients on bortezomib who are at risk for developing varicella herpes zoster.

Discussion

Although preclinical studies suggest a potential role for proteasome inhibitors in the treatment of hematologic malignancies, the studies identified in this review do not provide sufficient evidence to recommend the use of bortezomib in the treatment of NHL and related diseases. The quality of the uncontrolled Phase II studies was generally poor, and there were no randomized controlled trials that compared bortezomib to alternative therapies. Clinical response was highly variable, with CR and PR rates ranging from 0 to 90 percent. The patient populations represented in the studies were heterogeneous, as were the history of prior treatments and the other interventions used concurrently with bortezomib. Dosing of bortezomib ranged from 1.3 to 1.8 mg/m^2 at intervals ranging from 3 to 10 days.

The ASH 2006, ASH 2007, and ASCO 2007 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. The horizon scan revealed reports of cardiovascular toxicities, including arrhythmias, as well as a potentially higher incidence of varicella herpes zoster among patients being treated with bortezomib.

Further research is needed to determine what role, if any, bortezomib should have in the treatment of NHL, with the exception of mantle cell lymphoma.

Table A27: Bortezomib for Non-Hodgkin Lymphoma – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Goy, Younes, McLaughlin, et al., 2005[161]	**Design:** Prospective cohort, with patients enrolled into 1 of 2 arms (Arm A – Mantle Cell Lymphoma; or Arm B – Other B-Cel Lymphoma) based on histology of tumor **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Age 16 year or older - Relapsed or refractory B-cell NHL - Measurable disease	**No. in study:** 60 Arm A (mantle cell): 33 Arm B (other B-cell lymphomas): 27 **Age (median [range]):** Arm A: 61 (45-78) Arm B: 60 (38-81) **Previous treatment:** Yes (all); median 3 (1–12) **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.5 mg/m^2 on days 1, 4, 8, 11 of a 21-day cycle x 6 cycles **Outcomes sought:** Response according to Cheson criteria	**N:** 60 Arm A = 33 Arm B = 27 **CR (confirmed):** Arm A = 6 (18%) Arm B = 1 (4%) **CRu (unconfirmed):** Arm A = 0 (0%) Arm B = 1 (4%) **PR:** Arm A = 6 (18%) Arm B = 2 (7%) **Stable disease:** Arm A = 6 (18%) Arm B = 6 (22%) **Progressive disease:** Arm A = 11 (33%) Arm B = 11 (41%) **Not assessable:** Arm A = 4 (12%) Arm B = 6 (22%)	**Survival overall (from start of treatment):** **Median survival:** Arm A median f/u 8.5 mo (80% of pts still in response at 6 mo) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A30 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes
O'Connor, Wright, Moskowitz, et al., 2005[160]	**Design:** Prospective cohort, with a Simon two-stage design **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Lymphoma according to	**No. in study:** 26 enrolled (24 assessable = completed 2+ cycles of treatment) **Age:** 63 (44–78) **Previous treatment:** Yes (all) **Stage of disease:** For patients with follicular	**N:** Total: 24 - Follicular: 9 - Mantle cell: 10 - SLL/CLL: 3 - Marginal zone: 2 **CR (confirmed):** Total: 1 - Follicular: 1 - Mantle cell: 0 - SLL/CLL: 0	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** Median response duration: Follicular: 7.5 mo	**Adverse events & tolerability:** See Table A30 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
	WHO/Revised European-American Lymphoma classification - Measurable disease, or > 30% bone marrow lymphocytes - No more than 3 prior lines of conventional cytotoxic treatment - Age 18 years or older	lymphoma: Grade 1: 4/38 (15%) Grade 2: 4/38 (15%) Grade 3: 2/38 (8%) **Drug dose/day [followup]:** Bortezomib 1.5 mg/m^2 on days 1, 4, 8, 11 followed by 1-wk rest period **Outcomes sought:** Response according to Cheson criteria	- Marginal zone: 0 **CRu (unconfirmed):** Total: 2 - Follicular: 1 - Mantle cell: 1 - SLL/CLL: 0 - Marginal zone: 0 **PR:** Total: 11 - Follicular: 5 - Mantle cell: 4 - SLL/CLL: 0 - Marginal zone: 2 **Stable disease:** Total: 7 - Follicular: 1 - Mantle cell: 4 - SLL/CLL: 2 - Marginal zone: 0 **Progressive disease:** Total: 3 - Follicular: 1 - Mantle cell: 1 - SLL/CLL: 1 - Marginal zone: 0	Mantle cell: 7 mo SLL/CLL: N/A Marginal zone: 9.5 mo	

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete response; NHL = non-Hodgkin lymphoma; PR = partial response; SLL = small lymphocytic lymphoma; WHO = World Health Organization.

Table A28: Bortezomib for Non-Hodgkin Lymphoma: ASH 2006, ASH 2007, and ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Blum, Lucas, Johnston, et al., 2006[162] ASH 2006 Abstract #2768	**Disease:** Non-Hodgkin lymphoma **Design:** Single-center, non-randomized **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Follicular or mantle cell, > 1 previous treatments; CrCl > 30 Patients with > grade 2 neuropathy excluded	**No. in study:** 9 **Age:** 66 (55–81) **Previous treatment:** Previous treatment required, but number and type NR **Stage of disease:** Stage IV in 5 patients **Drug dose/day [followup]:** Bortezomib 1.5 mg/m^2 days 1, 4, 8, & 11, q 21 days for 6 cycles; *plus* Rituximab 375 mg/m^2 days 1 & 8. **Outcomes sought:** Toxicity, response	**N:** 7 **CR:** 2 (29%) follicular lymphoma responses, unclear type 3 (43%) PR + CR **PR:** Not reported **Stable disease:** 1 (14%) **Progressive disease:**	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 neuropathy in 5 patients (71%)
De Vos, Dakhil, McLaughlin, et al., 2006[163] ASH 2006 Abstract #694	**Disease:** Non-Hodgkin lymphoma **Design:** Multicenter, non-randomized Arm A = Bortezomib 1.3 mg/m^2 twice wkly Arm B = Bortezomib 1.6 mg/m^2 wkly **Phase:** Phase II **Selection/randomization:** Randomized **Eligibility criteria:** Follicular or marginal zone lymphoma with response >	**No. in study:** 81 **Age:** 64 **Previous treatment:** 45 (56%) had ≥ 2 previous treatments; 66 (81%) had previous CHOP/CVP **Stage of disease:** 38 (47%) Stage IV **Drug dose/day [followup]:** Bortezomib 1.3 mg/m^2 days 1, 4, 8, 11 q 21 days x 5 cycles; *versus* Bortezomib 1.6 mg/m^2 days 1, 8, 15, 22 q 35 days x 3	**N:** Bortezomib 1.3: 41 Bortezomib 1.6: 40 **CR:** Bortezomib 1.3: 4 (10%) Bortezomib 1.6: 1 (3%) **PR:** Bortezomib 1.3: 13 (32%) Bortezomib 1.6: 14 (35%) **Stable disease:** Bortezomib 1.3: 8 (20%) Bortezomib 1.6: 17 (43%) **Progressive disease:** Bortezomib 1.3: 11 (27%)	**Survival overall (from start of treatment):** **Median survival:** Median not reached **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Median not reached **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 or higher ADE in 54% of patients on bortezomib 1.3 mg/m^2 regimen vs. 35% on bortezomib 1.6 mg/m^2 regimen

Study	Study Design	Patients	Tumor Response	Survival	Other
	4 mo to previous rituximab	cycles. Both with rituximab 375 mg/m^2 q wk x 4 cycles. **Outcomes sought:** Response, toxicity	Bortezomib 1.6: 7 (18%)		
Dhillon, Bakkannagari, Ng, et al., 2006[164] ASH 2006 Abstract #2466	**Disease:** Non-Hodgkin lymphoma **Design:** Single-center, non-randomized **Phase:** Phase I **Selection/randomization:** Non-randomized **Eligibility criteria:** Cutaneous T-cell lymphoma	**No. in study:** 7 **Age:** Range 32–73 **Previous treatment:** Median of 6 previous treatments, range 1–6 **Stage of disease:** Stage II: 1 Stage IV: 6 **Drug dose/day [followup]:** Doxorubicin 24 mg/m^2 day 1; *plus* Gemcitabine 800 mg/m^2 days 1 and 8; *plus* Bortezomib 1.0 mg/m^2 days 1, 4, 8, & 11. **Outcomes sought:** Response, toxicity	**N:** 6 **CR:** 0 **PR:** 6 (100%) **Stable disease:** 0 **Progressive disease:** 0	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 4 patients (66%) had to be hospitalized for sepsis, all having advanced disease with ulcerating skin lesions
Gerecitano, Portlock, Noy, et al., 2006[165] ASH 2006 Abstract #2759	**Disease:** Non-Hodgkin lymphoma **Design:** Single-center, non-randomized **Phase:** Phase I **Selection/randomization:** Non-randomized	**No. in study:** 16 **Age:** Not reported **Previous treatment:** R-CVP or R-CHOP in all 9 assessable for disease **Stage of disease:**	**N:** 9 **CR:** Not reported **PR:** 2 (22%) **Stable disease:** 5 (56%) **Progressive disease:** 2	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):**	**Adverse events & tolerability:** Grade 3 or higher ADEs: Lymphopenia = 9 (56%) Neutropenia = 9 (56%) Diarrhea = 1 (6%) Electrolyte loss = 4 (25%)

Study	Study Design	Patients	Tumor Response	Survival	Other
		Not reported	(22%)	**Median survival:**	
	Eligibility criteria:			**1 yr:** NR	
	Not reported	**Drug dose/day [followup]:**		**2 yr:** NR	
		Bortezomib 1.3 to 1.8 mg/m^2, escalating; *plus* Cyclophosphamide (Cytoxan®) 750 to 1000 mg/m^2; *plus* Rituximab 375 mg/m^2; *plus* Prednisone 100 mg.		**3 yr:** NR	
		Outcomes sought: Response, toxicity			
Treon, Soumerai, Patterson, et al., 2006[166] ASH 2006 Abstract #2765	**Disease:** Non-Hodgkin lymphoma	**No. in study:** 10	**N:** 10	**Survival overall (from start of treatment):**	**Adverse events & tolerability:**
		Age:	**CR:**		Grade 3–4 toxicities:
	Design: Single-center, non-randomized	Not reported	5 major response (50%)	**Median survival:**	Sepsis: 1 (10%)
		Previous treatment:	5 minor response (50%)	**1 yr:** NR	Pneumonia: 1 (10%)
	Phase: Phase II	Not reported	**PR:**	**2 yr:** NR	Thrombocytopenia: 1 (10%)
		Stage of disease:	Not reported	**3 yr:** NR	Herpes zoster: 4 (40%)
	Selection/randomization: Non-randomized	Not reported	**Stable disease:** Not reported	**Survival (disease-free):**	
		Drug dose/day [followup]:		**Median survival:**	
	Eligibility criteria: Not reported	Bortezomib 1.3 mg/m^2 days 1, 4, 8, & 11; *plus* Dexamethasone 40 mg days 1, 4, 8, & 11; *plus* Rituximab 375 mg/m^2 day 11.	**Progressive disease:** Not reported	**1 yr:** NR **2 yr:** NR **3 yr:** NR	
		Repeat q 21 days x 4 cycles.			
		Outcomes sought: Response, toxicity			

Study	Study Design	Patients	Tumor Response	Survival	Other
Zinzani, Tani, Musuraca, et al., 2006[167] ASH 2006 Abstract #2462	**Disease:** Non-Hodgkin lymphoma **Design:** Single-center, non-randomized **Phase:** Phase II **Selection/randomization:** **Eligibility criteria:** Cutaneous T-cell lymphoma with ECOG PS < 3, normal organ function	**No. in study:** 15 **Age:** Range 48–80 **Previous treatment:** Previous treatment required, but number and type NR **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.3 mg/m^2 days 1, 4, 8, & 11. Repeat q 21 days. **Outcomes sought:** Response, toxicity	**N:** 12 **CR:** 2 (17%) **PR:** 6 (50%) **Stable disease:** Not reported **Progressive disease:** 4 (33%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 AEs in 5 patients (number of patients with each NR): Neutropenia Thrombocytopenia Neuropathy
Abbadessa, Monaco, Troiano, et al., 2007[168] ASH 2007 Abstract #4477	**Disease:** Non-Hodgkin lymphoma **Design:** Case report **Phase:** Horizon scan **Selection/randomization:** Non-randomized **Eligibility criteria:** Lymphoplasmacytic lymphoma	**No. in study:** 1 **Age:** 59 **Previous treatment:** CHOP, fludarabine, chlorambucil **Stage of disease:** Not reported **Drug dose/day [followup]:** Dexamethasone 20 mg; *plus* Bortezomib 1 mg/m^2 days 1, 4, 8, & 11 x 2 cycles. **Outcomes sought:** Response, toxicity	**N:** 1 **CR:** Not reported **PR:** 1 with resolution of renal failure **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Dose limiting neuropathy after 2 cycles, of planned 6 cycles

Study	Study Design	Patients	Tumor Response	Survival	Other
Agathocleous, Rule, Johnson, et al., 2007[169] ASH 2007 Abstract #2559	**Disease:** Non-Hodgkin lymphoma **Design:** RCT Arm A = Bortezomib 1.3 mg/m^2 twice wkly Arm B = Bortezomib 1.6 mg/m^2 wkly **Phase:** Phase I/II **Selection/randomization:** Randomized **Eligibility criteria:** Recurrent lymphoma	**No. in study:** 45 **Age:** 60 (45–79) **Previous treatment:** Median of 2 (range 1–7) **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.3 mg/m^2 days 1, 4, 8, & 11 q 21 days *plus* Rituximab 375 mg/m^2 day 1 x 8 cycles *versus* Bortezomib 1.6 mg/m^2 days 1, 8, 15, 22 q 35 days *plus* Rituximab days 1, 8, 15, 22 in cycles 1 and 4 x 8 cycles. **Outcomes sought:** Response, toxicity	**N:** 39 **CR:** 15 (38%) in CR, CRu, or PR **PR:** Not reported **Stable disease:** **Progressive disease:** 9 (23%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 2 patients with grade 3 neurotoxicity Grade 3 hematological toxicity: Neutropenia: 25% Thrombocytopenia: 22%
Conconi, Lopez-Guillermo, Martinelli, et al., 2007[170] ASH 2007 Abstract #2580	**Disease:** Non-Hodgkin lymphoma **Design:** Multicenter, non-randomized **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Previously treated MALT lymphoma	**No. in study:** 18 **Age:** 62 (38–77) **Previous treatment:** 1 previous treatment **Stage of disease:** 8 (44%) stage IV **Drug dose/day [followup]:** Bortezomib 1.3 mg/m^2 days 1, 4, 8, & 11 q 21 days up to 6 cycles **Outcomes sought:** Response, toxicity	**N:** 9 **CR:** 3 (33%) **PR:** 4 (44%) **Stable disease:** 2 (22%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 or higher peripheral neuropathy and fatigue (no number or % given)

Study	Study Design	Patients	Tumor Response	Survival	Other
Ghobrial, Padmanabhan, Badros, et al., 2007[171] ASH 2007 Abstract #4494	**Disease:** Non-Hodgkin lymphoma **Design:** Single-center, non-randomized **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** One previous treatment, symptomatic	**No. in study:** 17 **Age:** 62 (43–81) **Previous treatment:** Median 3 previous lines of therapy (range 1–5) **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.6 mg/m^2 days 1, 8, 15 q 28 days x 6 cycles; *plus* Rituximab 375 mg/m^2 days 1, 8, 15, 22 with cycles 1 and 4. **Outcomes sought:** Not reported	**N:** 13 **Min R:** 7 (54%) **CR:** 1 (8%) **PR:** 3 (23%) **Stable disease:** 2 (15%) **Progressive disease:** 0	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Median not reached	**Adverse events & tolerability:** Grade 3 neuropathy: 1after 6 cycles Grade3/4: Neutropenia: 3 Hyponatremia: 1
Jang, Sym, Kim, et al., 2007[172] ASH 2007 Abstract #4446	**Disease:** Non-Hodgkin lymphoma **Design:** Two centers, non-randomized **Phase:** Phase I **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated diffuse large B-cell	**No. in study:** 9 **Age:** Not reported **Previous treatment:** None **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.0, 1.3, and 1.6 mg/m^2 on days 1 & 4; *plus* CHOP chemo. **Outcomes sought:** Response, toxicity	**N:** 9 **CR:** 8 (89%) **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** 1 (11%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 5 pts with grade 3 or higher toxicity

Study	Study Design	Patients	Tumor Response	Survival	Other
Leonard, Furman, Cheung, et al., 2007[173] ASCO 2007 Abstract #8031	**Disease:** Non-Hodgkin lymphoma **Design:** Non-randomized, number of centers unclear **Phase:** Phase I/II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated DLBCL	**No. in study:** 40 **Age:** 58 (21–86) **Previous treatment:** None **Stage of disease:** Stage III/IV: 35 **Drug dose/day [followup]:** CHOP-21; Rituximab 375 mg/m^2; Either bortezomib 0.7 (Arm A), 1.0 (Arm B), or 1.3 (Arm C) mg/m^2 on days 1 & 4 of each cycle **Outcomes sought:** Response, toxicity	**N:** 36 **CR:** 27 (75%) **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 4 died prior to first response Grade 4 hematologic toxicity: Thrombocytopenia: 15% Leukopenia: 15% 5% developed Grade 3 peripheral neuropathy
Mounier, Ribrag, Haioun, et al., 2007[174] ASCO 2007 Abstract #8010	**Disease:** Non-Hodgkin lymphoma **Design:** Randomized, number of centers unclear **Phase:** Phase II **Selection/randomization:** Methods NR, randomization between days 1, 4, 8, & 11 vs. days 1 & 8 bortezomib **Eligibility criteria:** Not reported	**No. in study:** 49 **Age:** 63 (32–76) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** 6 cycles of: R-CHOP21; *plus either* Bortezomib Arm A or B, as follows: 1.0 mg/m^2 (Arm A) and 1.3 mg/m^2 (Arm B) for first 24 patients, then 1.3 mg/m^2 (Arm A) and 1.6 mg/m^2 (Arm B) for next 24 patients. **Outcomes sought:**	**N:** Arm A: 20 Arm B: 28 **CR:** Arm A: 18 (90%) Arm B: 22 (79%) **PR:** Arm A: 1 (5%) Arm B: 4 (14%) **Stable disease:** Arm A: 1 (5%) **Progressive disease:** Arm B: 2 (7%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** 100% **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3/4 neurotoxicity: 10 (20%) Serious ADRs with bortezomib: 6 (12%) Other grade 3–4 toxicities: Constipation: 1 (2%) Infection: 3 (6%) Cardiac events: 2 (4%)

Study	Study Design	Patients	Tumor Response	Survival	Other
		Response, toxicity			
O'Connor, Hamlin, Moskowitz, et al., 2007[175] ASCO 2007 Abstract #8051	**Disease:** Non-Hodgkin lymphoma **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 20 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.8 mg/m^2 weekly x 4-6 wk **Outcomes sought:** Response, toxicity	**N:** 14 **CR:** Not reported **PR:** 2 (14%) **Stable disease:** 8 (57%) **Progressive disease:** 4 (29%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 neuropathy: 1 (5%)

Abbreviations: ADE = adverse drug event; ADR = adverse drug reaction; AE = adverse event; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; chemo = chemotherapy; CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone; CR = complete response; CrCl = creatinine clearance; CRu = complete response unconfirmed; CVP = cyclophosphamide, vincristine, and prednisone; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Collaborative Oncology Group; MALT = mucosa-associated lymphoid tissue; NR = not reported; PR = partial response; PS = performance status; q = every; R = rituximab; RCT = randomized controlled trial.

Table A29: Bortezomib for Non-Hodgkin Lymphoma – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Erico, Gabriele, Nadia, et al., 2007[176]	Case report	1.3 mg/m^2 on days 1, 4, 8, and 11; recycling period was 3 wk	69 (8 with cardio-toxicity)	Report of 8/69 pts (2 with NHL, 6 with MM) who had bortezomib-related cardiotoxic effects. These included HF, angina, bradycardia, AV block, and AF. Authors state that bortezomib may cause atherosclerotic plaque progression and tendency to rupture, as well as facilitate ischemic heart complications. They hypothesize that these and other combined mechanisms may lead to cardiac complications in bortezomib-treated pts.
Gerecitano, Goy, Wright, et al., 2006[177]	Case series		26	This article described pts who developed a rash after treatment with bortezomib for NHL.
Mai, Meng, Jin, et al., 2006[178]	Case report	1.3 mg/m^2	1	38 y/o male with refractory T-cell lymphoblastic lymphoma. Pt initially treated with 2 cycles of CHOP, followed by 4 cycles of MINE after failure to respond to CHOP. Achieved 2 mo CR. After additional treatment without response, pt was started on bortezomib on days 1 and 4, dexamethasone (10 mg) on days 1-4, and doxorubicin (20 mg) on days 1 and 8. Treatment was well tolerated without severe AEs. 3 mo post-treatment, the pt continues in PR. Author states that these data suggest a possible synergistic effect with bortezomib in combination with doxorubicin and dexamethasone.
Stubblefield, Slovin, MacGregor-Cortelli, et al., 2006[179]	Case series		4	This article described pts who developed neuropathy after treatment with bortezomib for NHL or prostate cancer.
Tong, Qian, Li, et al., 2007[180]		1.3 mg/m^2	10 (7 were multiple myeloma, 1 AML, and 2 lymphoma)	All pts received bortezomib on days 1, 4, 8, and 11 of a 3-wk cycle. Pts with MM received dexamethasone (40 mg) on days 1-2, 4-5, 8-9, and 11-12 simultaneously. The combination with liposomal doxorubicin was used in 2 pts with lymphoma. Pts with acute myeloblastic leukemia received bortezomib in combination with amsacrine. This report is about VZV infections in pts receiving bortezomib. Authors suggest prophylactic antiviral medication be used in predisposed pts to reduce the incidence of varicella herpes zoster.

Abbreviations: AE(s) = adverse event(s); AF = atrial fibrillation; AML = acute myelocytic leukemia; AV = atrioventricular; CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone; CR = complete response; HF = heart failure; MCL = mantle cell lymphoma; MINE = mesna, ifosfamide, mitoxantrone, and etoposide; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; PR = partial response; VZV = varicella zoster virus; y/o = year-old.

Table A30.1: Bortezomib for Non-Hodgkin Lymphoma – Adverse Events (Grade 3/4+ Events Only) – Part 1

Article	Anemia	Leukopenia	Lymphopenia	Neutropenia/ granulocytopenia	Thrombocytopenia	Diarrhea	Nausea/vomiting	Constipation	Dermatitis or rash	Fatigue	Pain	Anorexia	Dizziness	Dyspnea	Myalgia or musculoskeletal pain
Goy et al., 2005[161]	-	-	-	15%	49%	3%	10%	2%	-	15%	-	3%	5%	2%	5%
O'Connor et al, 2005[160]	4%	4%	58%	4%	27%	0%	4%	4%	-	4%	-	4%	-	-	-

Table A30.2: Bortezomib for Non-Hodgkin Lymphoma – Adverse Events (Grade 3/4+ Events Only) – Part 2

Article	Infection	CHF	Hyponatremia	Neuropathy-sensory	Peripheral neuropathy	Neuropathic pain	Small bowel obstruction	Hypotension	Syncope	Hypoxia	Necrotizing vasculitis	AST/ALT elevation	Alkaline phosphatase	Potassium abnormality	Leg edema	Other
Goy et al., 2005[161]	3%	-	-	5%	-	-	3%	3%	2%	2%	3%	-	-	-	-	3%
O'Connor et al, 2005[160]	8%	-	13%	8%	-	-	-	-	-	-	-	4%	4%	12%	-	8%

Abbreviations: AST/ALT = aspartate aminotransferase/alanine transaminase; CHF = congestive heart failure.

Cetuximab for Pancreatic Adenocarcinoma

Background

Drug: Cetuximab (Erbitux®). Cetuximab is a recombinant, chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR), which is overexpressed on the cell surfaces of various solid tumors, and thus competitively inhibits its binding. It thereby prevents the activation and subsequent dimerization of the receptor, which may result in an inhibition in signal transduction and lead to anti-proliferative effects. Cetuximab is composed of the Fv regions of a murine anti-EGFR antibody with human IgG1 heavy and kappa light chain constant regions.

In February 2004, under accelerated approval regulations, cetuximab was approved for use, in combination with irinotecan, in the treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. It was also approved for use as a single agent for the treatment of EGFR-expressing, recurrent metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy. In October 2007, the Food and Drug Administration (FDA) expanded its labeling and granted regular approval for single-agent cetuximab for the treatment of EGFR-expressing metastatic colorectal cancer after failure of both irinotecan- and oxaliplatin-based regimens. In March 2008, the FDA granted approval to cetuximab for use in combination with radiation therapy for the initial treatment of locally or regionally advanced squamous cell carcinoma of the head and neck, or as a single agent for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck for whom prior platinum-based therapy has failed. It has been evaluated for off-label use in pancreatic adenocarcinoma.

Disease: Pancreatic adenocarcinoma. Pancreatic adenocarcinoma is a deadly disease that can affect both the exocrine and endocrine portions of the pancreas, although 95 percent of pancreatic tumors develop in the exocrine portion, including the ductal epithelium, acinar cells, connective tissue, and lymphatic tissue.[123,124] In the United States, the annual overall incidence is 8 to10 cases per 100,000 persons, with more than 35,000 new cases diagnosed each year and an almost identical number of deaths,[35] due to the aggressiveness of the disease and the inherent difficulties of early diagnosis. There has been a marked increase in the incidence of pancreatic cancer during the last few decades, and it is currently the fourth leading cause of death from cancer in the United States.[123]

Its prognosis is dismal, with an average median survival of 4 to 6 months and an overall 5-year survival rate of less than 4 percent. Patients with endocrine and cystic neoplasms fare better, but even among those who undergo successful curative resection, the median survival improves to only 12–19 months, with 15–20 percent 5-year survival rate.[123,124] Pancreaticoduodenectomy remains the only therapy that definitively improves survival. However, it is indicated only for patients with tumors affecting the head of the pancreas, and the procedure itself has been associated with significant mortality and morbidity. For patients with unresectable disease, palliative therapies are indicated.[124]

Although chronic inflammation and hereditary factors are common predisposing factors, the cause of pancreatic cancer is heterogeneous and remains elusive.[35,124] However, its underlying genetic and molecular abnormalities have been well documented, which may help clarify causality and improve strategies for screening and treatment. Research suggests that alterations to oncogenes, tumor suppressor genes, and the expression of regulatory proteins play a critical

role in the development of pancreatic cancer. In addition, a number of molecular determinants, including the EGFR, are expressed at higher levels in pancreatic cancer and may contribute to metastatic disease and induce resistance to current cytotoxic therapies.[125-127,181]

Drug/Disease: Cetuximab for pancreatic adenocarcinoma. Over the past few years, clinical research initiatives searching to improve the efficacy of pancreatic cancer therapies have targeted novel agents for augmenting responsiveness to radiotherapy and chemotherapy. Given the positive correlation of EGFR expression and cellular resistance to radiation,[182] along with the overexpression of EGFR that is associated with pancreatic adenocarcinoma,[183] cetuximab, as an EGFR inhibitor, has been the subject of considerable interest as an adjuvant therapy for patients with this cancer.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded a total of nine reports, one of which was a full report of a non-randomized Phase II clinical trial (Table A31), six were published abstracts from the American Society of Clinical Oncology (ASCO) conference (Table A32), and two were additional articles considered in the horizon scan (Table A33). Among the abstracts were two randomized Phase II trials, two non-randomized Phase II trials, one Phase I trial, and one retrospective review. The horizon scan articles included a review of adverse events associated with cetuximab, as well as a summary of treatment options for pancreatic cancer.

The fully published report was of a Phase II trial involving 41 patients with previously untreated advanced disease who received an initial dose of 400 mg/m2 of cetuximab followed by 250 mg/m2 weekly along with gemcitabine 1000 mg/m2. The partial response (PR) rate was 12 percent, with 26/41 patients (63 percent) with stable disease and 6/41 (15 percent) with progressive disease. There were no complete responses (CR). Outcomes were not assessable for 4/41 patients (10 percent).

Sample sizes for the seven trials (including the retrospective review) ranged from 20 to 92, with a total of 383 patients. Of these, a combined 166 patients presented were enrolled in the two randomized studies. Eligibility criteria for inclusion in the studies were generally uniform, and consistent with what would be expected from studies of pancreatic cancer. Most of the trials enrolled subjects whose advanced disease had not previously been treated. All of the studies involved only adults, with patient age ranging from 33 to 79 among the studies that reported age. Cetuximab was used in combination with other therapies, including oxaliplatin, gemcitabine, bortezomib, docetaxel, irinotecan, or radiation therapy. The dose of cetuximab studied was usually 400 mg/m2 as a loading dose followed by weekly administrations of 250 mg/m2.

Efficacy was reported in each of the seven studies represented in the full reports plus abstracts. The quality of the single full-published report was very good, with all five quality criteria having been met.

Efficacy. A CR was reported in only a single patient among the fully published report and abstracts combined. The PR range was 12 percent to 35 percent when considering the fully

published report and the abstracts. In both randomized phase II trials, the PR among patients who received cetuximab was 16 percent, compared to 8 percent among those randomized to an arm that did not include cetuximab.

Survival. In the fully published report, the median survival duration was 7.1 months, 1-year progression-free survival was 12 percent, and median time to disease progression was 3.8 months.

Adverse events. Acneiform rash was reported in 34/36 patients (94 percent) in one abstract (Table A34). Grade 3 or 4 neutropenia or granulocytopenia was reported in 16/41 (39 percent) of patients included in the fully published report.

Discussion

Results from the clinical trials published as abstracts demonstate that the use of cetuximab as an adjunct in the treatment of pancreatic adenocarcinoma is associated with an increase in partial response from 8 percent to 16 percent. Only a single subject who received cetuximab had a complete response. Further research is needed to evaluate the efficacy and safety of cetuximab for patients with this cancer.

Table A31: Cetuximab for Pancreatic Adenocarcinoma – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Xiong, Rosenberg, LoBuglio, et al., 2004[184]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization**: N/A **Eligibility criteria:** Measurable disease and evidence of EGFR expression	**No. in study:** 41 **Age**: NR **Previous treatment:** No previous treatment for advanced disease **Stage of disease**: NR **Drug dose/day [followup]:** 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly; Also gemcitabine 1000 mg/m^2 for 7 wks, then weekly **Outcomes sought:** WHO response criteria	**N**: 41 (37 assessable) **CR**: 0 **PR**: 5 (14%) **Stable disease:** 26 (70%) **Progressive disease:** 6 (16%)	**Survival overall (from start of treatment):** **Median survival:** median survival duration 7.1 mos; 1-yr PFS 12% **1 yr**: 32% **2 yr**: NR **3 yr**: NR **Survival (disease-free):** **Median survival:** Median time to disease progression 3.8 mos **1 yr**: NR **2 yr**: NR **3 yr**: NR	**Adverse events & tolerability:** See Table A34 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes

Abbreviations: CR = complete response; EGFR = epidermal growth factor receptor; NR = not reported; PFS = progression-free survival; PR = partial response; WHO = World Health Organization.

Table A32: Cetuximab for Pancreatic Adenocarcinoma - ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Burtness, Powell, Berlin, et al., 2007[185] ASCO 2007 Abstract #4519	**Disease:** Pancreatic cancer **Design:** Prospective, multicenter, randomized **Phase:** Phase II **Selection/randomization:** Randomized **Eligibility criteria:** Metastatic pancreatic cancer, ECOG PS 0–1, normal bilirubin	**No. in study:** 92 (Arm A, 47; Arm B, 45) **Age:** Arm A, 59.9; Arm B, 60.2 **Previous treatment:** Not reported **Stage of disease:** Stage IV **Drug dose/day [followup]:** Arm A: Docetaxel 35 mg/m^2 *plus* irinotecan 35 mg/m^2 q wk x 4 in 6 wk cycle Arm B: Same as A, but addition of cetuximab 400 mg/m^2 load then 250 mg/m^2 weekly **Outcomes sought:** Response	**N:** Not reported **CR:** Not reported **PR:** Arm A (no cetuximab): 3 (88%) Arm B (cetuximab): 6 (16%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Arm A: 6.5 mo Arm B: 7.4 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 or higher: Nausea: Arm A, 28%; Arm B, 18% Neutropenia: Arm A, 26%; Arm B, 33% Diarrhea: Arm A, 33%; Arm B, 44% 1 treatment-related death per arm (no cause given)
Cascinu, Berardi, Siena, et al., 2007[186] ASCO 2007 Abstract #4544	**Disease:** Pancreatic cancer **Design:** Prospective, multicenter, randomized **Phase:** Phase II **Selection/randomization:** Randomized **Eligibility criteria:** Advanced pancreatic	**No. in study:** 74 (Arm A, 37; Arm B, 37) **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:**	**N:** Arm A (no cetuximab) : 37 Arm B (cetuximab): 37 **CR:** 0 **PR:** Arm A: 3 (8%) Arm B: 6 (16%) **Stable disease:** Arm A: 22 (59%) Arm B: 17 (46%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Median TTP 5 mo in both arms	**Adverse events & tolerability:** Grade 3 to 4 toxicities: Arm A: 31% Arm B: 29%

Study	Study Design	Patients	Tumor Response	Survival	Other
	cancer	Arm A: Gemcitabine 1000 mg/m^2 days 1and 8 q 21 days *plus* cisplatin 35 mg/m^2 days 1 and 8 q 21 days Arm B: Same as A, but addition of cetuximab 400 mg/m^2 load then 250 mg/m^2 weekly **Outcomes sought:** Response	**Progressive disease:** Not reported	**1 yr:** NR **2 yr:** NR **3 yr:** NR	
Dudek, Gada, Mulamalla, et al., 2007[187] ASCO 2007 Abstract #18143	**Disease:** Pancreatic and other cancers **Design:** Prospective, number of centers unclear, non-randomized **Phase:** Phase I, dose escalation **Selection/randomization:** Non-randomized **Eligibility criteria:** EGFR expressing epithelial tumor	**No. in study:** 20 **Age:** 59.5 (41–68) **Previous treatment:** All patients pre-treated, variety of regimens **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.3 mg/m^2, increasing in 0.1 mg/m^2 increments to 2.0 mg/m^2, administered days 1 and 8, with concurrent cetuximab 400 mg/m^2 load followed by weekly 250 mg/m^2 **Outcomes sought:** Toxicity	**N:** 20 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** 13 (65%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3–4 toxicity seen in 14/20 patients after first cycle of chemo, but dose limiting toxicity not reached at doses up to bortezomib 1.8 mg/m^2 weekly Grade 3 nausea, vomiting, and dysphagia **Comments:** Authors note little anti-tumor activity

Study	Study Design	Patients	Tumor Response	Survival	Other
Krempien, Munter, Timke, et al., 2007[188] ASCO 2007 Abstract #4573	**Disease:** Pancreatic cancer **Design:** Prospective, number of centers unclear, non-randomized **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Locally advanced pancreatic cancer, no prior therapy	**No. in study:** 55 **Age:** 61.5 (48–79) **Previous treatment:** None **Stage of disease:** Stage III **Drug dose/day [followup]:** Radiation therapy 54 Gy, *plus* gemcitabine 300 mg/m^2 q wk x 3 in 4 wk, *plus* cetuximab 400 mg/m^2 load day 1, then 250 mg/m^2 with radiation therapy **Outcomes sought:** Response, toxicity	**N:** 36 **CR:** 0 **PR:** 12 (33%) **Stable disease:** 20 (56%) **Progressive disease:** 4 (11%)	**Survival overall (from start of treatment):** **Median survival:** Not reached **1 yr:** 57% **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 22 patients had some toxicity Acneiform rash: 34 (94%) Diarrhea: 5 (14%) Neutropenia: 10 (28%) Thrombocytopenia: 4 (11%) Vomiting: 4 (11%) 1 patient died of tumor hemorrhage
Kullman, Hollerbach, Dollinger, et al., 2007[189]	**Disease:** Pancreatic cancer **Design:** Prospective, non-randomized **Phase:** II **Selection/randomization:** Non-randomized **Eligibility criteria:** Metastatic pancreatic cancer	**No. in study:** 64 **Age:** 65 (33–75) **Previous treatment:** Yes (all but 4 pts) **Stage of disease:** Stage IV **Drug dose/day [followup]:** Cetux 400 mg/m2 initial dose, then 250 mg/m2 weekly, plus Oxaliplatin 100 mg/m^2, *plus* gemcitabine 1000 mg/m2. **Outcomes sought:** Overall survival	**N:** 34 evaluable **CR:** 1/34 (3%) **PR:** 12/34 (35%) **Stable disease:** 8/34 (44%) **Progressive disease:** 13/34 (38%)	**Survival overall (from start of treatment):** Preliminary 6-month survival 54%. **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported

Study	Study Design	Patients	Tumor Response	Survival	Other
Lee, Roach, Duong, et al., 2007[190] ASCO 2007 Abstract #15180	**Disease:** Pancreatic cancer **Design:** Retrospective review **Phase:** N/A **Selection/randomization:** Non-randomized **Eligibility criteria:** Metastatic pancreatic cancer	**No. in study:** 37 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Stage IV **Drug dose/day [followup]:** OIC = Oxaliplatin 60 mg/m^2, *plus* irinotecan 90 mg/m^2, *plus* cetuximab 250 mg/m^2 q 2 wks *versus* Historic control (gemcitabine or fluoropyrimidine) **Outcomes sought:** Overall survival	**N:** 11 OIC 26 Control **CR:** 50% overall response to OIC reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** OIC: 10 mo Control: 5 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported

Abbreviations: chemo = chemotherapy; CR = complete response; ECOG = Eastern Collaborative Oncology Group; EGFR = epidermal growth factor receptor; OIC = oxaliplatin, irinotecan, and cetuximab; PR = partial response; PS = performance status; q = every; TTP = time to tumor progression.

Table A33: Cetuximab for Pancreatic Adenocarcinoma - Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Needle, 2002[191]	Toxicity report from a Phase II study	Loading dose of 400 mg/m2 followed by a weekly maintenance dose of 250 mg/m2. Gemcitabine 1000 mg/m2 was started 1 hour after completion of the cetuximab infusion; administered weekly for 7 weeks.	41	Most pts experienced grade 3 or 4 toxicities, with the most common being leucopenia (35%), asthenia (20%), thrombocytopenia (18%) and abdominal pain (18%). Overall, the most commonly reported AEs were acne-like rash (85%), asthenia (83%), nausea (63%), and weight loss (58%). Author states combination of cetuximab with gemcitabine appears tolerable in patients with advanced pancreatic cancer.
Saif, 2007[131]	Report to the 2007 Gastro-intestinal Cancers Symposium	400 mg/m^2 initially, followed by weekly 250 mg/m^2 combined with gemcitabine 1000 mg/m^2 as a 100-minute infusion on day 1 and oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 2 every 2 weeks	64	The addition of cetuximab to the combination of gemcitabine and oxaliplatin exhibited a high response rate of 38%, with a 54% 6-mo survival. The regimen was well-tolerated. Author states further evaluation in a Phase III trial was warranted.

Abbreviation: AEs = adverse events.

Table A34: Cetuximab for Pancreatic Adenocarcinoma (Grade 3/4+ Events Only) - Adverse Events

Study	Tumor hemorrhage	Anemia	Neutropenia/ granulocytopenia	Leukopenia	Thrombocytopenia	Diarrhea	Nausea	Vomiting	Abdominal pain	Dermatitis or rash	Pain	Anorexia	Infection	Allergy	Asthenia
Xiong et al., 2004[184]	10%	12%	39%	-	17%	5%	12%	12%	22%	-	7%	7%	7%	-	22%

Study	Dehydration	Potassium abnormality	Weight loss	Hypotension	Hypertension	Pneumonia	CV disorder	Sepsis	Ileus	Intestinal obstruction	Cholangitis	Cachexia	Pulmonary embolism	Edema/effusion	Thrombosis
Xiong et al., 2004[184]	12%	-	7%	5%	2%	2%	2%	10%	7%	7%	5%	2%	5%	12%	2%

Abbreviation: CV = cardiovascular.

Erlotinib for Head and Neck Squamous Cell Carcinoma

Background

Drug: Erlotinib (Tarceva®). Erlotinib is the hydrochloride salt of a quinazoline derivative with antineoplastic properties. Although the mechanism of the clinical antitumor action of erlotinib is not fully characterized, it is known to reversibly bind to the intracellular catalytic domain of epidermal growth factor receptor (EGFR) tyrosine kinase, thereby reversibly inhibiting EGFR phosphorylation and blocking the signal transduction events and tumorigenic effects associated with EGFR activation.

In November 2004, the Food and Drug Administration (FDA) granted approval for the use of erlotinib hydrochloride for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. In November 2005, erlotinib received FDA approval for use, in combination with gemcitabine, for the first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer. It has been evaluated for off-label use in head and neck squamous cell carcinoma (HNSCC).

Disease: Head and neck squamous cell carcinoma (HNSCC). The term "head and neck cancer" encompasses a group of biologically similar cancers of the upper aerodigestive tract, the vast majority of which are squamous cell carcinomas. Usually presenting as surface lesions with erythema and slight elevation (erythroplasia), squamous cell carcinomas most often appear on the floor of the mouth, the tongue, the soft palate, the anterior pillar of the tonsils, and the retromolar trigone.[192]

Accounting for 3 to 5 percent of all malignancies in the United States, head and neck cancers typically affect people over the age of 50.[193] Estimates predicted that more than 48,000 persons would develop head and neck cancer in 2005, and that more than 11,000 would die of the disease.[194] Fully 85 percent of head and neck cancers are linked to tobacco use,[193] and concomitant alcohol use may have synergistic neoplastic influence.[195]

Prognosis varies according to tumor location and stage. Although primary HNSCC exhibits a 60 percent 5-year survival rate, a significant number of HNSCC patients develop second primary tumors as a result of the same carcinogenic exposures; the 5-year survival among such patients drops to 25 percent.[196] Furthermore, despite high cure rates among patients diagnosed with early stages of the disease, nearly 50 percent of HNSCC patients are diagnosed only after the disease has progressed.[197] In addition to shortened survival, those patients who do experience complete remission and those undergoing radical curative surgery face serious quality-of-life issues due to significant functional deficits.[192,193]

The treatment plan pursued is contingent on, among other things, tumor location, cancer stage, and the individual's age and overall health. When the patient presents with small primary cancer without regional metastases, radiotherapy or wide surgical resection may be used alone, with both treatments appearing to be equally curative. For patients with regional metastases or recurrent disease, combination radiation and surgical excision remains the standard of care, although chemotherapy may be used as well.[192,193]

Drug/Disease: Erlotinib for HNSCC. HNSCC is characterized by the overexpression of EGFR, where EGFR levels correlate to survival.[198] Over the past few years, clinical research initiatives seeking to develop more tolerable therapies, as well as to improve survival and quality of life among HNSCC patients, have investigated treatments that specifically interrupt the autocrine pathways of growth factor receptors, like EGFR, which are associated with adverse

cancer outcomes.[196] As an EGFR inhibitor, erlotinib has generated considerable interest as a novel therapeutic agent for patients with this cancer,[199] but early research has shown mixed results.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

The search strategy yielded at total of six reports, two of which were full reports of clinical trials (Table A35), and four of which were published abstracts from the American Society of Clinical Oncology (ASCO) 2007 conference (Table A36). All were non-randomized Phase I/II clinical trials. One was published in 2004 and three were published in 2007. Sample sizes ranged from seven to 115, with a total of 299 patients presented in the full reports plus abstracts.

The full report published in 2004 enrolled 115 patients with recurrent or metastatic HNSCC. Prior treatment had to have been completed at least 6 months before study entry. Ninety-seven percent of patients had previously undergone radiotherapy, 94 percent had undergone surgery, 37 percent had undergone induction chemotherapy, and 35 percent had had palliative chemotherapy. Median age was 62 (range, 27 to 80). Erlotinib was given as monotherapy at the dosage of 150 mg per day. No patients demonstrated a complete response (CR), 4 percent had a partial response (PR), 38 percent had stable disease (SD), and 47 percent had progressive disease (PD). Median overall survival was 6 months, and 1-year probability of overall survival was 20 percent. The most commonly reported Grade 3/4 adverse event was dermatitis (11 percent; Table A37). All five quality criteria were met for this study.

The second full report, published in 2007, was conducted by some of the same authors as the report summarized above. Eligibility criteria were similar in the two studies. Sample size was 51. Median age was 56 (range, 24 to 81). Three treatment regimens were compared: (1) erlotinib 100 mg orally daily plus cisplatin 75 mg/m^2 intravenously every 3 weeks; (2) erlotinib 150 mg orally daily plus cisplatin 75 mg/m^2 intravenously every 3 weeks; and (3) erlotinib 150 mg orally daily plus cisplatin 100 mg/m^2 every 3 weeks. Of the 43 evaluable patients, 1 (3 percent) had a CR, 8 (19 percent) had a PR, 21 (49 percent) had SD, and 9 (21 percent) had PD. Median overall survival and disease-free survival were 7.9 and 3.3 months, respectively. The most commonly reported Grade 3/4 adverse events were fatigue (3 percent) and lymphopenia (3 percent; Table A37). All five quality criteria were met for this study.

Sample sizes among the four abstracts ranged from seven to 48, with a total of 133 patients. Eligibility criteria for inclusion in the studies were not well described. Erlotinib was used in combination with chemotherapeutic agents in all four studies. Other agents used included cisplatin, docetaxel, and bevacizumab. CR and PR rates, respectively, were 84 percent and 8 percent in one study, and 9 percent and 58 percent in the other study that reported these outcomes. Median overall survival was 7.3 months in one of the studies that did not report response rates. Grade 3/4 adverse events included mucositis, sepsis, febrile neutropenia, dehydration, diarrhea, and gastrointestinal bleed.

Discussion

The overexpression of EGFR in 80 percent to 100 percent of HNSCC makes erlotinib a logical targeted therapy for HNSCC.[200] The two full reports and the four abstracts in this review provide emerging evidence for the role of erlotinib in the treatment of patients with HNSCC. Historically, single and combination chemotherapies for advanced disease have had low response rates and short median survivals. In Phase II reports, erlotinib compares favorably to existing treatment options.

This review identified two published Phase II reports suggesting some efficacy, with partial response and stable disease rates of 19 percent and 49 percent, respectively, in one of the studies. Complete response rates were highly variable across the six studies, ranging from 0 percent to 84 percent. There was a relatively low rate of toxicities reported in the two full reports, with dermatitis being the most commonly reported adverse event. The reports identified in this review did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates.

Table A35: Erlotinib for Head and Neck Squamous Cell Cancers – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Siu, Soulieres, Chen, et al., 2007[201]	**Design:** Not reported **Phase:** Phase I/II **Selection/ randomization:** Not reported **Eligibility criteria:** - Histologically or cytologically confirmed diagnosis of recurrent or metastatic HNSCC - May have had prior induction or concurrent chemotherapy delivered as part of their primary treatment but must have completed primary treatment at least 6 mo before study entry - Archival or fresh tumor specimens available and assessable for determination of expression of EGFR by immunohistochemistry. - Age ≥ 18 yr - ECOG 0–2 - Ability to swallow or PEG tube in place - Measurable disease - Adequate hematological, hepatic, and renal function - No prior treatment w/ EGFR agents	**No. in study:** 51 **Age:** 56 (24–81) **Previous treatment:** Surgery: 64% Radiotherapy: 75% Chemotherapy: 18% **Stage of disease:** Recurrent or metastatic **Drug dose/day [followup]:** Phase I: 3 dose levels were evaluated: Erlotinib 100 mg PO daily and cisplatin 75 mg/m^2 IV q 3 wk; Erlotinib 150 mg PO daily and cisplatin 75 mg/m^2 IV q 3 wk; Erlotinib 150 mg PO daily and cisplatin 100 mg/m^2 IV q 3 wk. Phase II: Erlotinib 100 mg PO daily and cisplatin 75 mg/m^2 IV q 3 wk. **Outcomes sought:** Primary objective of phase I: Determine the recommended phase II dose (RPTD). Primary objective of phase II: Elucidate the efficacy	**N:** 43 of 51 accessible **CR:** 1 of 43 (3%) **PR:** 8 of 43 (19%) **Stable disease:** 21 of 43 (49%) **Progressive disease:** 9 of 43 (21%)	**Survival overall (from start of treatment):** **Median survival:** 7.9 mo **1 yr:** 19.5% **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 3.3 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A37 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
		and toxicity of the combination of erlotinib and cisplatin in recurrent or metastatic HNSCC. Secondary objectives included measurements of SD rates, duration of responses, PFS, OS, pharmacokinetic profile of erlotinib administered with cisplatin, and pharmacodynamic effects of erlotinib in tumor and skin samples (reported in separate article).			
Soulieres, Senzer, Vokes, et al., 2004[202]	**Design:** Multicenter, unblended, single arm **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Histologically or cytologically confirmed diagnosis of recurrent or metastatic HNSCC - May have had prior induction or concurrent chemotherapy delivered as part of their primary treatment but must have completed primary treatment at least 6 mo before study entry - Archival or fresh tumor specimens available and assessable for determination of expression of EGFR by	**No. in study:** 115 **Age:** 62 (27–80) **Previous treatment:** Surgery: 94% Radiotherapy: 97% Chemotherapy (induction): 37% Chemotherapy (palliation): 35% **Stage of disease:** Recurrent or metastatic **Drug dose/day [followup]:** Erlotinib 150 mg per day **Outcomes sought:** Primary: Determine the efficacy of erlotinib administered as a single agent in pts w/ recurrent and/or metastatic HNSCC Secondary: (1) Measure	**N:** 115 **CR:** 0 (0%) **PR:** 5 (4.3%) **Stable disease:** 44 (38.3%) for median duration of 16.1 wk **Progressive disease:** 54 (47%)	**Survival overall (from start of treatment):** **Median survival:** 6 mo **1 yr:** 20% (95% CI 13-28%) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 9.6 wk (95% CI 8.1–12.1 wk) **1 yr:** 0.9% **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A37 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
	immunohistochemistry - Age ≥ 18 - ECOG 0–2 - Ability to swallow or PEG tube in place - Measurable disease - Adequate hematological, hepatic, and renal function - Not pregnant or lactating - No prior treatment w/ EGFR agents - No abnormalities of the cornea (based on history and slit lamp exam)	SD rates, duration of responses, PFS and OS; (2) characterize the safety and pharmacokinetic profiles of erlotinib administered daily in this population			

Abbreviations: CI = confidence interval; CR = complete response; ECOG = Eastern Collaborative Oncology Group; EGFR = epidermal growth factor receptor; HNSCC = head and neck squamous cell cancers; IV = intravenous; OS = overall survival; PEG = percutaneous endoscopic gastrostomy; PFS = progression-free survival; PO = orally; PR = partial response; q = every; RPTD = recommended phase two dose; SD = stable disease.

Table A36: Erlotinib for Head and Neck Squamous Cell Cancers – ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Arias de la Vega, Herruzo, de las Heras, et al., 2007[203] ASCO 2007 Abstract #16544	**Disease:** Head and neck cancer **Design:** Prospective **Phase:** Phase I **Selection/randomization:** Non-randomized **Eligibility criteria:** Surgically resected locally advanced HNSCC, T3 or T4 primary lesion, N2 or N3 disease, poor prognostic features; age 18–70, no metastatic disease	**No. in study:** 7 **Age:** 52 **Previous treatment:** Surgery **Stage of disease:** Stage III or higher **Drug dose/day [followup]:** Erlotinib 100–150 mg daily; *plus* Cisplatin 30–40 mg/m^2 IV day 1, XRT 1.8 Gy/day to 63 Gy over 7 wks **Outcomes sought:** Toxicity	**N:** 4 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 mucositis: 1
Herschenhorn, Dias, Pineda, et al., 2007[204] ASCO 2007 Abstract #6033	**Disease:** Head and neck cancer **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Stage III or IV disease	**No. in study:** 31 **Age:** 55 (35–73) **Previous treatment:** None **Stage of disease:** Stage III or higher **Drug dose/day [followup]:** Cisplatin 100 mg/m^2 day 8 q 21 days x 3 cycles; *plus* Erlotinib 150 mg day 1 and continuing until end of RT q day; *plus*	**N:** 25 **CR:** 21 (84%) **PR:** 2 (8%) **Stable disease:** Not reported **Progressive disease:** 1 (4%)	**Survival overall (from start of treatment):** **Median survival:** Not Reached **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** - 5 pts with local relapse - 19 disease free - 2 alive with disease - 3 died of disease progression at 10.8 mo	**Adverse events & tolerability:** 1 treatment-related death due to sepsis Other Grade 3/4 toxicities: Radiation dermatitis: 14 Nausea: 13 Mucositis: 9 Emesis: 8 Rash: 7 Fatigue: 7 Dysphagia: 6 Respiratory infection: 4 Neutropenia: 1 Cutaneous infection: 3

Study	Study Design	Patients	Tumor Response	Survival	Other
		XRT 70.2 Gy in 8 wk. **Outcomes sought:** Response, toxicity		median followup **1 yr:** NR **2 yr:** NR **3 yr:** NR	21 (84%) required enteral feeding
Kim, Kies, Glisson, et al., 2007[205] ASCO 2007 Abstract #6013	**Disease:** Head and neck cancer **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Recurrent or metastatic HNSCC, measurable disease, no previous EGFR therapy	**No. in study:** 47 **Age:** 56 (39–72) **Previous treatment**: May have received induction or adjuvant, no treatment for recurrent disease **Stage of disease:** Not reported **Drug dose/day [followup]:** Docetaxel 75 mg/m^2 IV q 3 wk; *plus* Cisplatin 75 mg/m^2 IV q 3 wk; *plus* Erlotinib 150 mg daily. **Outcomes sought:** Response, OS, PFS, toxicity	**N:** 43 **CR:** 4 (9%) **PR:** 25 (58%) **Stable disease:** 12 (28%) **Progressive disease:** 2 (5%)	**Survival overall (from start of treatment):** **Median survival:** 11 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 6 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3/4 toxicities: Febrile neutropenia: 6 Dehydration: 4 Diarrhea: 3 GI bleed: 2
Seiwert, Davis, Yan, et al., 2007[206] ASCO 2007 Abstract #6021	**Disease:** Head and neck cancer **Design:** Prospective cohort **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:**	**No. in study:** 48 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported	**N:** Not reported **CR:** Not reported **PR:** Not reported **Stable disease:**	**Survival overall (from start of treatment):** **Median survival:** 7.3 mo **1 yr:** At 6 mo, 30.6% **2 yr:** NR **3 yr:** NR **Survival (disease-free):**	**Adverse events & tolerability:** Not reported

Study	Study Design	Patients	Tumor Response	Survival	Other
	Recurrent or metastatic HNSCC	**Drug dose/day [followup]:** Erlotinib 150 mg q day; plus Bevacizumab escalated to maximum 15 mg/kg q 3 wk and continued at max dose in phase 2 portion. Bevacizumab was given on day 1 or day 15. **Outcomes sought:** Not reported	Not reported **Progressive disease:** Not reported	**Median survival:** 3.9 mo **1 yr:** At 6 mo, 8.2% **2 yr:** NR **3 yr:** NR	

Abbreviations: ASCO = American Society of Clinical Oncology; CR = complete response; EGFR = epidermal growth factor receptor; GI = gastrointestinal; HNSCC = head and neck squamous cell cancer; IV = intravenous; OS = overall survival; PFS = progression-free survival; PR = partial response; q = every; RT = radiation therapy; XRT = x-ray therapy.

Table A37: Erlotinib for Head and Neck Squamous Cell Cancers – Adverse Events (Grade 3/4+ Events Only)

Study	Anemia	Diarrhea	Nausea	Pruritus	Dermatitis or rash	Fatigue	Anorexia	Hypomagnesemia	Lymphopenia	Dry skin	Dry mouth	Hypoalbuminemia	Creatinine	Hypokalemia	Hyponatremia	Hyperkalemia	Alkaline phosphatase	Hypocalcemia	AST/ALT elevation	Stomatitis
Siu et al., 2007[201]	0%	1%	1%	-	0%	3%	1%	2%	3%	0%	0%	0%	1%	2%	1%	1%	0%	0%	0%	-
Soulieres et al., 2004[202]	-	3%	0%	3%	11%	2%	-	-	-	2%	-	-	-	-	-	-	-	-	-	3%

Abbreviations: AST/ALT = aspartate aminotransferase/alanine transaminase.

Gefitinib for Head and Neck Squamous Cell Carcinoma

Background

Drug: Gefitinib (Iressa®). Gefitinib is an anilinoquinazoline with antineoplastic activity. Although the mechanism of the clinical antitumor action of gefitinib is not fully characterized, it is known to inhibit the catalytic activity of numerous tyrosine kinases, including the epidermal growth factor receptor (EGFR). Specifically, by competing with the binding of adenosine triphosphate (ATP) to the tyrosine kinase domain of EGFR, gefitinib interferes with receptor autophosphorylation and thus downregulates signal transduction, which may interrupt tyrosine kinase-dependent tumor growth.

In May 2003, gefitinib received Food and Drug Administration (FDA) approval for patients with non-small cell lung cancer who were refractory to established platinum-based and docetaxel chemotherapies; this approval was granted under accelerated regulations that allow products to be approved on the basis of a surrogate end point for clinical efficacy, the surrogate end point for gefitinib being tumor response rate. In June 2005, the FDA approved new labeling for gefitinib that limits the indication to cancer patients who, in the opinion of their treating physician, are currently benefiting, or have previously benefited, from gefitinib treatment. It has been evaluated for off-label use in head and neck squamous cell carcinoma (HNSCC).

Disease: Head and neck squamous cell carcinoma (HNSCC). The term "head and neck cancer" encompasses a group of biologically similar cancers of the upper aerodigestive tract, the vast majority of which are squamous cell carcinomas. Usually presenting as surface lesions with erythema and slight elevation (erythroplasia), squamous cell carcinomas most often appear on the floor of the mouth, the tongue, the soft palate, the anterior pillar of the tonsils, and the retromolar trigone.[192]

Accounting for 3 percent to 5 percent of all malignancies in the United States, head and neck cancers typically affect people over the age of 50.[193] Estimates predicted that more than 48,000 persons would develop head and neck cancer in 2005, and that more than 11,000 would die of the disease.[194] Fully 85 percent of head and neck cancers are linked to tobacco use,[193] and concomitant alcohol use may have synergistic neoplastic influence.[195]

Prognosis varies according to tumor location and stage. Although primary HNSCC exhibits a 60 percent 5-year survival rate, a significant number of HNSCC patients develop second primary tumors as a result of the same carcinogenic exposures; the 5-year survival among such patients drops to 25 percent.[196] Furthermore, despite high cure rates among patients diagnosed with early stages of the disease, nearly 50 percent of HNSCC patients are diagnosed only after the disease has progressed.[197] In addition to shortened survival, those patients who do experience complete remission and those undergoing radical curative surgery face serious quality-of-life issues due to significant functional deficits.[192,193]

The treatment plan pursued is contingent on, among other things, tumor location, cancer stage, and the individual's age and overall health. When the patient presents with small primary cancer without regional metastases, radiotherapy or wide surgical resection may be used alone, with both treatments appearing to be equally curative. For patients with regional metastases or recurrent disease, combination radiation and surgical excision remains the standard of care, although chemotherapy may be used as well.[192,193]

Drug/Disease: Gefitinib for HNSCC. HNSCC is characterized by the overexpression of EGFR, where EGFR levels correlate to survival.[198] Over the past few years, clinical research

initiatives seeking to develop more tolerable therapies, as well as to improve survival and quality of life among HNSCC patients, have investigated treatments that specifically interrupt the autocrine pathways of growth factor receptors, like EGFR, which are associated with adverse cancer outcomes.[196] Cetuximab, a monoclonal antibody that targets EGFR, has been approved in the treatment of HNSCC. Gefitinib, as an EGFR inhibitor, has been the subject of widespread interest as a novel therapeutic agent for patients with this cancer,[199] but early research has shown mixed results.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

The search strategy yielded at total of 12 reports; three of these were published full reports (Table A38), five were published abstracts from the American Society of Clinical Oncology (ASCO) 2007 conference (Table A39), and four were articles considered in the horizon scan (Table A40). The full reports and abstracts combined included seven Phase II trials and one Phase I trial. The horizon scan included three Phase I trials and one review article that summarized the findings of two of the Phase I trials, both published in 2002. The third Phase I trial included in the horizon scan was published in 2005. Insufficient information was reported to assess the quality of the full reports.

Sample sizes of the seven Phase II clinical trials ranged from 10 to 71; all patients were adults. Eligibility criteria were not clearly reported in the abstracts, but appeared to vary across the studies. The dosage of gefitinib ranged from 250 mg to 500 mg per day. Gefitinib was used as monotherapy in all these studies. Grade 3/4 adverse events reported in the three full reports (Table A41) included low rates of skin rash and diarrhea. Complete response (CR) rates were 0 percent in two studies and 2 percent in the third. Partial response (PR) rates ranged from 2 percent to 9 percent. Median survival ranged from 4.3 to 8.1 months.

Discussion

The paucity of published reports and the heterogeneity of the patient populations and the dosages studied preclude drawing conclusions at this time regarding the role of gefitinib in the treatment of HNSCC. Data available do not support its off-label use. Access to this drug has been severely restricted in the United States following the FDA approved labeling change in June 2005, such that gefitinib is seldom used either on-label for lung cancer or off-label for HNSCC. Interest in further clinical trials of this agent has also waned in the United States due to issues of access.

Table A38: Gefitinib for Head and Neck Squamous Cell Carcinoma – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Cohen, Kane, List, et al., 2005[207]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** No **Eligibility criteria:** Metastatic or recurrent squamous cell head and neck cancer	**No. in study:** 71 **Age:** 58 (30–87) **Previous treatment:** Yes, but no chemotherapy in the prior 4 wks, and no prior EGFR-based treatment **Stage of disease:** Not reported **Drug dose/day [followup]:** 250 mg/day **Outcomes sought:** Objective response as defined by Response Evaluation Criteria in Solid Tumors	**N:** 64 evaluable **CR:** 0 **PR:** 1 (2%) **Stable disease:** 23 (36%) **Progressive disease:** 41 (63%)	**Survival overall (from start of treatment):** **Median survival:** 5.5 mo (95% CI: 4.0, 7.0) **6 mo:** 47% **1 yr:** 19% **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 1.8 mo (95% CI: 1.7, 3.1) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A41 **Quality assessment:** 6) Representative sample from a relevant population?: Yes 7) Explicit eligibility criteria?: Yes 8) Patients entered at similar point in disease progression?: No 9) Adequate followup period?: Yes 10) Objective outcomes assessments?: Yes **Comments:** Gefitinib monotherapy at 250 mg/day has less activity than previously observed for 500 mg/day
Cohen, Rosen, Stadler, et al., 2003[208]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not reported **Eligibility criteria:** Metastatic or recurrent squamous cell head and neck cancer	**No. in study:** 52 **Age:** 59 (34–84) **Previous treatment:** No more than 1 prior chemotherapy or XRT No chemotherapy or XRT in the prior 4 wk No prior EGFR-based treatment **Stage of disease:** Not reported	**N:** 47 evaluable **CR:** 1 (2%) **PR:** 4 (9%) **Stable disease:** 20 (43%) **Progressive disease:** 22 (47%)	**Survival overall (from start of treatment):** **Median survival:** 8.1 mo (95% CI: 5.2, 9.4) Median f/u 11.4 mo 1 yr survival probability 29% **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **3 mo:** 53% **6 mo:** 13%	**Adverse events & tolerability:** See Table A41 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** Performance status and development of skin toxicity were predictors of response,

Study	Study Design	Patients	Tumor Response	Survival	Other
		Drug dose/day [followup]: ZD1839 500 mg/day **Outcomes sought:** Clinical response as defined by Response Evaluation Criteria in Solid Tumors		**9 mo:** 6% **1 yr:** NR **2 yr:** NR **3 yr:** NR	progression, and survival
Kirby, A'Hern, D'Ambrosio, et al., 2006[209]	**Design:** Expanded access program (prospective case series) **Phase:** Phase II **Selection/ randomization:** Not reported **Eligibility criteria:** Metastatic or recurrent squamous cell head and neck cancer Had to have prior chemotherapy or XRT, or be ineligible for such treatment	**No. in study:** 47 **Age:** 62 (18–93) **Previous treatment:** Yes; 18 (38%) had received prior platinum-based chemotherapy **Stage of disease:** Not reported **Drug dose/day [followup]:** 500 mg/day **Outcomes sought:** Primary: response rate and TTP Secondary: Survival and toxicity	**N:** 47 **CR:** 0 **PR:** 4 (8%) **Stable disease:** 13 (28%) **Progressive disease:** 30 (64%)	**Survival overall (from start of treatment):** **Median survival:** 4.3 mo (0–13 mo) Median f/u 5 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Median TTP 2.6 mo Median survival 4.3 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A41 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** Disease stage was the only significant factor affecting PFS

Abbreviations: CI =confidence interval; CR = complete response; EGFR = epidermal growth factor receptor; PFS = progression-free survival; PR = partial response; TTP = time to tumor progression; XRT = X-ray therapy.

Table A39: Gefitinib for Head and Neck Squamous Cell Carcinoma – ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Ahmed, Cohen, Haraf, et al., 2007[210] ASCO 2007 Abstract #6028	**Disease:** Head and neck cancer **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Stage III, Iva or IVb SCC of H&N	**No. in study:** 67 **Age:** Median 56 **Previous treatment:** Not reported **Stage of disease:** Stage IV in 61 (91%) **Drug dose/day [followup]:** 2 cycles carboplatin, paclitaxel followed by CRT with concurrent gefitinib 250 mg PO q day; *plus* 5-FU, hydroxyurea. Gefitinib continued x 2 yr. **Outcomes sought:** Toxicity, response	**N:** 56 **CR:** 51 (91%) **PR:** 4 (7%) **Stable disease:** 0 **Progressive disease:** 1 (2%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** 83% **3 yr:** 73% **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** 77% **3 yr:** 64%	**Adverse events & tolerability:** Grade 3: Mucositis: 75 Dermatitis: 29% Rash: 4% Diarrhea: 1% Grade 4: Mucositis: 10% Dermatitis: 3% Rash: 0% Diarrhea: 0%
Chua, Sham, and Au, 2007[211] ASCO 2007 Abstract #6042	**Disease:** Head and neck cancer **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Recurrent or metastatic nasopharyngeal cancer Pretreated with platinum-based chemotherapy	**No. in study:** 19 **Age:** Not reported **Previous treatment:** All patients previously received platinum-based chemo, either adjuvant or palliative **Stage of disease:** Not reported **Drug dose/day [followup]:** Gefitinib 250 mg PO daily **Outcomes sought:** Not reported	**N:** 19 **CR:** 0 **PR:** 0 **Stable disease:** 7 (37%) **Progressive disease:** 12 (63%)	**Survival overall (from start of treatment):** **Median survival:** 14 mo **1 yr:** 70% **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Time to progression 4 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** No Grade 3/4 ADE **Comments:** Little activity in NPC, but patients did have SD or symptom improvement

Study	Study Design	Patients	Tumor Response	Survival	Other
Morris, Allen, Citrin, et al., 2007[212] ASCO 2007 Abstract #16526	**Disease:** Head and neck cancer **Design:** Prospective **Phase:** Phase I **Selection/randomization:** Non-randomized **Eligibility criteria:** Stage III–IVb squamous cell of H&N, no previous treatment	**No. in study:** 10 **Age:** 60.7 (41–83) **Previous treatment:** None allowed **Stage of disease:** Not reported **Drug dose/day [followup]:** Gefitinib 250 mg daily; *plus* Paclitaxel 45 mg/m^2 q wk x 6; *plus* XRT to 72 Gy concurrent. **Outcomes sought:** Toxicity, response	**N:** Unclear **CR:** 5 **PR:** 1 **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Prolonged mucositis in 7 patients Infection in 1 patient Interstitial pneumonitis in 1 patient **Comments:** Mucositis was considered dose-limiting toxicity
Rueda, Medina, Mesia, et al., 2007[213] ASCO 2007 Abstract #6031	**Disease:** Head and neck cancer **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Unresectable Stage III or IV SCC, nasopharyngeal excluded	**No. in study:** 46 **Age:** 55 (39–75) **Previous treatment:** None **Stage of disease:** Stage IV 93% **Drug dose/day [followup]:** Cisplatin 40 mg/m2 q wk x 4; *plus* Gefitinib 250 mg q day, one day before XRT to 3 mo after. **Outcomes sought:** Response, toxicity	**N:** 46 **CR:** 24 (52%) **PR:** 5 (11%) **Stable disease:** 17 (37%) non-responders (includes SD, PD, & not evaluable) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** 56% **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr: 47%** **3 yr:** NR	**Adverse events & tolerability:** Grade 3/4 toxicities: 47% mucositis 14% radiation dermatitis 5% rash 2 % diarrhea

Study	Study Design	Patients	Tumor Response	Survival	Other
Weber, Lustig, Glisson, et al., 2007[214] ASCO 2007 Abstract #6038	**Disease:** Head and neck cancer **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Cutaneous SCC of H&N with > 2 cm primary, regional nodal metastases, peri-neural invasion, or deep invasion	**No. in study:** 14 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Gefitinib 250 mg daily x 30 days Second 30-day cycle at 250 mg if response (500 mg if stable disease, 0 mg if progression) Followed by definitive treatment **Outcomes sought:** Toxicity, response	**N:** 10 **CR:** 3 (30%) **PR:** 2 (20%) **Stable disease:** 2 (20%) **Progressive disease:** 3 (30%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 toxicity (rash, diarrhea, elevated LFTs) seen in patients

Abbreviations: ADE = adverse drug event; ASCO = American Society of Clinical Oncology; chemo = chemotherapy; CR = complete response; CRT = cathode ray tube; H&N = head and neck; LFTs = liver function tests; NPC = nasopharyngeal carcinoma; PD = progressive disease; PO = orally; PR = partial response; q = every; SCC = squamous cell carcinoma; SD = stable disease; XRT = X-ray therapy.

Table A40: Gefitinib for Head and Neck Squamous Cell Carcinoma – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Baselga, Rischin, Ransom, et al., 2002[215]	Phase I, dose-escalating trial	150-1,000 mg/day for at least 28 days	88 (8 with head/neck cancer)	Of 8 head and neck pts: 1 received 150 mg/day; 1 received 225 mg/day; 2 received 300 mg/day; 1 received 400 mg/day; 2 received 600 mg/day; 1 received 800 mg/day. For these 8 pts, the only reported severe AE during treatment was somnolence in 3 pts. Did not report on pts specifically, but for those with gefitinib on treatment > 6 mo, none were head and neck pts.
Herbst, Maddox, Rothenberg, et al., 2002[216]	Phase I, dose-escalating trial	150-1,000 mg/day for at least 28 days	71 (18 with head/neck cancer)	Of 18 head and neck pts: 4 received 150 mg/day; 5 received 225 mg/day; 3 received 300 mg/day; 4 received 400 mg/day; 2 received 600 mg/day. Did not report on head and neck pts specifically, but 3 pts with gefitinib on treatment > 6 mo were head and neck, 1 pt on treatment > 34 mo.
Lorusso, 2003[217]	Review of Phase I dosing trials	50-925 mg/day	242 (30 with head/neck cancer)	These 30 head and neck pts were treated from 3 to 18+ mo. Article reported on four Phase I trials, including Baselga et al., 2002,[215] and Herbst et al., 2002,[216] immediately above.
Wirth, Haddad, Lindeman, et al., 2005[218]	Phase I, dose-escalating trial	250-500 mg/day	19 (1 lost to f/u at 4 wk)	Pts were divided into 3 levels of dosing: For cycle 1, pts received celecoxib 200 mg bid and gefitinib 250 mg/day; for cycle 2, pts received celecoxib 400 mg bid and gefitinib 250 mg/day; for cycle 3, pts received celecoxib 400 mg bid and gefitinib 500 mg/day. No dose-limiting toxicities were encountered at any dose level. Most common AEs were acneiform rash, diarrhea, hand reaction, dyspepsia, and anemia. 4/18 assessable pts (22%) achieved a confirmed PR. Authors state the combination of gefitinib 500 mg/day plus celecoxib 400 mg bid is well tolerated. No CRs were seen. Responses were seen in all dose levels. 6 pts achieved SD. Median duration of response was 19 wk. Median PFS and OS were 12 wk and 24 wk, respectively.

Abbreviations: AE(s) = adverse event(s); bid = twice daily; CR = complete response; OS = overall survival; PFS = progression-free survival; PR = partial response; SD = stable disease.

Table A41: Gefitinib for Head and Neck Squamous Cell Carcinoma – Adverse Events (Grade 3/4+ Events Only)

Study	Diarrhea	Nausea	Vomiting	Fatigue	Anorexia	Dyspnea	Cutaneous	Stomatitis	Keratoconjunctivitis	Respiratory	Hepatic transaminase elevation	Hypercalcemia	Creatinine	Skin rash	Lung toxicity
Cohen et al., 2005[207]	3%	1%	0%	-	0%	-	1%	0%	0%	2%	0%	-	-	-	-
Cohen et al., 2003[208]	6%	4%	0%	-	6%	0%	-	-	-	-	-	6%	0%	-	-
Kirby et al., 2006[209]	0%	-	-	0%	0%	-	-	-	-	-	-	-	-	12%	0%

Imatinib Mesylate for Acute Lymphoblastic Leukemia

Background

Drug: Imatinib mesylate (Gleevec®). Imatinib is a tyrosine kinase inhibitor with antineoplastic activity. Imatinib binds to an intracellular pocket located within specific tyrosine kinases (TK), thereby inhibiting adenosine triphosphate (ATP) binding and preventing phosphorylation and the subsequent activation of growth receptors and their downstream signal-transduction pathways. This agent inhibits TK encoded by the bcr-abl oncogene as well as receptor TKs encoded by the c-Kit and platelet-derived growth factor receptor (PDGFRα) oncogenes. Inhibition of the bcr-abl TK results in decreased proliferation and enhanced apoptosis in malignant cells of Philadelphia chromosome-positive (Ph+) hematological malignancies; effects on c-Kit TK activity inhibit mast-cell and other cellular proliferation in diseases that overexpress c-Kit.

Imatinib has received Food and Drug Administration (FDA) approval for treatment of newly diagnosed adult patients with: Ph+ chronic myeloid leukemia (CML) in chronic phase; Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy; and c-Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. It has also been approved by the FDA for treating pediatric patients with Ph+ CML in chronic phase who are newly diagnosed, or whose disease has recurred after stem cell transplant, or who are resistant to interferon-therapy. It has also been approved by the FDA for treating pediatric patients with Ph+ CML in chronic phase who are newly diagnosed, or whose disease has recurred after stem cell transplant, or who are resistant to interferon-therapy. Since the time of initiation of this review, it has been approved by the FDA for use in myelodysplastic syndrome (MDS), chronic eosinophilic leukemia (CEL), systemic mastocytosis (SM), dermatofibrosarcoma protuberans (DFSP), and relapsed/refractory Ph+ acute lymphoblastic leukemia (ALL).

Disease: Acute lymphoblastic leukemia. ALL is a clonal disease in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow. The arrested development of lymphoblasts is due to chromosomal translocations that cause abnormal gene expression. When this occurs, the healthy constituents of marrow are replaced by malignant lymphoid clones and production of normal blood cells decreases markedly.[219] ALL is characterized by peripheral blasts with anemia, thrombocytopenia, and neutropenia.[220]

The most common form of childhood cancer, ALL has a peak incidence at 2–5 years of age, but it also demonstrates another peak around 50 years of age. Estimates predicted that more than 5,400 new ALL cases would be diagnosed in 2008, of which two out of three would be pediatric. Of the 1,460 deaths predicted for 2008, about 75 percent were predicted to be among adults. Survival varies widely, depending on various prognostic factors, including cytogenetic subtype, age, white blood cell count, and complete remission rate. Most ALL patients have no known risk factors.[219,221]

Treatment for acute leukemia depends on the specific disease subtype and can include chemotherapy, radiation therapy, intensive combined treatments (including bone marrow or stem cell transplants), and growth factors, with current research investigating various molecular targeted therapies. Because leukemia is a systemic disease, the standard of care is chemotherapy, delivered in a regimen that is usually intensive, complex, and protracted, lasting up to 2 or 3 years and involving the administration of multiple drugs on a precise schedule.

Although ALL can be fatal within weeks or months if left untreated, the overall cure rate among children is 85 percent, and about half of adult patients experience long-term disease-free survival.[219,221,222]

Drug/Disease: Imatinib mesylate for ALL. The constitutively activated tyrosine kinase bcr-abl, a product of the Philadelphia chromosome, is present in 20 percent to 30 percent of ALL cases[221,223] and is associated with a poor therapeutic response among both pediatric and adult patients.[224,225] Therefore, over the past few years, clinical research initiatives searching to develop more tolerable therapies, as well as to improve outcomes and quality of life among refractory ALL patients, have investigated treatments, including imatinib, that specifically target cells with the Philadelphia chromosome.[221] In addition to having demonstrated significant anti-leukemic activity, imatinib mesylate is known to be a potent and selective inhibitor of the tyrosine kinase activity of bcr-abl and thus has generated interest as a promising adjuvant therapy for patients with Ph+ ALL. It is generally well tolerated.[219,223]

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded a total of 65 reports, 12 of which were full reports of clinical trials (Table A42), 15 were published abstracts from the 2006 and 2007 American Society of Hematology (ASH) conferences (Table A43), and 38 were additional articles considered in the horizon scan (Table A44). One of the 12 full reports provided data used in another published report in our analysis, thereby resulting in a total of 11 different clinical trials represented among the 12 papers identified by our search strategy. Of the 15 published abstracts, 13 reported results of clinical trials. Study designs included 22 uncontrolled clinical trials, one Phase III randomized clinical trial that compared imatinib to no imatinib during induction, one randomized clinical trial that compared imatinib plus low-dose interferon versus imatinib plus zoledronic acid versus imatinib as a single agent, 26 case reports or series, and 15 other types of reports. The earliest publication was seen in the literature in 2001. The first full report of a clinical trial was seen in the literature in 2002, and this study started accruing patients in 2001.

Sample sizes for the clinical trials ranged from 20 to 94, with a total of 436 patients presented in the full reports and 994 patients presented in the full reports plus abstracts. Of these, a total of 88 patients were enrolled in the two reported randomized studies. Eligibility criteria for inclusion in the studies were generally uniform, and consistent with what would be expected from studies of ALL. The vast majority of patients had Philadelphia chromosome positive ALL. Most of the full report trials enrolled subjects who had not previously been treated for ALL, representing 375 (87 percent) patients. All of the studies involved adults, but some included one or two children. Patient age across the full reports ranged from 10–70.

Imatinib was used either in combination with or alternating with chemotherapy in five of the 11 full reports. The dosages of imatinib ranged from 400 to 800 mg per day, administered orally, with 600 mg/day being the most common dose studied.

Efficacy was reported in each of the 11 studies represented in the full reports. Nine of these 11 studies reported adverse events. Hematologic remission was the primary outcome sought in all of the full reports. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

Study quality of the full published reports was generally good. The frequency of the quality criteria was 18 percent for five of five criteria being met, 73 percent for four criteria, and 9 percent for three criteria. Most frequently, the missing quality criteria was a sufficiently long followup period.

Efficacy. The range of complete response (CR) rates was 19 percent to 100 percent when the fully published reports were considered alone or in conjunction with abstracts. The most common partial response (PR) rate in the full reports was 0 percent, with a range of 0 percent to 42 percent. Only two of the 13 trials reported in abstract form reported PR rates; both of these studies reported a PR rate of 2 percent.

Survival. Survival data was reported in all but one of the 11 studies represented in the full reports. One-year or 18-month overall survival ranged from 65 percent to 76 percent in the four studies that reported OS. Median survival ranged from 14 to 30 months in the five studies that reported this measure. The sole Phase III randomized controlled trial (RCT) demonstrated a significant improvement in median survival in the imatinib arm compared to chemotherapy when administered during induction (24 months vs. 12 months), but the probability of being without recurrence at 12 months was essentially the same between arms (70 percent for imatinib, 74 percent for chemotherapy). In this study, randomization to the two study arms was for induction only; all subjects received 600 mg/day imatinib plus chemotherapy during consolidation treatment. The only other randomized clinical trial we identified was in abstract form. It compared imatinib as a single agent to imatinib with either interferon or zoledronic acid. Survival data were not reported in the abstract.

Adverse events. Data in Table A45 were derived from nine of the full reports. Grade 3 to 4 nausea (range: 2 percent to 31 percent) was reported in eight studies, liver enzyme abnormalities (range: 4 percent to 25 percent) were reported in seven studies, and sepsis (range: 6 percent to 30 percent) was reported in five studies. One study reported an 83 percent incidence of infection; two studies reported neutropenic fever (29 percent to 50 percent). These data suggest that the most common adverse events other than nausea among patients with ALL treated with imatinib are hematologic or infectious in nature.

Horizon scan. The horizon scan identified reports that suggest that imatinib may:

- Be cardiotoxic;
- Turn bcr-abl+ ALL into a favorable sub-group among the elderly;
- Be associated with acute tumor lysis syndrome;
- Be indicated during induction therapy;
- Cause a rash;
- Be useful as salvage therapy for Ph+ ALL;
- Cause pleural effusion;
- Contribute to resolution of bone pain;
- Have specific activity in Ph+ ALL;
- Not be curative in ALL;
- Be indicated after allogenic stem cell transplant;
- Poorly penetrate the blood-brain barrier.

Discussion

The constitutively activated tyrosine kinase bcr-abl, a product of the Philadelphia chromosome, is present in 20 percent to 30 percent of ALL cases.[221,223] Because imatinib specifically targets cells with the Philadelphia chromosome, it is potentially useful as adjuvant therapy for patients with Ph+ ALL. This review identified two randomized clinical trials and 22 uncontrolled trials involving 1430 patients with ALL, the vast majority of whom were previously untreated and were Philadelphia chromosome positive.

Neither of the two randomized clinical trials identified in this review evaluated the efficacy of imatinib for ongoing treatment. One randomized trial demonstrated improved median survival when imatinib was added to ongoing to the induction regimen; all patients received imatinib during the ongoing treatment period in this study (the other randomized study did not have response or survival data available yet at the time of this review). The evidence from the Phase II trials suggests that this targeted therapy may be effective either as monotherapy or as combination therapy in the treatment of ALL, across the treatment settings studied, with CR rates in some studies reaching 100 percent. These favorable results must be considered in the context of the expected treatment success rates of existing therapies, which are generally high in the initial treatment of Ph+ ALL, maintained across treatment plans in children, and lead to treatment failure in adults; it follows that imatinib is usually used in adults with Ph+ ALL.

The ASH/American Society of Clinical Oncology (ASCO) abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. These reports did, however, suggest that imatinib may be associated with a variety of different adverse events, including acute tumor lysis syndrome, cardiotoxicity, or pleural effusion.

Table A42: Imatinib for Acute Lymphoblastic Leukemia (ALL) – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
de Labarthe, Rousselot, Huguet-Rigal, et al., 2007[226]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not randomized. Induction therapy stratified (HAMI vs. DIV) according to Ph+ diagnosis and early response **Eligibility criteria:** Newly diagnosed Ph+ ALL.	**No. in study:** 45 **Age:** 45 (16 to 59) **Previous treatment:** No **Stage of disease:** Newly diagnosed **Drug dose/day [followup]:** Imatinib 600 mg/day x 90 days for pts with hematologic CR after induction if given HAMI (intermediate dose cytarabine, mitoxantrone, imatinib) regimen Imatinib 800 mg/day if given DIV (Dexamethasone, Imatinib, vincristine) regimen **Outcomes sought:** Hematologic remission	**N:** 45 **CR:** 43 (96%) DIV: 29/31 (94%) HAMI: 14/14 (100%) **PR:** 0 **Stable disease:** 0 **Progressive disease:** 2 early deaths in the DIV group	**Survival overall (from start of treatment):** 10 deaths: 2 early during DIV treatment; 3 after relapse; 5 in first CR At 18 mo, overall survival 65% (95% CI: 43,81) **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse Events & Tolerability:** See Table A45 **Quality Assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Corroborates prior evidence that imatinib plus chemotherapy improves prognosis for Ph+ ALL
Delannoy, Delabesse, Lheritier, et al., 2006[227]	**Design:** Clinical trial w/ historical controls (21 pts treated w/ LALAG97 protocol w/o imatinib) **Phase:** Phase II **Selection/ randomization:** Not randomized	**No. in study:** 30 **Age:** 66 (58 to 78) **Previous treatment:** No **Stage of disease:** Newly diagnosed **Drug dose/day [followup]:**	**N:** 30 **CR:** After induction: 21/30 (70%) After salvage therapy: 27/30 (90%). (Salvage with imatinib & steroids successful in 5/6 pts). **PR:** Not reported	**Survival overall (from start of treatment):** 1-yr OS = 66% (95% CI: 49–83). **Median survival:** Median f/u = 24 mo (12–32) Median survival = 23 mo **1 yr:** NR **2 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes

Study	Study Design	Patients	Tumor Response	Survival	Other
	Eligibility criteria: - Age >54 -Untreated Ph+ ALL, confirmed by cytogenetics or molecular techniques **Exclusion:** LFTs > 2.5x ULN Bili > 1.5x ULN NYHA CHF > 2	Imatinib 600 mg/day given during consolidation/salvage phase (days 36–95) and Blocks 2 and 4, alternating with chemo Rx. **Outcomes sought:** CALGB criteria	**Stable disease:** Not reported **Progressive disease:** Not reported	**3 yr:** NR **Survival (disease-free):** Median relapse-free survival 20 mo **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	assessments?: Yes **Comments:** Corroborates prior evidence that imatinib plus chemotherapy improves prognosis for Ph+ ALL
Lee, Lee, Choi, et al., 2005[228]	**Design:** Clinical trial w/ historical controls (18 pts treated similarly but w/o Imatinib) Chemotherapy: Consolidation A = daunorubicin, vincristine, prednisolone, l-asparaginase Consolidation B = cytarabine, etoposide Plus Imatinib **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Ph+ ALL	**No. in study:** 20 **Age:** 37 (15 to 67) **Previous treatment:** None **Stage of disease:** Newly diagnosed **Drug dose/day [followup]:** Imatinib 600 mg/d during remission induction Imatinib 400 mg/d during consolidation courses **Outcomes sought:** Hematologic remission	**N:** 20 **CR:** 19 (95%); 1 (5%) died of sepsis during induction **PR:** 0 **Stable disease:** 0 **Progressive disease:** 0	**Survival overall (from start of treatment):** **Median survival:** Median f/u 799 days (275–991) Median duration of CR 821 days (89–964+) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Median OS 894 days (13–991+) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Imatinib enhanced the antileukemic effect of combination chemotherapy in pts w/Ph+ ALL

Study	Study Design	Patients	Tumor Response	Survival	Other
Lee, Kim, Min, et al., 2005[229]	**Design:** Clinical trial w/ historical controls. Incorporate imatinib into conventional chemotherapy. **Phase:** Phase II **Selection/ randomization:** Pts who achieved CR after induction therapy randomized to imatinib 400 mg/d vs. 600 mg/d **Eligibility criteria:** Newly diagnosed Ph+ ALL	**No. in study:** 29 **Age:** 36 (18 to 55) **Previous treatment:** None **Stage of disease:** Newly diagnosed **Drug dose/day [followup]:** Imatinib 400–600 mg/d x 4 wk added to hyper-CVAD regimen **Outcomes sought:** Hematologic remission; CR = return to normal bone marrow cellularity	**N:** 29 **CR:** 23 (79%) after induction (no Imatinib). Of these 23, 1 (4%) relapsed (and died) after imatinib treatment before SCT. Among 6 in refractory group, 3 (50%) achieved CR after imatinib. **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Median f/u 25 mo (12–45+) after SCT **1 yr:** NR **2 yr:** NR **3 yr:** NR 3-yr estimated probabilities: Relapse: 3.8% Non-relapse survival: 18.7% DFS: 78.1% OS: 78.1% **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes
Ottmann, Druker, Sawyers, et al., 2002[230] AND Scheuring, Pfeifer, Wassman, et al., 2003[231]	**Design:** Uncontrolled clinical trial **Phase:** Phase II/III **Selection/ randomization:** Not randomized **Eligibility criteria:** Relapsed or refractory Ph+ ALL or chronic myeloid leukemia (CML) in lymphoid blast crisis (LyBC)	**No. in study:** 56 (48 w/ALL, 8 w/LyBC) **Age:** ALL: 50 (22 to 78) LyBC: 60 (49 to 68) **Previous treatment:** Yes **Stage of disease:** **Drug dose/day [followup]:** Imatinib 400–600 mg/d Imatinib could be increased up to 400 mg	**N:** 56 (48 w/ALL, 8 w/LyBC) **CR:** ALL: 9/48 (19%) LyBC: 4/8 (50%) **PR:** ALL: 20/48 (42%) LyBC: 0 **Stable disease:** Not reported **Progressive disease:** ALL: No response 12 (25%); not evaluable: 7	**Survival overall (from start of treatment):** **Median survival:** ALL: - Estimated median time to progression 2.2 mo - Estimated progression-free rate at 6 mo 12% - Median OS 4.9 mo - OS at 6 mo 40% LyBC: Median OS 6.6 mo **Survival (disease-free):** **1 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** - Imatinib associated w/ significant but short-lived hematologic response

Study	Study Design	Patients	Tumor Response	Survival	Other
		BID **Outcomes sought:** Hematologic response	(15%) LyBC: No response 4 (50%)	**2 yr:** NR **3 yr:** NR	- Low Bcr-Abl levels after 2 wk of imatinib treatment associated w/ better hematologic response
Ottmann, Wassmann, Pfeifer, et al., 2007[232]	**Design:** RCT; imatinib vs. chemotherapy for induction treatment; imatinib then co-administered w/ consolidation chemotherapy **Phase:** Phase II/III **Selection/ randomization:** Randomized **Eligibility criteria:** Age > 54 Newly diagnosed Ph+ ALL or Ph+ CML	**No. in study:** 55 **Age:** 68 (54 to 79) **Previous treatment:** None **Stage of disease:** Newly diagnosed **Drug dose/day [followup]:** Imatinib randomized to either 0 mg/d or 600 mg/d during induction; Then imatinib 600 mg/d with chemotherapy during consolidation treatment **Outcomes sought:** Hematologic remission (bone marrow blasts, ANC, platelet count)	**N:** Imatinib (n = 28) Chemotherapy (n = 27) **CR:** Induction: Imatinib: 96% Chemotherapy: 50% Treatment – ongoing CR: Imatinib: 25% Chemotherapy: 30% **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Median OS: - Imatinib: 24 mo - Chemotherapy: 12 mo Estimated median remission duration: - Imatinib: 17 mo - Chemotherapy: 20 mo Probability of recurrence free at 12 mo: - Imatinib: 70% - Chemotherapy: 74% **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** Median DFS: - Imatinib: 14 mo - Chemotherapy: 15 mo **1 yr:** DFS, entire cohort: 54% **2 yr:** DFS, entire cohort: 19% **3 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Imatinib superior to chemotherapy for induction, but no difference in long-term survival (but imatinib administered in both study arms after induction)

Study	Study Design	Patients	Tumor Response	Survival	Other
Rea, Legros, Raffoux, et al., 2006[233]	**Design:** Uncontrolled clinical trial. High-dose imatinib w/ less intensive chemotherapy induction (DIV induction regimen). **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Relapsing or refractory Ph+ ALL or lymphoid blast crisis CLL	**No. in study:** 31 (18 w/ALL, 13 w/LBC) **Age:** 45 (10 to 70) **Previous treatment:** Yes **Stage of disease:** **Drug dose/day [followup]:** Imatinib 400 mg BID for up to 56 days **Outcomes sought:** Hematologic remission	**N:** 31 **CR:** 28 (90%); of these, 17/18 had ALL and 11/13 had LBC **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** After a median f/u of 256 days (28–1049), 20/31 (65%) of pts remained alive **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** DIV regimen w/ high-dose imatinib induces high CHR rates, but treatment less efficacious among pts previously treated w/ imatinib
Towatari, Yanada, Usui, et al., 2004[234]	**Design:** Uncontrolled clinical trial; interim analysis **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Ph+ ALL	**No. in study:** 24 **Age:** 42 (15 to 59) **Previous treatment:** None **Stage of disease:** Newly diagnosed **Drug dose/day [followup]:** Imatinib 600 mg/d during induction, and then during 1 of 2 alternating consolidation treatments **Outcomes sought:** Hematologic remission	**N:** 24 **CR:** 23 (96%; early death from bleed on day 3 of Imatinib) **PR:** 0 **Stable disease:** 0 **Progressive disease:** 0	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Suggests that combination of intensive chemotherapy and imatinib can produce high-quality CR in pts w/ BCR-ABL-positive ALL

Study	Study Design	Patients	Tumor Response	Survival	Other
Vignetti, Fazi, Cimino, et al., 2007[235]	**Design:** Uncontrolled clinical trial. GIMEMA LALA0201-B protocol. Imatinib plus prednisone w/o chemotherapy as frontline treatment. **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Ph+ ALL - Age > 60 yr	**No. in study:** 30 **Age:** 69 (61 to 83) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 800 mg/d for 45 days **Outcomes sought:** Hematologic remission	**N:** 29 evaluable **CR:** 29 (100%) **PR:** 0 **Stable disease:** 0 **Progressive disease:** 0	**Survival overall (from start of treatment):** **Median survival:** Median survival from time of diagnosis: 20 mo Median duration of hematologic response: 8 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Suggests that elderly Ph+ ALL pts may benefit from imatinib-steroids protocol w/o conventional chemotherapy
Wassmann, Pfeifer, Goekbuget, et al.,2006[236]	**Design:** Two sequential prospective cohorts, comparing alternating vs. concurrent imatinib and chemotherapy. **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Ph+ ALL or CML lymphoid blast crisis	**No. in study:** 92 (47 in alternating schedule, 45 in concurrent schedule) **Age:** 44 (19 to 65) **Previous treatment:** No **Stage of disease:** Newly diagnosed **Drug dose/day [followup]:** Imatinib 400–600 mg/d **Outcomes sought:** Hematologic remission	**N:** 92 **CR:** Alternating: 47/47 (100%) Concurrent: 40/42 (95%) **PR:** 0 **Stable disease:** 0 **Progressive disease:** Alternating: 0/47 Concurrent: 1/42 (2%) Not evaluable: 1/42 (2%)	**Survival overall (from start of treatment):** Estimated probability of remission at 12 mo after 1st documented CR: Alternating: 65% Concurrent: 71% Estimated probability of remission at 24 mo after 1st documented CR: Alternating: 52% Concurrent: 61% **Median survival:** Alternating: 16 mo Concurrent: 20 mo Estimated probability of survival 12 mo after	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Concurrent administration of imatinib and chemotherapy has greater antileukemic efficacy compared to an alternating regimen

Study	Study Design	Patients	Tumor Response	Survival	Other
				diagnosis: Alternating: 72% Concurrent: 61% Estimated probability of survival 24 mo after diagnosis: Alternating: 36% Concurrent: 43% **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	
Yanada, Takeuchi, Sugiura, et al., 2006[237]	**Design:** Uncontrolled clinical trial. Design: Japan Adult Leukemia Study Group (JALSG). Compared to historic controls from JALSG ALL93 study. **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Newly diagnosed BCR-ABL-positive ALL	**No. in study:** 80 **Age:** 48 (15 to 63) **Previous treatment:** No **Stage of disease:** **Drug dose/day [followup]:** Imatinib 600 mg q day alternating with MTX and Ara-C chemotherapy **Outcomes sought:** Hematologic response	**N:** 80 **CR:** 77 (96%; 1 pt had resistant disease and 2 had early deaths) **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** EFS and OS at 1 yr estimated at 60% and 76% **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A45 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Abbreviations: AE = adverse event; ALL = acute lymphocytic leukemia; ANC = absolute neutrophil count; BID = twice daily; bili = bilirubin; chemo Rx = chemo therapy; CHF = congestive heart failure; CI = confidence interval; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CR = complete response; CVAD = cyclophosphamide, vincristine, Adriamycin and dexamethasone; DFS = disease-free survival; DIV = dexamethasone, Imatinib, and vincristine; JALSG =

Japan Adult Leukemia Study Group; LFT = liver function test; LyBC = lymphoid blast crisis; MTX = methotrexate; NYHA = New York Heart Association; OS = overall survival; Ph+ = Philadelphia chromosome positive; PR = partial response; q = every; RCT = randomized controlled trial; SCT = stem cell transplantation; ULN = upper limit of normal.

Table A43: Imatinib for Acute Lymphoblastic Leukemia - ASH 2006 and ASH 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Cimino, Elia, Pane, et al., 2006[238] ASH 2006 Abstract #638	**Disease:** Philadelphia positive acute lymphocytic leukemia (Ph+ ALL) **Design:** Prospective **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Non-elderly patients who responded to intensive induction chemotherapy	**No. in study:** 36 **Age:** 44 (20 to 60) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 400 BID for at least 6 mo and up to 1 yr **Outcomes sought:** Response	**N:** 36 total: 18 with > 2.1 log BCR/ABL reduction; and 18 with ≤ 2.1 log reduction due to induction chemo **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** > 2.1 log reduction: 76% < 2.1 log reduction: 32% **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** > 2.1 log reduction: 65% < 2.1 log reduction: 33% **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Response to imatinib appears related to response to induction chemotherapy
Leguay, Witz, De Botton, et al., 2006[239] ASH 2006 Abstract #1877	**Disease:** Ph+ ALL **Design:** Prospective **Phase:** Phase I/II **Selection/ randomization:** Non-randomized **Eligibility criteria:** In complete remission before transplant for Ph+ ALL	**No. in study:** 36 **Age:** 42 (19 to 60) **Previous treatment:** **Stage of disease:** **Drug dose/day [followup]:** Ara-C 2g/m^2 q 12 h days 1–4, *plus* Mitoxant 10 mg/m^2 daily days 1–3; *plus* Imatinib 400 mg, 600 mg, or 800 mg days 1–45 **Outcomes sought:** Survival	**N:** 36 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** 71% with or without allogeneic donor **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** 52% **3 yr:** NR	**Adverse events & tolerability:** Not reported

Study	Study Design	Patients	Tumor Response	Survival	Other
Pfeifer, Wassmann, Pavlova, et al., 2006[240] ASH 2006 Abstract #639	**Disease:** Ph+ ALL **Design:** Prospective **Phase:** Horizon scan **Selection/ randomization:** Non-randomized **Eligibility criteria:** Analysis of data collected as part of GMALL study	**No. in study:** 51 new diagnosis, 68 who failed prior chemo **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Not reported **Outcomes sought:** Not reported	**N:** 51 de novo **CR:** 46 (90%) in "de novo" patients, irrespective of detectable mutations pre-study **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported
Schultz, Aledo, Bowman, et al., 2006[241] ASH 2006 Abstract #283	**Disease:** Ph+ ALL **Design:** Prospective **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Age 1–21 yr, Ph+, induction failure, hypodiploidy	**No. in study:** 160 total: 94 treated with imatinib 66 treated without imatinib **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib in doses escalating up to 340 mg/m^2 daily in 44 patients, continuous in 50 patients **Outcomes sought:** Toxicity	**N:** Not reported **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease- free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Higher incidence of ALT elevation in consolidation or maintenance phases **Comments:** Fewer RBC transfusions in patients receiving imatinib Lower incidence of infection with grade 3–4 neutropenia with imatinib

Study	Study Design	Patients	Tumor Response	Survival	Other
Thomas, Kantarjian, Cortes, et al., 2006[242] ASH 2006 Abstract #284	**Disease:** Ph+ ALL **Design:** Prospective **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Adults with newly diagnosed or minimally treated Ph+ ALL	**No. in study:** 52 **Age:** 51 (17 to 84) **Previous treatment:** **Stage of disease:** **Drug dose/day [followup]:** Imatinib 400 mg days 1–14 during 8 cycles; *followed by* Hyper-CVAD then continuous with VCR and prednisone and imatinib maintenance **Outcomes sought:** Response	**N:** 43 **CR:** 39 (91%) Molecular response by BCR/ABL PCR was 58% in 33 patients that did not get allogeneic stem cell transplant **PR:** 1 (2%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** 60% with allogeneic stem cell transplant, 56% without **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** 55% with imatinib, 14% without	**Adverse events & tolerability:** 1 died from sepsis early in study
Fielding, Richards, Lazarus, et al., 2007[243] ASH 2007 Abstract #8	**Disease:** Ph+ ALL **Design:** Prospective, multicenter, intergroup (ECOG) trial **Phase:** Phase II **Selection/ randomization:** Sequential comparison of outcomes in Ph+ ALL in the pre- and post- imatinib era, treated on E2993 protocol **Eligibility criteria:** Ph+ ALL	**No. in study:** 267 No imatinib 153 With imatinib **Age:** 40 (15 to 60) No Imatinib 42 (16 to 64) With Imatinib **Previous treatment:** Standard induction and transplant; or Induction followed by imatinib and transplant **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 600 mg q d, up to 2 yr after transplant	**N:** 267 No imatinib 64 imatinib in induction 89 imatinib following induction **CR:** 83% No imatinib 91% imatinib in induction 81% imatinib in consolidation **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** With imatinib 23%; No imatinib 26% **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Imatinib may be beneficial with induction, but not post-induction

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Overall survival			
Mukhopadhyay, Mukho-padhyay, Gupta, et al., 2007[244] ASH 2007 Abstract #4339	**Disease:** Ph+ ALL **Design:** Prospective, single center **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Ph+ ALL, age > 50	**No. in study:** 10 **Age:** 64 (51 to 77) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 400 mg daily; *plus* Prednisone 40 mg/m^2 over 6 wk, followed by 2 wk taper; *plus* Vincristine 2 mg/m^2 q wk x 6 wk **Outcomes sought:** Not reported	**N:** 10 **CR:** 10 (100%) at 3 mo **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** 90% at 8 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 80% at 8 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** All completed on outpatient basis
Pfeifer, Wassmann, Wystub, et al., 2007[245] ASH 2007 Abstract #2817	**Disease:** Ph+ ALL **Design:** Prospective, multicenter **Phase:** Phase II **Selection/ randomization:** Randomized **Eligibility criteria:** Ph+ ALL in remission after imatinib and cytotoxic chemotherapy induction	**No. in study:** 33 **Age:** 69.5 (58 to 75) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Arm A: Imatinib plus low-dose interferon; *versus* Arm B: Imatinib plus	**N:** 19 imatinib + interferon 4 zoledronic acid 8 imatinib alone **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:**	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** At 17 mo, 14 in continued CR **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported

Study	Study Design	Patients	Tumor Response	Survival	Other
		zoledronic acid; *versus* Arm C: Imatinib as a single agent **Outcomes sought:** Not reported	Not reported		
Rousselot, Huguet, Vey, et al., 2007[246] ASH 2007 Abstract #2812	**Disease:** Ph+ALL **Design:** Prospective, multicenter **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Ph+ ALL, relapsed, refractory, or de novo. No previous imatinib.	**No. in study:** 54 **Age:** 62 (22 to 83) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 800 mg q d during induction, Imatinib 600 mg q d during consolidation with 6-Mercaptopurine, Imatinib 400 mg q d maintenance for 2 yrs with Pegasys 45 g SC q wk IV Vincristine 2 mg day 1 x 4 during induction, then monthly x 4 during consolidation Dexamethasone 40 mg po days 1–2 q wk x 4, then monthly x 4 during consolidation **Outcomes sought:** Median survival, response rate	**N:** Not reported **CR:** 85% **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** 29.9 mo with transplant 27.9 mo without transplant **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 2–4 neutropenia and/or thrombocytopenia in 33% during main treatment Grade 3–4 toxicities: Papillary edema: 1 Infections: 2

Study	Study Design	Patients	Tumor Response	Survival	Other
Rousselot, Recher, Buzyn, et al., 2007[247] ASH 2007 Abstract #2816	**Disease:** Ph+ ALL **Design:** Prospective, multicenter **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Ph+ ALL, relapsed, refractory, or de novo; no previous imatinib; age > 55	**No. in study:** 25 **Age:** median 68 (all > 55) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 800 mg q d during induction, Imatinib 600 mg q d during consolidation with 6 Mercaptopurine, Imatinib 400 mg q d maintenance for 2 yrs with Pegasys 45 g SC q wk IV Vincristine 2 mg day 1 x 4 during induction, then monthly x 4 during consolidation Dexamethasone 40 mg po days 1–2 q wk x 4, then monthly x 4 during consolidation **Outcomes sought:** Not reported	**N:** Not reported **CR:** 84% **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 53% at 18 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** This is a subgroup of old patients from study above (Rousselot, Huguet, Vey, et al., 2007)

Study	Study Design	Patients	Tumor Response	Survival	Other
Schultz, Bowman, Slayton, et al., 2007[248] ASH 2007 Abstract #4	**Disease:** Ph+ ALL **Design:** Prospective, multicenter intergroup (COG) trial **Phase:** Phase II **Selection/ randomization:** Sequential enrollment **Eligibility criteria:** Children with Ph+ ALL	**No. in study:** 93 total in 5 cohorts **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** 340 mg/m^2 daily for 42, 63, 84, 126, or 280 days **Outcomes sought:** Event-free survival	**N:** 31 imatinib x 280 days **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Imatinib provides benefit in event-free survival
Suzuki, Abe, Mori, et al., 2007[249] ASH 2007 Abstract #4327	**Disease:** Ph+ALL **Design:** Case report **Phase:** Not reported **Selection/ randomization:** Not reported **Eligibility criteria:** 31 year old female 25 wk, 5 days pregnant diagnosed with Ph+ ALL	**No. in study:** 1 **Age:** 31 **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 600 mg daily after C section at 26 wk, 2 days, followed by dose-reduced hyper-CVAD one wk later; plus [Following all on day 8?] Intra-thecal MTX 15 mg Ara-C 40 mg, PSL 20 mg injection on day 8	**N:** 1 **CR:** 100% **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Healthy infant female child born without any observed hematological problems

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Not reported			
Thomas, Kantarjian, Ravandi, et al., 2007[250] ASH 2007 Abstract #9	**Disease:** Ph+ ALL **Design:** Prospective, single center **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Ph+ ALL	**No. in study:** 54 **Age:** 51 (17 to 84) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 600 mg q d with hyper-CVAD x 8 cycles, then 800 mg daily indefinitely **Outcomes sought:** Not reported	**N:** 45 **CR:** 42 (93%) **PR:** 1 (2%) **Stable disease:** Not reported **Progressive disease:**	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** 66% **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** 55%	**Adverse events & tolerability:** Not reported
Wetzler, Stock, Donohue, et al., 2007[251] ASH 2007 Abstract #2869	**Disease:** Ph+ ALL **Design:** Prospective, intergroup **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Ph+ ALL in CR or PR after one cycle combination chemotherapy	**No. in study:** 35 **Age:** 41 (27 to 54) in 8 allo, 47 (24 to 56) for 8 auto **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 400 mg BID x 8 wk pre-transplant, 12 mo post-transplant; *plus* CNS prophylaxis	**N: 16** **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Early results of longer trial with higher target enrollment

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Minimal residual disease, CD34+ yield, time to relapse			
Yanada, Takeuchi, Sugiura, et al., 2007[252] ASH 2007 Abstract #2813	**Disease:** Ph+ ALL **Design:** Prospective, multicenter **Phase:** Phase II **Selection/ randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 80 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 600 mg daily in consolidation and for up to 2 yr after CR **Outcomes sought:** Predictive factors of RFS	**N:** 80 **CR:** 77 (96%) **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease- free):** **Median survival:** **1 yr:** NR **2 yr:** 50.5% RFS **3 yr:** NR	**Adverse events & tolerability:** Not reported

Abbreviations: ALL = acute lymphocytic leukemia; allo = allograft; ALT = alanine transaminase; ASH = American Society of Hematology; BID = twice daily; chemo = chemotherapy; CNS = central nervous system; COG = Children's Oncology Group; CR = complete response; CVAD = cyclophosphamide, vincristine, Adriamycin and dexamethasone; ECOG = Eastern Collaborative Oncology Group; GMALL = German Multicenter Study Group for Adult ALL; IV = intravenous; MTX = methotrexate; PCR = pathological complete response; Ph+ = Philadelphia chromosome positive; RFS = relapse-free survival; po = orally; PR = partial response; q = every; RBC = red blood cell; SC = subcutaneous; VCR = vincristine.

Table A44: Imatinib for Acute Lymphoblastic Leukemia – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Anonymous, 2007[253]	News editorial	NR	10	Editorial warning that imatinib may be heart toxic. 10 pts treated w/ imatinib developed severe congestive heart failure 2–14 mo after taking imatinib.
Baron, Frere, Fillet, et al., 2001[254]	Case report	600 mg/day	1	33 y/o female w/ biphenotypic Ph-chromosome-positive acute leukemia in first relapse had peripheral blood stem cell transplant from unrelated male donor. STI-571 (imatinib) was begun on day 160. A new analysis on day 240 evidenced a complete molecular response, and the pt remains in CR for more than 150 days after the onset of STI-571 treatment.
Brandwein, Gupta, Wells, et al., 2005[255]	Retro-spective analysis	400–600 mg daily	45 (9 received imatinib)	9 BCR-ABL+ pts received imatinib at 400-600 mg daily. 5 received in combination w/ modified DFCI induction therapy (3 achieved CR and 2 died during induction). 6 pts received imatinib as part of post-remission treatment. Authors state data should be interpreted w/ caution, this was not a prospective trial, treatments used were heterogeneous, and overall numbers small. It does suggest that imatinib may be turning BCR-ABL+ ALL into a relatively favorable sub-group in the elderly.
Bujassoum, Rifkind, and Lipton, 2004[256]	Case reports	Pt 1: 300 mg PO BID Pt 2: 600 mg PO once daily	2	Pt 1: 42 y/o female diagnosed w/ CML chronic phase (Ph+). Treatment imatinib (300 mg PO BID). Hematological and complete cytogenetic remission achieved within 3 mo. Pt 2: 57 y/o female diagnosed w/ ALL (Ph+). Following complications, she was treated w/ imatinib (600 mg PO once daily) achieving a good hematologic response. Author states particular attention should be paid to pts in lymphoid blast crisis CML or ALL, as CNS treatment may play a role in complementing imatinib treatment and prolonging response.
Dann, Fineman, and Rowe, 2002[257]	Case report	600 mg/d	1	74 y/o male diagnosed w/ Ph+ ALL. This report details an apparent episode of acute tumor lysis syndrome following 2 days of treatment w/ STI-571 (imatinib). Author suggests pts receiving STI-571 be monitored closely for this possibility.
De Vita, De Matteis, Laurenti, et al., 2006[258]	Case report	800 mg daily	1	40 y/o male affected by grade IV GBM. Imatinib was added to standard induction treatment according to the presence of Philadelphia chromosome. At end of induction treatment he was in complete hematological and cytogenetic remission. Pt is now in continuous complete remission of the hematological disease.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Dogra and Kanwar, 2003[259]	Case report	300 mg daily; increased to 400 mg daily after 7 days	1	Case of 45 y/o female diagnosed w/ CML who exhibited imatinib-induced maculopapular drug rash. She developed itchy erythematous skin lesions which gradually increased in severity and distribution. Imatinib was stopped, and lesions started regressing and subsided completely in 5 days.
Druker, Sawyers, Kantarjian, et al., 2001[223]	Dose-escalating, Phase I pilot study	300 to 1,000 mg PO daily	58 (38 w/ myeloid blast crisis; 20 w/ ALL or lymphoid blast crisis)	58 pts given STI-571 (imatinib). Responses occurred in 21 (55%) of myeloid-blast-crisis phenotype (4 of these had complete hematologic response). Of pts w/ lymphoid blast crisis or ALL, 14 (70%) had a response (including 4 w/ complete response). 7 pts w/ myeloid blast crisis continue to receive treatments and remain in remission from 101 to 349 days after starting treatment. Most frequent AEs were nausea, vomiting, edema, thrombocytopenia, and neutropenia.
Fruehauf, Topaly, Buss, et al., 2002[260]	Case report	600 mg/day	1	19 y/o w/ refractory BCR-ABL-positive ALL who received imatinib-based combination treatment. PR was noted within the first week. Results show that combination treatment w/ imatinib and synergistically active chemotherapeutic drugs or irradiation can be safely administered and can induce a leukemic cell depletion that was not possible by either high-dose induction chemotherapy or imatinib alone. Although the combination modality treatment was not curative by itself, it helped achieve a state of minimal residual disease which allowed potentially curative allogeneic stem cell transplantation.
Gupta, Kamel-Reid, Minden, et al., 2003[261]	Case reports	600 mg/day	4	4 cases of relapsed/refractory Ph+ acute leukemias were treated w/ imatinib as monotherapy. Significant clinical and molecular responses were observed in these pts, which allowed authors to deliver highly intensive treatments such as second allogenic stem cell transplant and matched unrelated transplant in these pts. Imatinib may prove to be a useful agent in the salvage treatment of such pts.
Houot, Tavernier, Le, et al., 2004[262]	Retro-spective analysis of cases		25 (only 8 received imatinib at some point)	All pts diagnosed w/ Ph+ ALL aged 55 or older seen at this institution over a 17-yr period (median age = 64 yr). Overall CR rate was 76%. Median DFS was 5.6 mo for entire cohort, and median overall survival was 10.1 mo. Authors state the very poor overall outcome in elderly pts w/ Ph+ ALL may be significantly improved by the introduction of imatinib into current treatment regimens. All 4 who received 1st line in CR (DFS 1.9–7.2 mo), no CR in those who received as 2nd or 3rd line.
Hurtado-Sarrio, Duch-Samper, Taboada-Esteve, et al., 2005[263]	Case report		1	55 y/o female w/ Ph+ ALL in complete remission w/ imatinib. This pt had developed anterior chamber infiltration w/o hematological relapse while treated w/ imatinib. Authors state their opinion that paracentesis should be performed w/o delay when uveitis develops in ALL, regardless of systemic relapse.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Ishii, Shoji, Kimura, et al., 2006[264]	Case report		1	51 y/o female w/ Ph+ ALL treated w/ imatinib, showing recurrent unilateral pleural effusion. Authors state although abundant pleural effusion in adult ALL pts treated w/ imatinib has not been documented, this might be an AE of imatinib and management for this AE should be emphasized.
Lahaye, Riehm, Berger, et al., 2005[265]	Consecu-tive pt study	400 mg daily for 155 pts; subsequent pts w/ advanced-stage disease were given 600 mg per day	300 (only 2 w/ ALL, 3 w/ CML blast crisis)	Objectives of this study were 1) to analyze the long-term efficacy and tolerability of imatinib; 2) to evaluate the rate of imatinib-refractory disease and the frequency and pathogenesis of secondary resistance; and 3) to assess the efficacy of additional drugs as therapeutic strategy for treatment optimization.
Leis, Stepan, Curtin, et al., 2004[266]	Multi-center clinical trial	Various doses from 400 to 1,000 mg daily	42	Pts diagnosed w/ CML in blast crisis or Ph+ ALL in trials to assess the toxicity and efficacy of imatinib. Pts received continuous treatment unless AE or disease progression occurred. Authors state their results show that imatinib may not penetrate the CNS at adequate levels to treat occult CNS leukemia and that pts w/ CML-LBC and Ph+ ALL treated w/ the drug are at high risk for CNS relapse even in the setting of complete hematologic remission.
Matsue, Takeuchi, Koseki, et al., 2006[267]	Case report	600 mg daily imatinib w/ 60 mg daily of predinisone	1	73 y/o male referred for treatment of ALL. Pt received imatinib in addition to a hyper-CVAD regimen. Pt achieved complete hematological and molecular remission on day 42, demonstrated by bone marrow aspiration and biopsy. Although imatinib has been used extensively for treatment of BCR/ABL-related disorders throughout the world, this is the first report of BMN associated w/ the use of imatinib in a pt w/ ALL.
Morgensztern, Rosado, Raez, et al., 2005[268]	Case report	400 mg PO daily w/ 20 mg/m^2 SC daily for 5 days q 28 days	1	63 y/o female diagnosed w/ Ph+ ALL. After 4 wk of standard treatment, pt began imatinib treatment. Within 2 wk pt had complete resolution of bone pain. Treatment was well-tolerated except for mild nausea and fatigue. 24 mo after starting treatment, pt remains asymptomatic and w/ normal peripheral blood counts.
Nakajima, Tauchi, and Ohyashiki, 2001[269]	In vitro study results	NR	NR	Authors state their results demonstrate that STI571 (imatinib) exhibits specific activity in Ph+ ALL and some cases of CML-BC *in vitro*. Given the extremely poor prognosis of pts w/ Ph+ ALL or CML-BC, the results may provide a basis for attractive therapeutic strategies in treating these diseases.
Nishii, Sakakura, Tsukada, et al., 2007[270]	Case report	600 mg daily	1	77 y/o female Ph+ ALL was started on imatinib combined w/ less intensive chemotherapy. Pt, in complete remission after induction chemotherapy, was given maintenance treatment of 600 mg imatinib daily. 10 mo later, this pt is still in complete remission and is free of transfusions and infection.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Onozawa, Fukuhara, Takahata, et al., 2003[271]	Case report		1	73 y/o male initially diagnosed as refractory anemia w/ excess blasts (RAEB) subclass of MDS w/ normal karyotype. Complete hematological remission was achieved after 3 mo treatment w/ imatinib. Hepatosplenomegaly vanished soon after administration of imatinib. Despite optimal supportive treatment, pt died of pneumonia 1 yr after development of CML blast crisis. Authors strongly suggest that acquisition of Ph chromosome is an infrequent but important genetic change triggering leukemogenesis in MDS.
Ottmann, Wassmann, and Hoelzer, 2002[272]	Brief review			Review of various doses of imatinib.
Piccaluga, Malagola, Amabile, et al., 2004[273]	Letter to editor, case report	Varied between 400 and 800 mg	12	Uses quantitative reverse-transcription polymerase chain reaction to investigate the significance of achieving molecular CR in pts w/ BCR/ABL-positive ALL treated w/ imatinib. Study investigated whether the achievement of a mCR correlated w/ RFS and OS. Secondly, studied whether the MDR levels after 4 and 8 wk of imatinib treatment correlated w/ RFS and OS. Authors conclude that MRD monitoring by quantitative RT-PCR during imatinib treatment may allow BCR/ABL-positive ALL pts w/ relatively different prognoses to be identified and may improve the pt's management. However, imatinib does not appear to be curative in ALL, and further treatment should be promptly planned whenever possible.
Piccaluga, Malagola, Rondoni, et al., 2004[274]	Case report	600 mg daily	1	35 y/o male diagnosed w/ BCR/ABL-positive ALL. Achieved complete hematologic, cytogenetic and molecular remission w/ standard induction treatment. 8 mo later, had relapse and began imatinib treatment. In order to avoid the impending clinical relapse, the dose of imatinib was increased to 800 mg/day. Authors documented a new molecular CR. 3 mo later, pt was submitted to allogenic SCT from voluntary unrelated donor, while in molecular CR. Pt is alive and well 3 mo post-SCT.
Potenza, Luppi, Riva, et al., 2005[275]	Case series	800 mg/day	7	Ph+ ALL pts in first complete remission received maintenance treatment w/ imatinib alone. 2-yr PFS was 75%. Quantitative polymerase-chain-reaction monitoring of BCR/ABL showed: that persisting molecular CR was associated w/ long-lasting CR; that molecular relapse did not invariably mean hematologic relapse; and that only the wide and rapid increment of BCR/ABL values was predictive of leukemia relapse.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Raanani, Trakhtenbrot, Rechavi, et al., 2005[276]	Case reports		2	Pt 1: 45 y/o male had been treated w/ German Multicenter Trial for Adult Acute Lymphoblastic Leukemia (GMALL) protocol w/ complete hematological and cytogenetic remission achieved. 3 yr later, relapse occurred. Pt was treated w/ donor lymphocyte infusion, imatinib, radiotherapy, chemotherapy, and interferon w/o achieving remission. Pt died 2 yr later. Pt 2: 55 y/o female was treated according to GMALL protocol and hematological and cytogenetic remission was achieved. Relapse occurred after 4 mo. PR was achieved w/ imatinib and myeloablative stem cell transplant from unrelated donor with TBI/cyclophosphamide conditioning. Pt died 1 mo later from septic shock.
Sakai, Ohashi, Kobayashi, et al., 2005[277]	Case report	600 mg	1	56 y/o female with Ph+ ALL in which emergence of non-clonal random cytogenetic abnormalities in Ph-negative host-derived cells was transiently observed, but the pt maintained a sustained molecular remission after myeloablative SCT. 1 mo after treatment complete cytogenetic remission was obtained.
Sanchez-Gonzalez, Pasual-Ramirez, Fernandez-Abellan, et al., 2003[278]	Case report	400 mg/day	1	72 y/o female w/ Ph+ ALL showed hematologic response w/ induction treatment. Maintenance was started w/ mercaptopurine after which imatinib was continued at 400 mg/d. After AE pt developed erythema multiforme, pt went off imatinib and relapsed.
Savani, Srinivasan, Espinoza-Delgado, et al., 2005[279]	Case reports	Varied 400-800 mg/day	2	Pt 1: 55 y/o female diagnosed w/ Ph+ ALL. Achieved hematologic remission after induction treatment w/ hyper-CVAD. After relapse, pt was given 600 mg/d imatinib for 3 wk, after which she showed complete remission. Pt went on to allogeneic SCT, 32 mo remission, relapsed, restarted imatinib at 600 mg/d w/ DLI, went into molecular remission at 6 wk and d/c imatinib. Pt 2: 66 y/o male diagnosed w/ chronic-phase chronic myeloid leukemia, given imatinib 800 mg/d w/ DLI until AEs required reduction to 400 mg/d.
Scheuring, Pfeifer, Wassmann, et al., 2003[280]	2 separate succes-sive Phase II trials		56 (24 evaluable)	Study designed to determine the safety and efficacy of imatinib in pts w/ relapsed or refractory Ph+ ALL.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Shimoni, Kroger, Zander, et al., 2003[281]	Case series; patients were enrolled in different Phase II studies	400–600 mg/daily	16	This study was to demonstrate short-term imatinib to induce or maintain remission, followed by allogeneic transplantation or DLI and the impact on transplantation/DLI outcome. Authors state more study is needed to assess the impact on long-term outcome and the role of post-transplant imatinib in controlling residual disease.
Shin, Chung, and Cho, 2005[282]	Case report	400 mg/day x 4 wk	1	43 y/o female diagnosed w/ Ph+ ALL. In addition to courses of hyper-CVAD, pt received imatinib between chemotherapy cycles and for 2 wk during 3rd cycle of chemo for purging of leukemic blasts. Pt subsequently received imatinib to bridge the time to ASCT. Authors state imatinib comb w/ chemotherapy and *in vivo* purging of minimal residual disease before stem cell mobilization to remove Ph+ cells, followed by ASCT and imatinib maintenance treatment, appear to be an effective therapeutic strategy in pts with Ph+ ALL who do not have an HLA-matched donor.
Stergianou, Mikoshiba, Ohashi, et al., 2002[283]	Case report	400 mg daily	1	43 y/o male w/ T-ALL had achieved complete remission following treatment w/ MRC UKALLXII protocol, but relapsed while on maintenance treatment. Pt was started on imatinib treatment. Pt underwent marrow transplant but relapsed again after 4 mo. Authors state response to imatinib in this case was disappointing.
Sugimoto, Mikoshiba, Ohashi, et al., 2002[284]	Case reports	400–600 mg/day	2	Pt 1: 34 y/o male w/ ALL received allogeneic bone marrow transplant from HLA-identical sister. Pt relapsed 5 mo after transplantation. Pt given intensive salvage chemotherapy, but relapsed again 1 yr later. After 3rd attempt pt was given imatinib as possible salvage treatment. Imatinib was increased to 600 mg/d and 2 wk later, PR was confirmed. Pt tolerated imatinib well w/ no severe AEs except periorbital edema and muscle cramps. After 4 mo w/ imatinib, leukemia was considered resistant to all treatment. Pt 2: 42 y/o female w/ Ph+ ALL was treated w/ induction chemo, resulting in complete remission. Pt relapsed 1 mo later. Imatinib (600 mg/d) started and 20 days later pt achieved hematological remission. During imatinib treatment no severe AEs were observed. 2 mo later, leukemia suddenly became resistant to treatment.
Takami, Shimadoi, Sugimori, et al., 2006[285]	Case report	600 mg/day	1	35 y/o female with Ph+ ALL received allogeneic sibling donor peripheral blood stem cell transplantation, entered 2nd complete remission. Pt received imatinib, leading to molecular remission. Authors state that because of lack of AEs of imatinib on transplantation outcome, a treatment strategy consisting of molecular monitoring-guided initiation of imatinib followed by RI-UCBT may be promising in the management of Ph+ ALL after allogeneic SCT.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Takayama, Sato, O'Brien, et al., 2002[286]	Case report	600 mg/day	1	32 y/o female with relapsed Ph+ ALL was treated w/ imatinib. Although initial marrow response was good and stably maintained, she relapsed w/ extensive infiltration of leukemic cells into the central nervous system. Authors state the results shown suggest that imatinib poorly penetrates the blood-brain barrier and has limited activity against CNS leukemia.
Visani, Isidori, Malagola, et al., 2002[287]	Case report	600 mg/daily	1	45 y/o female was referred w/ ALL. Pt received modified L-20 regimen. After 2 yr of morphological CR a second relapse occurred. Pt was enrolled in Phase II imatinib trial. Following 18 mo of combined treatment, pt is in morphological and molecular CR. Treatment was well tolerated with only minor nausea, vomiting, and perimalleolar edema.
Wassmann, Pfeifer, Scheuring, et al., 2002[288]	Case series	600 mg single daily dose	46	Authors state Imatinib is a well-tolerated salvage therapy prior to allogeneic SCT in patients with Ph+ ALL, but requires that SCT be performed within a few weeks of starting treatment to avoid resistance. Disease status at time of transplantation is an important determinant of DFS and TRM.
Wernstedt, Brune, Andersson, et al., 2002[289]	Case report	600 mg daily	1	43 y/o female with Ph+ ALL refractory to standard induction chemotherapy. After 25 days, pt was enrolled in the STI571 (imatinib) expanded access program. After 14 days, night sweats had disappeared. Only slight and transient nausea was observed. 4 mo since the stem cell transplant, pt achieved molecular remission, which has been stable since then.

Abbreviations: AE(s) = adverse event(s); ALL = acute lymphocytic leukemia; BC = blast crisis; BID = twice daily; BMN = bone marrow necrosis; chemo = chemotherapy; CML = chronic myelogenous leukemia; CNS = central nervous system; CR = complete response; CVAD = cyclophosphamide, vincristine, Adriamycin, and dexamethasone; d/c = discontinued; DFCI = Dana Farber Consortium Induction; DFS = disease-free survival; DLI = donor lymphocyte infusion; GBM = glioblastoma multiforme; GMALL = German Multicenter Study Group for Adult ALL; HLA = human leukocyte antigen;; MDS = myelodysplastic syndrome; MRD = minimal residual disease; NR = not reported; OS = overall survival; PFS = progression-free survival; Ph = Philadelphia; Ph+ = Philadelphia chromosome positive; po = orally; PR = partial response; q = every; RAEB = refractory anemia with excess blasts; RFS = relapse-free survival; RI-UCBT = reduced intensity unrelated cord blood transplantation; RT-PCR = reverse transcription polymerase chain reaction; SC = subcutaneous; SCT = stem cell transplantation; T-ALL = T-cell ALLTRM = transplantation-related mortality; y/o = years old.

Table A45.1: Imatinib for Acute Lymphoblastic Leukemia – Adverse Events (Grade 3/4+ Events Only), Part 1

Study	Superficial edema	Edema	Tumor hemorrhage	Anemia	Neutropenia/ granulocytopenia	Leukocytopenia	Thrombocytopenia	Diarrhea	Nausea	Vomiting	Dyspepsia	Constipation	Other digestive	Dermatitis or rash	Myalgia or musculoskeletal pain	Infection
de Labarthe et al., 2007[226]	-	-	-	-	-	-	-	-	10%	10%	-	17%	-	-	-	-
Delannoy et al., 2006[227]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	83%
Lee et al., 2005[228]	-	-	-	-	-	-	-	-	10%	-	5%	-	-	-	5%	-
Ottmann et al., 2002[230]	-	4%	-	37%	67%	68%	48%	0%	2%	0%	-	-	-	2%	-	-
Ottmann et al., 2007[232]	-	-	-	-	-	-	-	4%	7%	7%	-	-	-	7%	4%	-
Rea et al., 2006[233]	3%	-	-	-	-	-	-	-	10%		-	-	-	-	-	32%
Towatari et al., 2004[234]	-	-	4%	-	26%	-	-	4%	17%	-	-	-	-	-	-	8%
Vignetti et al., 2007[235]	15%	-	-	-	-	-	-	-	31%	31%	-	-	15%	-	-	-
Yanada et al., 2006[237]	3%	-	1%	-	20%	-	-	1%	8%	-	-	-	3%	3%	-	-

Table A45.2: Imatinib for Acute Lymphoblastic Leukemia – Adverse Events (Grade 3/4+ Events Only), Part 2

Study	Neutropenic fever	Liver enzyme abnormality	Peripheral neuropathy	Venous thrombosis	Pulmonary infection	Hypofibrinogenemia	Hemorrhage	Hyperbilirubinemia	Subdural hematoma	Sepsis	Enterocolitis	Ileus	Muscle weakness	Pancreatitis	Other
de Labarthe et al., 2007[226]	-	7%	7%	-	-	-	-	-	-	-	-	-	-	-	3%
Delannoy et al., 2006[227]	-	-	-	7%	10%	3%	3%	-	-	30%	-	-	-	-	3%
Lee et al., 2005[228]	50%	25%	-	-	-	-	-	20%	-	-	-	-	-	-	-
Ottmann et al., 2002[230]	-	4%	-	-	-	-	-	4%	-	-	-	-	-	-	2%
Ottmann et al., 2007[232]	29%	7%	-	-	36%	-	4%	-	4%	18%	18%	-	-	-	4%
Rea et al., 2006[233]	-	13%	-	-	6%	-	-	-	3%	6%	-	-	-	-	6%
Towatari et al., 2004[234]	-	-	-	-	-	-	-	-	-	13%	-	8%	4%	4%	13%
Vignetti et al., 2007[235]	-	15%	15%	-	-	-	-	-	-	-	-	-	-	-	-
Yanada et al., 2006[237]	-	15%	-	-	3%	-	-	-	-	14%	-	8%	1%	-	1%

Imatinib Mesylate for Chronic Eosinophilic Leukemia

Background

Drug: Imatinib mesylate (Gleevec®). Imatinib is a tyrosine kinase inhibitor with antineoplastic activity. Imatinib binds to an intracellular pocket located within specific tyrosine kinases (TK), thereby inhibiting adenosine triphosphate (ATP) binding and preventing phosphorylation and the subsequent activation of growth receptors and their downstream signal-transduction pathways. This agent inhibits TK encoded by the bcr-abl oncogene as well as receptor TKs encoded by the c-Kit and platelet-derived growth factor (PDGF) receptor oncogenes. Inhibition of the bcr-abl TK results in decreased proliferation and enhanced apoptosis in malignant cells of Philadelphia chromosome-positive (Ph+) hematological malignancies; effects on c-Kit TK activity inhibit mast-cell and cellular proliferation in diseases that over-express c-Kit.

Imatinib has received Food and Drug Administration (FDA) approval for treatment of newly diagnosed adult patients with: Ph+ chronic myeloid leukemia (CML) in chronic phase; Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy; and c-Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. It has also been approved by the FDA for treating pediatric patients with Ph+ CML in chronic phase who are newly diagnosed, or whose disease has recurred after stem cell transplant, or who are resistant to interferon-therapy. It has also been approved by the FDA for treating pediatric patients with Ph+ CML in chronic phase who are newly diagnosed, or whose disease has recurred after stem cell transplant, or who are resistant to interferon-therapy. Since the time of initiation of this review, it has been approved by the FDA for use in myelodysplastic syndrome (MDS), chronic eosinophilic leukemia (CEL), systemic mastocytosis (SM), dermatofibrosarcoma protuberans (DFSP), and relapsed/refractory Ph+ acute lymphoblastic leukemia (ALL).

Disease: Chronic Eosinophilic Leukemia (CEL). CEL is a subtype of clonal eosinophilia that is classified as a myeloproliferative disorder. Diagnostic criteria include: 1) an eosinophilic count greater than or equal to 1.5×10^9 /L which persists over time; 2) the absence of parasitic, allergic, or other causes of eosinophilia; and 3) organ system involvement or dysfunction directly related to eosinophilia. The character of the disease is clonal, caused by the mutation in the tyrosine kinase gene F1P1L1-PDGFRA.

Drug/Disease: Imatinib mesylate for CEL. Imatinib's activity as a tyrosine kinase inhibitor is theoretically well suited as an adjunct treatment for CEL, which is is characterized by a mutation in the tyrosine kinase gene F1P1L1-PDGFRA.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded a total of 14 reports, none of which was a full report. Five were published abstracts from the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) conferences (Table A46), and nine were additional articles considered in the horizon scan (Table A47). Study designs included four uncontrolled, Phase II clinical trials, nine case reports or series, and one report of reverse transcriptase-polymerase chain reaction (RT-PCR) analysis among 40 patients who had been treated with imatinib at doses ranging from 100 to 400 mg/day. The earliest publication was seen in the literature in 2004, with the first Phase II clinical trial published in abstract form in 2006.

Sample sizes for the four clinical trials published in abstract form ranged from seven to 72, with a total of 135 patients. Eligibility criteria included eosinophilic myeloproliferation, with and without PDGFR mutations. One of the studies included some patients who had been previously treated with steroids or hydroxyurea. Previous treatment status was not reported in the other three abstracts. Only adults were included in these studies, with an age range of 20 to 80 years.

Imatinib was used as monotherapy in dosages ranging from 100 to 400 mg/day. Outcomes assessed included undefined clinical response and end-organ damage. Adverse events data were reported in three of the four studies.

Efficacy. The CR was 100 percent at three months in one study among 15 patients with the PDGFR alpha mutation, and among the four patients with PDGFR beta mutation, but only 21 percent among the 14 patients with no specific marker. Another study reported a "response" among four out of six evaluable patients. A CR of 100 percent at one month was reported among 21 patients with the PDGFR alpha gene mutation in the third study, and 100 percent among patients with the same mutation in the fourth study. In the fourth study, the CR was only 13 percent among patients without the PDGFR mutation. Survival data were not reported.

Adverse events. None of the three abstracts that provided toxicity data reported Grade 3 or Grade 4 adverse events.

Horizon scan. Each of the nine case reports or series considered in the horizon scan reported favorable responses to imatinib without significant toxicity. The RT-PCR analysis suggests that there is sensitivity of the PDGFR alpha fusion to imatinib.

Discussion

Each of the nine case reports or series considered in the horizon scan reported favorable responses to imatinib without significant toxicity in the treatment of chronic eosinophilic leukemia. The RT-PCR analysis suggests that there is sensitivity of the PDGFR alpha fusion to imatinib.

Table A46: Imatinib for Chronic Eosinophilic Leukemia -- ASH 2006, ASH 2007, and ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Metzgeroth, Popp, Walz, et al., 2006[290] ASH 2006 Abstract #671	**Disease:** Hypereosinophilic syndrome **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Eosinophilic myeloproliferation, with and without PDGFR mutations	**No. in study:** 35 total: 17 PDGF alpha 4 PDGF beta 14 no specific marker **Age:** 52 (20 to 72) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 100 mg to 400 mg daily **Outcomes sought:** Response, toxicity	**N:** 33 total 15 PDGF alpha 4 PDGF beta 14 no specific marker **CR:** 15/15 (100%) with PDGFR alpha at 3 mo 4/4 (100&) with PDGFR beta at 3 mo 3/14 (21%) with no specific marker at 3 mo **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** No grade 3–4 toxicities
Mitra, Murphy, and Thornton, 2006[291] ASH 2006 Abstract #4922	**Disease:** Hypereosinophilic syndrome **Design:** Retrospective **Phase:** Horizon scan **Selection/randomization:** Non-randomized **Eligibility criteria:** Treated with imatinib for hypereosinophilic syndrome	**No. in study:** 7 **Age:** 56 (37 to 80) **Previous treatment:** Steroids in 2 patients, hydroxyurea in 1 patient **Stage of disease:** Not reported **Drug dose/day [followup]:** Not reported **Outcomes sought:** Response	**N:** 6 **CR:** "Response" seen in 4 patients (66%) **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Response in fusion gene negative patients suggests this may be useful approach for all hypereosinophilic syndrome patients

Study	Study Design	Patients	Tumor Response	Survival	Other
Rondoni, Ottaviani, Piccaluga, 2006[292] ASH 2006 Abstract #2700	**Disease:** Hypereosinophilic syndrome **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** PDGFR alpha gene mutation positive	**No. in study:** 21 **Age:** 48 (25 to 71) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 400 mg daily **Outcomes sought:** Not reported	**N:** 21 **CR:** 21 (100%) within 1 mo **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** 13/13 (100%) with 2-yr follow up are disease free, PCR negative. All patients still on Imatinib (100–400 mg daily). **3 yr:** NR	**Adverse events & tolerability:** No heart failure
Rondoni, Paolini, Vigna, et al., 2007[293] ASH 2007 Abstract #3557	**Disease:** Hypereosinophilic syndrome **Design:** Prospective, multicenter **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Hypereosinophilic syndrome	**No. in study:** 33 with PDGF alpha mutation 39 PDGFR mutation negative **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 100 mg to 400 mg daily **Outcomes sought:** Response, end-organ damage	**N:** 33 with PDGFR mutation 39 without PDGFR mutation **CR:** 100% with PDGFR mutation 5 (13%) without PDGFR mutation **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Organ involvement in 42% FP+ and 51% FP- Without durable effects

Study	Study Design	Patients	Tumor Response	Survival	Other
Mitra, Power, Thornton, et al., 2007[294] ASCO 2007 Abstract #17529	**Disease:** Hypereosinophilic syndrome **Design:** Retrospective review **Phase:** Horizon scan **Selection/randomization:** Not reported **Eligibility criteria:** Elevated eosinophil count	**No. in study:** 7 **Age:** 56 (37 to 80) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib (no dose given) ± steroids ± hydroxyurea ± alpha-interferon **Outcomes sought:** Not reported	**N:** 6 **CR:** Not reported **PR:** "4 of 6 patient receiving imatinib responded to it" **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Responses seen even in patients without PDGF alpha mutation

Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; CR = complete response; FP = FIP1L1-PDGFR; PDGFR = platelet-derived growth factor receptor; PCR = pathological complete response; PR = partial response.

Table A47: Imatinib for Chronic Eosinophilic Leukemia – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Frickhofen, Marker-Hermann, Reiter, et al., 2004[295]	Case report	200 mg/day	1	33 y/o male w/ CNS manifestations of CEL and an excellent response to low-dose imatinib. Within 2 wk eosinophils decreased to counts below $0.3x10^9$/L and they remained normal during continued treatment w/ imatinib. Pt now working full-time and feeling well w/o any AEs of imatinib.
Ishii, Ito, Kuriyama, et al., 2004[296]	Case report	100 mg/day	1	41 y/o male diagnosed w/ HES and myelofibrosis. Tests indicated disease progression to CEL. On 7^{th} day of imatinib administration, absolute eosinophil fell to w/i the normal range. Authors state although the exact mechanism of efficacy of imatinib for HES is still unknown, imatinib might be a powerful agent for the treatment of HES pts, including those w/ cells of a neoplastic nature, i.e., CEL.
Jovanovic, Score, Waghorn, et al., 2007[297]	PCR assays on specimens from UK ref. lab	100-200 mg/day	376	Pts w/ unexplained hypereosinophilia were screened revealing 40 (11%) cases. This report deals w/ the importance of identifying the FIP1L1-PDGFRA fusion, since it predicts a favorable response to molecularly targeted treatment w/ imatinib. Overall, 11/11 evaluable pts achieved at least a 3-log reduction in FPI1L1-PDGFRA fusion transcripts relative to the pretreatment level within 12 mo, w/ achievement of molecular remission in 9/11. in 2 pts, withdrawal of imatinib was followed by a rapid rise in FIP1L1-PDGFRA transcript levels.
Kamineni, Baptiste, Hassan, et al., 2006[298]	Case report	400 mg/day	1	45 y/o male w/ hepatitis C and sustained peripheral blood eosinophilia. Pt was treated w/ imatinib w/ improvement of symptoms, reduction of lymphadenopathy and normalization of the eosinophil count. In addition, the role of hepatitis C in inducing clonal proliferation of eosinophils is unclear.
Malagola, Martinelli, Rondoni, et al., 2004[299]	Case report	100 to 400 mg/day escalating by 100 each wk	1	47 y/o male was diagnosed w/ CEL. 7 days after treatment with imatinib, the WBC and eosinophils were dramatically reduced and maintained constantly within normal ranges after 120 days of observation. A hematologic response was obtained rapidly within the first 3 wk of treatment w/ imatinib. No significant toxicities were observed. Authors state this case confirms that imatinib is highly effective in cases of CEL carrying rearrangements of FIP1L1-PDGFR-alpha.
Smith, Jacobson, Hamza, et al., 2004[300]	Case reports	Pt #1: 600 mg/day; Pts 2 & 3: 400 mg/day	3	All 3 pts were originally diagnosed w/ idiopathic HES, but after evaluation and demonstration of molecular abnormalities, they were classified as having eosinophilic leukemia. Pt 1 showed initial rapid resolution of symptoms and eosinophilia. After 4 mo of imatinib treatment, pt experienced blast crisis and was administered flavopiridol and depsipeptide. Pts 2 & 3 both had rapid clearing of symptoms w/ normalization of eosinophil counts. They have remained clear for more than 8 mo, w/ no apparent AEs from the medication.
Tanaka, Kurata, Togami, et al., 2006[301]	Case report	300 mg/day	1	43 y/o male diagnosed w/ HES which did not respond to treatment. Imatinib brought about complete remission.
Tashiro,	Case	200 mg/day	1	38 y/o male treated for acute respiratory failure w/ severe eosinophilia. Despite treatment w/ steroid

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Shirasaki, Noguchi, et al., 2006[302]	report	for 2 days; then 100 mg/day for 3 days		pulse treatment and cytarabine, the blood eosinophil count did not decrease, and the pt's respiratory condition worsened. After imatinib treatment, the pt's blood eosinophil count decreased dramatically and the pt's condition rapidly improved, such that the pt could be discharged.
Walz, Curtis, Schnittger, et al., 2006[303]	Case report	400 mg/day	1	71 y/o female was diagnosed w/ an accelerated phase of chronic eosinophilic leukemia. Pt was not eligible for intensive chemotherapy because of comorbidity. Pt was treated w/ imatinib. Pt achieved a complete cytogenetic and molecular remission, however hematologic response was only partial w/ residual blasts repeatedly detectable in the blood and marrow. Pt developed acute appendicitis and died soon after surgery because of rapid increase of blasts and septic shock syndrome.

Abbreviations: AE(s) = adverse event(s); CEL = chronic eosinophilic leukemia; CNS = central nervous system; HES = hyper eosinophilic syndrome; PCR = polymerase chain reaction; ref. = reference; UK = United Kingdom; WBC = white blood cell(s); y/o = year(s) old.

Imatinib Mesylate for Dermatofibrosarcoma Protuberans

Background

Drug: Imatinib mesylate (Gleevec®). Imatinib is a tyrosine kinase inhibitor with antineoplastic activity. Imatinib binds to an intracellular pocket located within specific tyrosine kinases (TK), thereby inhibiting adenosine triphosphate (ATP) binding and preventing phosphorylation and the subsequent activation of growth receptors and their downstream signal-transduction pathways. This agent inhibits TK encoded by the bcr-abl oncogene as well as receptor TKs encoded by the c-Kit and platelet-derived growth factor receptor (PDGFRα) oncogenes. Inhibition of the bcr-abl TK results in decreased proliferation and enhanced apoptosis in malignant cells of Philadelphia chromosome-positive (Ph+) hematological malignancies; effects on c-Kit TK activity inhibit mast-cell and cellular proliferation in diseases that over-express c-Kit.

Imatinib has received Food and Drug Administration (FDA) approval for treatment of newly diagnosed adult patients with: Ph+ chronic myeloid leukemia (CML) in chronic phase; Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy; and c-Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. It has also been approved by the FDA for treating pediatric patients with Ph+ CML in chronic phase who are newly diagnosed, or whose disease has recurred after stem cell transplant, or who are resistant to interferon therapy. It has been evaluated for off-label use in myelodysplastic syndrome (MDS), systemic mastocytosis (SM), dermatofibrosarcoma protuberans (DFSP), and Ph+ acute lymphoblastic leukemia (ALL).

Disease: Dermatofibrosarcoma protuberans (DFSP). An uncommon neoplasm of the dermis, DFSP is a slow-growing, painless tumor that most often appears on the trunk. In its early manifestations, it often masquerades as benign, presenting as an asymptomatic, indolent, indurated plaque. Although DFSP rarely metastasizes, initial misdiagnosis, prolonged time to accurate diagnosis, and large tumor size at the time of diagnosis is frequent. As disease progresses, the tumor gradually evolves into a lumpy nodule or an atrophic, sclerotic plaque that eventually ulcerates. Its cellular origin remains unclear.[304,305]

With an annual incidence of 4.2 cases per million population annually , DFSP accounts for less than 0.1 percent of all malignant neoplasms.[306] It largely affects adults aged 20 to 50 years.[304,305]

For the most part, DFSP is locally aggressive and responds well to surgery, especially Mohs micrographic surgery.[307] However, it exhibits an infiltrating growth pattern, often extending well beyond the clinical margins of the tumor, so incomplete removal is common, which may account for its 75 percent 5-year recurrence rate following surgical excision.[304,305] Recurrent tumors can transform into a malignant fibrosarcoma capable of regional and distant spread.[304] Occurring in 1 percent to 4 percent of cases, metastatic disease has a poor prognosis, with death usually occurring within 2 years.[305,307]

Drug/Disease: Imatinib mesylate for DFSP. Recent advances in the understanding of the molecular pathogenesis of DFSP have led to the investigation of a new therapeutic approach that is based on targeted inhibition of the PDGF receptor protein-tyrosine kinase.[308] The vast majority of DFSP tumors have a chromosomal translocation that fuses the collagen gene with the PDGF gene, the result of which is the production of a self-stimulatory growth signal, rapid cell division, and tumor formation.[305] This process involves the constitutive activation of the PDGF

receptor, which provides a rationale for targeted inhibition of the PDGF receptor as a treatment strategy for patients with unresectable locally advanced or metastatic DFSP.[309] Clinically, imatinib, a potent, selective inhibitor of PDGF receptor, has demonstrated activity in patients with metastatic or unresectable DFSP.[310]

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded one full report of a clinical trial (Table A48), one American Society of Clinical Oncology (ASCO) 2007 abstract (Table A49), and 10 case reports considered in the horizon scan (Table A50). The full report, published in 2005, was a Phase II trial designed to correlate molecular, cytogenic, and kinase activation profiles to clinical response. Only 10 patients were enrolled in this study, so no statistically significant clinical correlates were found. The abstract reported on a Phase II clinical trial with a sample size of 25 that evaluated the safety and efficacy of imatinib 600 mg/day for 2 months prior to surgical resection.

Imatinib was used as monotherapy in both clinical trials at dosages of either 400 mg twice daily or 600 mg per day.

Efficacy was defined according to the Southwest Oncology Group criteria in the full report and as "clinical response" in the abstract. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

The full report met three of five quality criteria (e.g., representative sample, explicit eligibility criteria, and use of objective outcomes assessments).

Efficacy. Forty percent of the 10 patients in the full report had a complete response (CR). In the abstract, nine of the 25 patients (36 percent) demonstrated a "clinical response." Fifty percent of the 10 patients in the full report had a partial response (PR), and 10 percent had stable disease.

Adverse events. The abstract reported one case of Grade 3 neutropenia and one case of Grade 3 maculopapular rash.

Horizon scan. The horizon scan identified reports that suggest that imatinib with DFSP may reduce the size of metastatic lesions, be useful for gastrointestinal bleeds from metastatic DFSP, and be associated with a low rate of serious adverse events.

Discussion

The vast majority of DFSP tumors have a chromosomal translocation that fuses the collagen gene with the PDGF gene, the result of which is the production of a self-stimulatory growth signal, rapid cell division, and tumor formation.[305] This process involves the constitutive activation of the PDGF receptor, which provides a rationale for targeted inhibition of the PDGF receptor as a treatment strategy for patients with unresectable locally advanced or metastatic DFSP.[309] This review identified two Phase II reports involving 35 patients with DFSP treated

with imatinib as monotherapy. Neutropenia and maculopapular rash were the only Grade 3 adverse events reported. Fifty percent of patients in the full report demonstrated a PR and 36 percent of patients in the trial published as an abstract demonstrated a clinical response. In these Phase II reports, imatinib compares favorably to existing treatment options. The ASCO 2007 abstract and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates.

Given the rarity of DFSP tumors, the substantial mortality risk for those that transform into a sarcoma or metastasize, the lack of other systemic therapeutic interventions for DFSP, and the presence of the PDGF receptor as a target in DFSP, treatment with imatinib in DFSP is a sensible strategy even in the setting of few published reports and incomplete exploration in clinical trials identified in this review.

Table A48: Imatinib for Dermatofibrosarcoma Protuberans – Full Report

Study	Study Design	Patients	Tumor Response	Survival	Other
McArthur, Demetri, van Oosterom, et al., 2005[310]	**Design:** Uncontrolled clinical trial. Aim: to correlate molecular, cytogenetic, and kinase activation profiles with clinical response. **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Dermatofibrosarcoma protuberans (DFSP)	**No. in study:** 10 **Age:** 47 (23 to 68) **Previous treatment:** Yes **Stage of disease:** Locally advanced (n = 8); metastatic (n = 2) **Drug dose/day [followup]:** Imatinib 400 mg BID **Outcomes sought:** Clinical response (Southwest Oncology Group criteria)	**N:** 10 **CR:** 4 (40%) **PR:** 5 (50%) **Stable disease:** 1 (10%) **Progressive disease:** 0	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Abbreviations: BID = twice daily; CR = complete response; DFSP = dermatofibrosarcoma protuberans; PR = partial response.

Table A49: Imatinib for Dermatofibrosarcoma Protuberans – ASCO 2007 Abstract

Study	Study Design	Patients	Tumor Response	Survival	Other
Lebbe, Kerob, Porcher, et al., 2007[311] ASCO Abstract #10032	**Disease:** Dermatofibro-sarcoma protuberans **Design:** Prospective, multicenter **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 25 **Age:** 42.4 (23 to 72.5) **Previous treatment:** None **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 600 mg qd x 2 mo before surgical resection **Outcomes sought:** Not reported	**N:** 25 **CR:** Not reported **PR:** "Clinical response" in 9 (36%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3: Neutropenia: 1 Maculopapular rash: 1 Grade 4: Transaminitis: 1

Abbreviations: CR = complete response; PR = partial response; q = every.

Table A50: Imatinib for Dermatofibrosarcoma Protuberans – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Bigby, Oei, Lambie, et al., 2006[312]	Case report	400 mg/day	1	33 y/o female presented w/ lesions of the right anterior chest wall. Original histological diagnosis was unknown. 2 yr later, pt was found to have nodules of metastatic DFSP in both breasts. Left mastectomy performed. Imatinib was commenced. Lung and right breast metastases decreased in size, with maximal effect at 9 mo. An increase in size of one right breast nodule prompted a wide local resection. 2 yr later, her lung nodules remain in remission.
Kasper, Lossignol, Gil, et al., 2006[313]	Case report	400 mg/day	1	50 y/o male w/ DSFP underwent multiple surgical resections. Pt developed gastrointestinal bleeding of the duodenum. Imatinib was started and after 7 days w/o AEs, dose was increased to 400 mg BID. 1 mo after imatinib treatment, PET examination showed a decrease of the SUV indicating a metabolic PR.
Labropoulos, Fletcher, Oliveira, et al., 2005[314]	Case report	400 mg/day	1	48 y/o female, histology showed transformation to a high-grade fibrosarcomatous DFSP w/ nuclear atypia and a high miotic index. After failure to achieve response with initial treatment, pt was started on imatinib. 1 mo after initiating imatinib treatment, examination showed a dramatic tumor response w/ disappearance of the palpable back lesion. 3 mo after treatment, a CT of the chest showed resolution of the 3 lung nodules. Pt has now remained in clinical complete remission for over 20 mo on imatinib 400 mg/day treatment.
Maki, Awan, Dixon, et al., 2002[315]	Case reports	400 mg PO q day	2	Pt 1: 19 y/o male w/ DFSP. Pt received several cycles of chemotherapy. Was given imatinib. There was transient response of visible subcutaneous lesions after 4 wk treatment, but the pt progressed rapidly thereafter and died. Pt 2: 29 y/o male w/ DFSP required 2 resections for right shoulder mass. After failure to respond to treatment, pt was started on imatinib. CT showed reduction in all masses, multiple small lung nodules resolved, a right paratracheal mass also resolved completely. He had continuing improvement in the remaining disease after 2 more mo of imatinib treatment.
Mehrany, Swanson, Heinrich, et al., 2006[316]	Case report	400 mg PO BID	1	46 y/o male diagnosed w/ DFSP enrolled in trial for imatinib. Pt had no significant AEs. Clinically significant improvement in tumor size and firmness was appreciated within 8 wk. By 16 mo of treatment, tumor continued to gradually soften, flatten, and decrease. 18 mo after surgery, pt had nearly full function of his muscles of facial expression and no evidence of recurrent disease.
Mizutani, Tamada, Hara, et al., 2004[317]	Case report	400 mg daily	1	49 y/o male presented w/ histology of DFSP. A lung tumor appeared about 1 yr after surgery, and resected tissue showed FS change similar to that in primary lesion. After 1 mo of imatinib treatment the metastatic foci were reduced in size on CT and in the course of 2-3 more mo, no new metastatic foci appeared and the existing foci were further reduced in size. Authors state that DFSP has a strong tendency for local recurrence and metastasis to other organs. Wide resection is currently the fundamental basis in that it targets molecular biological abnormalities, and it provides new possibilities for the treatment of DFSP.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Price, Fletcher, Zielenska, et al., 2005[318]	Case report	400 mg/m^2/day	1	18 mo old female presented w/ h/o enlarging subcutaneous mass in right lower extremity since birth which was presumed to be a hemangioma. Findings of incisional biopsy were typical of DFSP. It became obvious that resection of the tumor would cause unacceptable cosmetic and functional defects. Parental and institutional ethics board approval was obtained to use imatinib in an attempt to induce tumor reduction before local control. Tolerance, toxicity from treatment, and response were assessed weekly during the 1st 4 wk. Clinical improvement was evident after 1 wk of imatinib treatment. After 4 wk there was no palpable mass, the only clinical evidence of the mass being a circumferential area of skin discoloration. Due to slow radiological response and since the family reported that only 50% of dose was actually being ingested by pt, dose was increased to 520 mg/m^2/day.
Rubin, Schuetze, Eary, et al., 2002[319]	Case report	400 mg BID	1	25 y/o male with unresectable, metastatic DFSP received imatinib. Pt was treated for 4 mo. Hypermetabolic uptake of FDG fell to background levels within 2 wk, and the tumor volume shrank by over 75% during the 4 mo of treatment, allowing for resection of the mass. There was no residual viable tumor in the resected specimen, indicating a complete histologic response to treatment w/ imatinib.
Savoia, Ortoncelli, Quaglino, et al., 2006[320]	Case report	400 mg/m^2/day	1	46 y/o female presented w/ large tumor lesion extending symmetrically across the anterior chest wall. Surgery was excluded because it would have provoked unacceptable aesthetic defects, due to the large extension of the tumor, w/o effective probabilities of cure. Treatment w/ imatinib was started. From week 2, a progressive reduction in size, thickness, and infiltration of the tumoral mass was observed. Treatment was discontinued because of a diffuse edema. Treatment was restarted 2 mo later and after additional 8 mo there continues to be significant clinical improvement.
Wright and Petersen, 2007[321]	Case report	400 mg/day	1	43 y/o female diagnosed w/ DFSP who had 2 resections w/ subsequent recurrence. Imatinib was started, then a third resection. Pt is now tumor-free after 16 mo.

Abbreviations: AE(s) = adverse event(s); BID = twice daily; CT = computerized tomography; DFSP = dermatofibrosarcoma protuberans; FDG = fluorodeoxyglucose; h/o = history of; PET = positron emission tomography; po = orally; PR = partial response; SUV = standardized uptake value; y/o = years old.

Imatinib Mesylate for Myelodysplastic Syndrome

Background

Drug: Imatinib mesylate (Gleevec®). Imatinib is a tyrosine kinase inhibitor with antineoplastic activity. Imatinib binds to an intracellular pocket located within specific tyrosine kinases (TK), thereby inhibiting adenosine triphosphate (ATP) binding and preventing phosphorylation and the subsequent activation of growth receptors and their downstream signal-transduction pathways. This agent inhibits TK encoded by the bcr-abl oncogene as well as receptor TKs encoded by the c-Kit and platelet-derived growth factor receptor (PDGFRα) oncogenes. Inhibition of the bcr-abl TK results in decreased proliferation and enhanced apoptosis in malignant cells of Philadelphia chromosome-positive (Ph+) hematological malignancies; effects on c-Kit TK activity inhibit mast-cell and cellular proliferation in diseases that over-express c-Kit.

Imatinib has received Food and Drug Administration (FDA) approval for treatment of newly diagnosed adult patients with: Ph+ chronic myeloid leukemia (CML) in chronic phase; Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy; and c-Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. It has also been approved by the FDA for treating pediatric patients with Ph+ CML in chronic phase who are newly diagnosed, or whose disease has recurred after stem cell transplant, or who are resistant to interferon-therapy. Since the time of initiation of this review, it has been approved by the FDA for use in myelodysplastic syndrome (MDS), chronic eosinophilic leukemia (CEL), systemic mastocytosis (SM), dermatofibrosarcoma protuberans (DFSP), and relapsed/refractory Ph+ acute lymphoblastic leukemia (ALL).

Disease: Myelodysplastic syndrome (MDS). MDS describes a heterogeneous group of hematological diseases in which progenitor cells produced by the bone marrow fail to mature properly. Normally, blood stem cells differentiate into red blood cells, platelets, and white blood cells, but in MDS this process is arrested, resulting in the proliferation of blasts (immature blood cells) and disorderly, ineffective hematopoiesis.[322] Many patients present with cytopenia in one or more hematopoietic cell lines and its complications, including infection, bleeding, and fatigue; patients with proliferative subtypes of MDS may also present with fever, splenomegaly, and leukocytosis.[323]

The incidence of MDS has not been documented, although 1999 statistics suggest that about 13,000 new cases are diagnosed each year. MDS tends to strike an older population, the median age at diagnosis being 65, but it can occur even among pediatric patients.[324]

Prognosis depends on whether MDS is primary or secondary (emerging as a complication of aggressive courses of chemotherapy or radiation for other cancers), on the percentage of blasts, on the number of blood cell types affected, on the degree of cytopenia, and on cytogenetic factors.[322,324] For the majority of patients, the condition is chronic and progressive, with about one third of MDS patients developing acute myelogenous leukemia within months or years; when leukemia results from myelodysplasia, it is extremely resistant to treatment. Most MDS-related deaths, however, are due to bleeding or infection.

Treatment options depend on whether MDS occurred after chemotherapy or radiotherapy, whether MDS has progressed following prior treatment, and the patient's age and general health. Depending on these factors, patients generally receive one of three standard treatments: chemotherapy, for delaying progression of the disease; chemotherapy with stem-cell transplant, a

more aggressive approach that remains the only curative treatment option; and supportive care, including transfusion therapy, growth factor therapy, and drug therapy, for easing symptoms.[322] However, even among patients with the best prognostic profile, median survival is only 5.7 years.[325]

Drug/Disease: Imatinib mesylate for MDS. The development of molecular therapeutics for the treatment of MDS has been constrained by the lack of validated targets, as understanding of the characteristic genetic and biological abnormalities of MDS progenitor cells is limited.[323,326] However, recent research suggests that some MDS patients express the PDGF receptor oncogene, and that PDGF has been implicated in the pathogenesis of various myeloproliferative disorders.[327] This offers a rationale for targeted inhibition of the c-kit and PDGF receptor oncogenes as an MDS treatment strategy. With its potent, selective inhibition of both receptors, imatinib has drawn the attention of clinical investigators seeking to improve outcomes and quality of life for patients with MDS.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded a total of four reports, two of which were full reports of clinical trials published in 2003 and 2007 (Table A51), and two of which were case reports published in 2003 and considered in the horizon scan (Table A52).

The Phase II clinical trial published in 2003 evaluated the safety and efficacy of imatinib 400 mg/day as monotherapy among a sample of 48 patients who had either acute myeloid leukemia (AML; n = 10), MDS (n = 8), myelofibrosis (MF; n = 18), atypical chronic myeloid leukemia (CML; n = 7), chronic myelomonocytic leukemia (CMML; n = 3; note that CMML is now classified by the World Health Organization as a myeloproliferative neoplasm [MPN] rather than as MDS), or polycythemia vera (n = 2). Eligibility criteria included the presence of > 10 percent c-kit expression in bone marrow blasts. Only adults were included in this study, with ages ranging from 23 to 83 years. Patients were enrolled in this study beginning in 2001. The vast majority of patients in this study had undergone treatment prior to enrollment.

The Phase II trial published in 2007 evaluated the safety and efficacy of adding imatinib 600 mg/day for up to twelve 21-day cycles to low-dose Ara-C (LDAC) among a sample of 40 patients with c-Kit+ AML or high-risk myelodysplastic syndrome (HR-MDS). The results of this study were not stratified by AML versus HR-MDS. The primary clinical outcome assessed was hematologic changes. Only adults were included in this study, with ages ranging from 42 to 82 years.

Efficacy and toxicity were reported in both studies represented in the full reports. Hematologic remission was the primary outcome sought. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria (CTC).

Study quality of the two full published reports was variable. The study published in 2007 met four of the five quality criteria, whereas the one published in 2003 met only the explicit eligibility criteria and objective outcomes assessment criteria.

Efficacy. None of the 18 patients with AML or MDS in the trial published in 2003 had a complete response (CR) or partial response (PR) by standard criteria. Thirteen of the 18 patients with MF demonstrated an objective improvement. Only one of seven patients with atypical CML had a major hematologic improvement, and none of the three patients with CMML responded to treatment. Of the 38 evaluable patients in the 2007 study, only one (3 percent) had a CR, and one (3 percent) had a PR. The mortality rate in this study was 19 percent after the first 6 weeks of treatment, and 33 percent after 3 months. Median progression-free survival was 41 days, and median overall survival was 138 days.

Adverse events. Adverse events data from the two full reports are summarized in Table A53. Grade 3/4 superficial edema (3 percent, 4 percent), nausea (2 percent, 3 percent), and myalgia or musculoskeletal pain (4 percent, 8 percent) were reported in both clinical trials. In one trial, 21 percent of patients had neutropenic fever.

Horizon scan. The horizon scan identified two case reports. One described a 67 year-old female with mild pancytopenia who did well on 600 mg/day of imatinib, and the other a 74 year-old male with refractory cytopenias with multilineage dysplasia who did not respond to imatinib therapy.

Discussion

Recent research suggests that some MDS patients express the PDGF receptor oncogene, and that PDGF has been implicated in the pathogenesis of various myeloproliferative disorders.[327] This offers a rationale for targeted inhibition of the c-kit and PDGF receptor oncogenes as an MDS treatment strategy. This rationale, combined with the fact that MDS is often refractory to existing treatments, suggests that imatinib may be a potentially important targeted therapy for MDS. The published data described in this review suggest that imatinib is well tolerated in this patient population, with the only commonly occurring adverse event being neutropenic fever (21 percent). The two studies involving a total of fewer than 50 patients provide insufficient data to support firm conclusions, but their findings suggest that imatinib is not effective in the treatment of MDS. Complete response was achieved in a single patient, and only one patient achieved a partial response.

Table A51: Imatinib with Myelodysplastic Syndrome – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Cortes, Giles, O'Brien, et al., 2003[327]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Pts with AML or high-risk MDS who failed prior chemotherapy, or previously untreated pts > 60 yr old who were not candidates for chemotherapy, or low-risk MDS, CMML, MF, PV, or atypical CML regardless of treatment history All pts had to have > 10% c-kit expression in bone marrow blasts	**No. in study:** 48 **Age:** 66 (23–83) **Previous treatment:** Yes, for some **Type of disease:** AML (n = 10) Refractory anemia (n = 8) RAEB (n = 7) MF (n = 18) Ph- CML (n = 7) CMML (n = 3) PV (n = 2) **Drug dose/day [followup]:** Imatinib 400 mg/day **Outcomes sought:** Not reported	**N:** 48 **PR:** MF: 13/18 (72%) had an objective improvement **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** AML or MDS: 15 wk **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A53 **Quality assessment:** 1) Representative sample from a relevant population?: No 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Single-agent imatinib was not associated with significant clinically meaningful response for any of the diseases included in this study

Study	Study Design	Patients	Tumor Response	Survival	Other
Heidel, Cortes, Ricker, et al., 2007[328]	**Design:** Uncontrolled clinical trial evaluating the safety & efficacy of adding imatinib to LDAC **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** c-Kit+ AML or high-risk myelodysplastic syndrome (HR-MDS)	**No. in study:** 40 **Age:** 73 (42–82) **Previous treatment:** Yes, for some **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 600 mg daily, 21-day cycles, up to 12 cycles **Outcomes sought:** Hematologic changes (e.g., blast response)	**N:** 38 evaluable **CR:** 1 (3%) **PR**: 1 (3%) **Stable disease:** 8 (21%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** Mortality rate 19% after 1st 6 wk of treatment and 33% after 3 mo **Median survival:** Median PFS = 41 days (range up to 405) Median overall survival = 138 days, w/ 20% of pts alive after 600 days **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A53 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** LDAC/IM not more effective than LDAC monotherapy

Abbreviations: AML = acute myelocytic leukemia; CML = chronic myelogenous leukemia; CMML = chronic myelomonocytic leukemia; CR = complete response; HR = high risk; IM = imatinib; LDAC = low dose Ara-C; MDS = myelodysplastic syndrome; MF = myelofibrosis; PFS = progression-free survival; Ph = Philadelphia chromosome; PR = partial response; PV = polycythemia vera; RAEB = refractory anemia with excess of blasts.

Table A52: Imatinib for Myelodysplastic Syndrome – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Drummond, Lush, Vickers, et al., 2003[329]	Case report	600 mg/day	1	67 y/o female presented with mild pancytopenia. Imatinib was initiated 23 mo after initial diagnosis. Transient Grade 3 neutropenia and Grade 2 thrombocytopenia and anemia occurred in first 10 wk of treatment, requiring transfusion of 2 units of packed red cells. Only minor residual dysplastic changes were observed and blasts were absent. Currently, pt has mild pancytopenia on 600 mg/day and remains well.
Mesa, Steensma, Hoyer, et al., 2003[330]	Case report	400 mg/day	1	74 y/o male with slowly progressive leucopenia, macrocytic anemia, and thrombocytopenia over a 10-yr period presented at reporting institution. Pt was diagnosed with refractory cytopenias with multilineage dysplasia. Owing to marked progression, imatinib was begun as treatment. Pt remained on imatinib for 6 mo. Pt had no improvement in anemia or thrombocytopenia. Pt developed pneumonia and died. Autopsy demonstrated an infiltration of myeloid progenitors in all major organs.

Abbreviations: y/o = year-old.

Table A53: Imatinib for Myelodysplastic Syndrome – Adverse Events (Grade 3/4+ Events Only)

Study	Superficial edema	Diarrhea	Nausea	Vomiting	Dyspepsia	Constipation	Dermatitis or rash	Fatigue	Headache	Pain	Anorexia	Myalgia or musculoskeletal pain	Neutropenic fever	Upper respiratory tract infection	Thrombosis/embolism	Cardiac arrhythmia	Depression/anxiety	Agitation/confusion	Syncope/TIA	Musculoskeletal/fracture	Hemorrhage	Hypokalemia	Creatinine elevation	Allergic rhinitis
Cortes et al., 2003[327]	4%	-	2%	-	2%	-	-	2%	-	-	-	4%	-	-	-	-	-	-	-	-	-	-	-	-
Heidel et al., 2007[328]	3%	0%	3%	3%	-	0%	8%	0%	0%	0%	0%	8%	21%	3%	5%	3%	0%	3%	5%	0%	0%	3%	3%	0%

Abbreviation: TIA = transient ischemic attack.

Imatinib for Systemic Mastocytosis

Background

Drug: Imatinib mesylate (Gleevec®). Imatinib is a tyrosine kinase inhibitor with antineoplastic activity. Imatinib binds to an intracellular pocket located within specific tyrosine kinases (TK), thereby inhibiting adenosine triphosphate (ATP) binding and preventing phosphorylation and the subsequent activation of growth receptors and their downstream signal-transduction pathways. This agent inhibits TK encoded by the bcr-abl oncogene as well as receptor TKs encoded by the c-Kit and platelet-derived growth factor receptor (PDGFRα) oncogenes. Inhibition of the bcr-abl TK results in decreased proliferation and enhanced apoptosis in malignant cells of Philadelphia chromosome-positive (Ph+) hematological malignancies; effects on c-Kit TK activity inhibit mast-cell and cellular proliferation in diseases that over-express c-Kit.

Imatinib has received Food and Drug Administration (FDA) approval for treatment of newly diagnosed adult patients with: Ph+ chronic myeloid leukemia (CML) in chronic phase; Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy; and c-Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal (GI) stromal tumors. It has also been approved by the FDA for treating pediatric patients with Ph+ CML in chronic phase who are newly diagnosed, or whose disease has recurred after stem cell transplant, or who are resistant to interferon-therapy. Since the time of initiation of this review, it has been approved by the FDA for use in myelodysplastic syndrome (MDS), chronic eosinophilic leukemia (CEL), systemic mastocytosis (SM), dermatofibrosarcoma protuberans (DFSP), and relapsed/refractory Ph+ acute lymphoblastic leukemia (ALL).

Disease: Systemic mastocytosis. A clonal eosinophilic disorder of the mast cell and its precursor cells, SM is a progressive neoplastic condition characterized by mast cell infiltration of extracutaneous organs. An extremely rare condition, whose incidence remains undocumented, SM affects people of all ages, but occurs more commonly in older patients, especially in its more aggressive forms.[331] Prognosis varies depending on the subtype, with patients with aggressive SM having a life expectancy of a few years.[332]

Although 90 percent of adult SM patients present with focal mast cell lesions in the bone marrow, which often leads to involvement of the peripheral blood and coagulation system, SM mast cells also commonly accumulate in the skin, GI tract, liver, spleen, and lymph nodes.[331] Symptoms occur with the release of mast cell mediators, including histamine, prostaglandins, and leukotrienes, which lead to flushing, itching, GI problems, urticaria, and even syncope or anaphylactic episodes.[333,334] Moreover, the mast cell infiltration can itself manifest as skin lesions, organomegaly, organopathy, and pancytopenia.[333]

Given SM's heterogeneous manifestations, therapy must be individualized. For patients with indolent forms, intensive therapy is not justified, so treatment remains primarily symptomatic, directed at addressing anaphylaxis, pruritis, flushing, and problems associated with intestinal malabsorption.[331] Patients with aggressive disease require cytoreductive therapy, which may involve the use of interferon-alpha or 2-chlorodeoxyadenosine (cladribine), both of which are associated with considerable toxicity. More recently, molecularly targeted therapies have come under investigation as alternative first-line treatments.[335]

Drug/Disease: Imatinib mesylate for systemic mastocytosis. Several types of mutations of the c-Kit proto-oncogene, which stimulates mast cell proliferation, have been demonstrated to

cause mastocytosis.[331] The FIP1L1-PDGFRα fusion protein has also been implicated in mastocytosis.[336] Therefore, over the past few years, clinical research initiatives seeking to develop more tolerable therapies, as well as to improve outcomes and quality of life among patients with SM, have investigated treatments, including imatinib, that specifically target the constitutive kinase activity of the mutated c-Kit proto-oncogene, and the FIP1L1-PDGFRα fusion gene.[332]

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded at total of 14 reports; two of these were full reports of clinical trials (Table A54), three were published abstracts from the American Society of Hematology (ASH) 2006 conference (Table A55), and nine were additional articles considered in the horizon scan (Table A56). Both full reports were of Phase II clinical trials. One of the abstracts reported the findings of a Phase II trial, one was a retrospective survey, and the third was a case report. Eight of the horizon scans were case reports or case series, and one was a retrospective review of 18 patients, 15 of whom had SM. The earliest publication seen in the literature was a full report published in 2003.

Sample sizes for the three clinical trials ranged from four to 14, with a total of 26 patients described in the full reports, and 30 in the full reports plus abstract. Eligibility criteria were previously treated, histology-proven, symptomatic SM for two trials (sample sizes of 12 and 14), and SM with wild-type c-kit exon 17 for the third trial (sample size of four). Patient age across the full reports ranged from 10 to 70. All studies involved only adults, with ages ranging from 31–85.

Imatinib was used at a dose of 400 mg per day for 3 or more months in combination with prednisone (15 mg twice per day for 2 weeks); or as monotherapy, initially at 100 mg per day, then increased to 400 mg per day, or at 400 mg per day advanced to 800 mg per day as tolerated for 6 months.

Efficacy was reported in each of the three studies. Outcomes sought included reduction in serum tryptase activity or reduction in urinary N-methylhistamine in one study, mast cell cytoreduction in another study, and "clinical response" in the third study.

Only one of the studies provided data on adverse events.

The two full reports met three of five quality criteria (e.g., representative sample, explicit eligibility criteria, and use of objective outcomes assessments).

Efficacy. Only two of the 27 evaluable patients (7 percent) in the three trials combined demonstrated a complete response (CR). Thirty-eight percent of the 13 evaluable patients demonstrated a "major" response in one study, 30 percent had a partial response (PR) in another study, and all four of the patients in the study reported as an abstract had a PR. The two patients who did not respond to treatment in one of the studies were the only two patients with the c-Kit D816V mutation.

Survival. Survival data were not reported in any of the studies.

Adverse events. Only one of the two full reports provided data on adverse events.[337] In this study, the only Grade 3/4 adverse event reported was toxicodermia, which occurred in one patient (7 percent) taking imatinib 400 mg per day in combination with prednisone.

Horizon scan. The horizon scan identified reports that suggest that imatinib for SM may:

- Be associated with reduction in bone marrow mast cell infiltration;
- Help resolve hepatosplenomegaly and lymphadenopathy;
- Decrease eosinophil counts;
- Be associated with transient symptom improvement.

Discussion

Over the past few years, clinical research initiatives aimed at developing more tolerable and effective therapies for SM have investigated treatments, including imatinib, that specifically target the constitutive kinase activity of the mutated c-kit proto-oncogene and the FIP1L1-PDGFRα fusion gene. This review identified three Phase II reports involving 29 patients with SM treated with imatinib as monotherapy or in combination with prednisone. The results suggest that imatinib is well tolerated among patients with SM, with the only commonly occurring Grade 3/4 adverse event (7 percent) being toxicoderma. These three reports provide insufficient data to support firm conclusions, but their findings suggest some efficacy of imatinib in the treatment of SM, with PR rates ranging between 30 percent and 100 percent. The ASH 2006 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates.

Given the rarity of SM (and lack of patients for clinical trials), the need for systemic therapeutic interventions among some patients with severe and/or highly symptomatic disease, and the presence of a target for imatinib in this disease, treatment with imatinib in SM is a sensible strategy even in the setting of few published data and the incomplete exploration in clinical trials identified in this review.

Table A54: Imatinib for Systemic Mastocytosis – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Droogendijk, Kluin-Nelemans, van Doormaal, et al., 2006[337]	**Design:** Uncontrolled trial **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Histology-proven systemic mastocytosis - High tryptase, and/or high urinary-methylhistamine excretion - Symptoms unresponsive to prior treatment	**No. in study:** 14 **Age:** 51 (43–73) **Previous treatment:** Yes **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 400 mg q day x 3 or more mo Prednisone 15 mg BID also during 1st 2 wk **Outcomes sought:** Reduction in serum tryptase activity and urinary N-methylhistamine	**N:** 13 evaluable. Decrease in urinary-methylhistamine excretion in all pts **CR:** 0 **PR:** 5 (38%) "major" response **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 toxicodermia occurred in one patient (7%). **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Imatinib was effective in pts w/ SM, including D816V+ mutations
Pardanani, Elliott, Reeder, et al., 2003[338]	**Design:** Uncontrolled trial **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Adults w/ bone-marrow biopsy proven, symptomatic mast-cell disease	**No. in study:** 12 **Age:** Not reported **Previous treatment:** Yes **Stage of disease:** Aggressive SM = 7 Indolent SM = 4 Mast-cell leukemia = 1 **Drug dose/day [followup]:** Imatinib 100 mg q day initially, then 400 mg q day **Outcomes sought:**	**N:** Not reported **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Suggests that imatinib curbs the growth-promoting role of wild type c-kit or targets an as yet undefined oncogenic kinase

Study	Study Design	Patients	Tumor Response	Survival	Other
		Mast cell cytoreduction			

Abbreviations: BID = twice daily; CR = complete response; PR = partial response; q = every; SM = systemic mastocytosis.

Table A55: Imatinib for Systemic Mastocytosis – ASH 2006 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Hsieh, Lichtin, Katz, et al., 2006[339] ASH 2006 Abstract #4926	**Disease:** Systemic mastocytosis **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Systemic mastocytosis with wild-type c-kit exon 17 (since D816V mutation resistant to imatinib)	**No. in study:** 4 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** 400 mg daily advanced to 800 mg daily as tolerated for 6 mo **Outcomes sought:** Response	**N:** 4 **CR:** Not reported **PR:** 4 (100%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Low-grade toxicity, including edema, nausea, muscle cramps, conjunctivitis, fatigue, and cough
Pagano, Valentini, Musto, et al., 2006[340] ASH 2006 Abstract #4874	**Disease:** Systemic mastocytosis **Design:** Retrospective survey, multicenter **Phase:** Not reported **Selection/randomization:** Not reported **Eligibility criteria:** Not reported	**No. in study:** 30 **Age:** 62 **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib at any time during treatment **Outcomes sought:** Response	**N:** 17 **CR:** 1 (6%) **PR**: 4 (24%) **Stable disease:** 5 (29%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** 10 yr overall survival 87% in 30 patients with or without imatinib **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Imatinib effective only in D816V mutation negative patients

Study	Study Design	Patients	Tumor Response	Survival	Other
Sohal, Hammour, Chamorthy, et al., 2006[341] ASH 2006 Abstract #4451	**Disease:** Systemic mastocytosis with mast cell sarcoma **Design:** Case report **Phase:** Not reported **Selection/randomization:** Not reported **Eligibility criteria:** Not reported	**No. in study:** 1 **Age:** 22 **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Imatinib 400 mg daily, given after initial partial resection of tumor **Outcomes sought:** Not reported	**N:** 1 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive Disease**: 1	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease-free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported

Abbreviations: ASH = American Society of Hematology; CR = complete response; PR = partial response.

Table A56: Imatinib for Systemic Mastocytosis – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Akin, Fumo, Yavuz, et al., 2004[342]	Case report	Escalating to 400 mg/day	1	25 y/o female presented for evaluation of SM. After no response from initial treatment, pt was started on imatinib, given in increasing doses until 400 mg/day was reached. Pt experienced headaches, nausea, and vomiting at full dosage, which gradually resolved after several weeks of treatment. A bone marrow biopsy and aspirate after 2 mo treatment revealed a notable reduction in the extent of bone marrow mast cell infiltration, with mast cells representing less than 10% of the bone marrow biopsy and approximately 2% of the aspirate. The reduction in mast cell numbers in bone marrow and serum tryptase was accompanied by a dramatic improvement in symptoms. 5 mo after initiation of imatinib, pt reported resolution of episodes of lightheadedness, improvement in energy level, and a reduction of musculoskeletal pain with discontinuation of narcotic analgesics and as-needed use of H_1 antihistamines.
Callera and Chauffaille, 2005[343]	Case report	400 mg/day	1	20 y/o male referred with mediastinal and retroperitoneum lymphadenopathy, hepatomegaly, and splenomegaly was diagnosed with aggressive SM. Pt received imatinib in association with interferon alpha 2b (5 million units 3x/wk). 1 mo later, pt reported abdominal pain had greatly improved, weight was stable. 5 mo after initial treatment, chest and abdominopelvic scanning showed no evidence of mediastinal or retroperitoneum lymphadenopathy but pt continued to have splenomegaly. 10 mo after diagnosis, pt had sudden death at home. Family did not authorize necropsy.
Dalal, Horsman, Bruyere, et al., 2007[344]	Case report	100 mg/day	1	45 y/o male presented with 3-yr h/o fatigue, urticaria and dermatographism. There was no hepatosplenomegaly. Proton pump inhibitor provided little improvement. Diagnosis of ASM. After several cycles of treatment with little or no response, pt was started on low-dose imatinib. Within weeks pt demonstrated complete disappearance of his symptoms along with resolution of the hepatosplenomegaly and lymphadenopathy. Pt remains asymptomatic on low-dose imatinib.
Elliott, Pardanani, Li, et al., 2004[345]	Case report	400 mg/day	1	30 y/o male with 5-mo h/o fatigue, fever, night sweats, and weight loss. Diagnosed with SM with associated eosinophilia. After failing initial treatment with interferon-α, pt was started on imatinib. Within 2 days, the leukocyte count decreased and the platelet count remained stable. The dose of imatinib was reduced to 100 mg/day after 1 wk of treatment. Within 6 wk the platelet, neutrophil and hemoglobin normalized, and pt achieved complete clinical remission. Pt remains in complete remission at 19 mo f/u. Author states this case demonstrated the value of bone marrow histology enhanced with tryptase or CD117-based immunohistochemistry, as well as bone marrow mast cell immunophenotyping, in the monitoring of effective treatment in SM.
Florian, Esterbauer, Binder, et al., 2006[346]	Case report	100 mg/day	1	51 y/o male presented with 6-mo h/o unexplained dyspnea and cough as well as pruritus and weight loss. Diagnosis of HES with associated SM was established. Treatment with hydroxyurea, corticosteroids, and interferon-alpha-2b did not lead to satisfactory decrease in eosinophils or to clinical improvement. Pt was started on imatinib. According to WHO criteria, pt was diagnosed as SM with associated CEL. After 2 wk, eosinophil counts had decreased. Treatment was well tolerated without any side effects. On day 73, dose was reduced to 50 mg/day. After f/u of 187 days, eosinophil counts appeared to remain consistently normal.
Hennessy	Retro-	Pt 1: 200 mg	18 (15 had	Of these 15 pts, 2 diagnosed with aggressive SM who received imatinib. Pt 1 achieved transient

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Giles, Cortes, et al., 2004[347]	spective review of data-base cases	PO bid Pt 2: 200 mg PO daily	SM and available clinical charts)	symptom improvement and is alive at 72 mo. Pt 2 achieved transient symptom improvement, and interval from diagnosis to death was 73 mo.
Merante, Chichino, Boveri, et al., 2006[348]	Case report	Escalating dose from 100-400 mg/day	1	32 y/o male, HIV-1 infected, with 1-yr h/o severe asthma, cough, leukocytosis, and hypereosinophilia. Recurrent episodes of popular eruptions were reported. Pt received imatinib according to institution's HES protocol. Pt obtained complete hematologic response and the resolution of symptoms after the 1st wk of treatment. Pt obtained a complete molecular remission after 8 wk. Imatinib treatment was well tolerated and no AEs have been reported. At 6 mo f/u pt was still in complete hematologic and molecular response.
Musto, Falcone, Sanpaolo, et al., 2004[349]	Case report	400 mg/day	1	33 y/o male with 3-yr h/o aggressive, sporadic SM. Pt received imatinib. No significant AEs occurred. However, neither improvement of the clinical symptoms nor reduction of cutaneous, GI, and marrow mastocytic infiltration was observed after 16 wk. Treatment was stopped. Pt transferred to trial evaluating effect of thalidomide on SM.
Pardanani, Ketterling, Brockman, et al., 2003[336]	Case reports		12 (5 with eosino-philia)	12 pts, including 5 with associated eosinophilia, were prospectively treated with imatinib. Testing for presence of F1PILI-PDGFRA rearrangement on these pts as well as loss of CH1C2 allele.

Abbreviations: AE(s) = adverse event(s); bid = twice per day; CEL = chronic eosinophilic leukemia; f/u = followup; GI = gastrointestinal; HES = hyper-eosinophilic syndrome; HIV-1 = human immunodeficiency virus-1; h/o = history of; PO = per os (orally); SM = systemic mastocytosis; WHO = World Health Organization; y/o = year-old.

Rituximab for Chronic Lymphocytic Leukemia

Background

Drug: Rituximab (Rituxan®). Rituximab is a humanized monoclonal antibody that binds to the CD20 protein, which is expressed on pre-B and mature B lymphocytes but not on hematopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissues. Possible mechanisms of action include induction of antibody dependent cell-mediated cytotoxicity, complement mediated lysis, phagocytosis of antibody-coupled tumor cells, and induction of apoptosis.

In November 1997, rituximab received Food and Drug Administration (FDA) approval as a treatment for relapsed or refractory non-Hodgkins lymphoma. Rituximab then received FDA approval in February 2006 for first-line treatment of diffuse large B-cell, CD20-positive non-Hodgkin lymphoma, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or other anthracycline-based chemotherapy regimens. In September 2006, the FDA approved two rituximab supplemental applications for the first-line treatment of patients with low grade or follicular B-cell, CD20-positive non-Hodgkin lymphoma: first, for use in combination with cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; second, for use following CVP chemotherapy. Rituximab has been evaluated for off-label use in nodular lymphocyte predominant Hodgkin disease (NLPHD), Waldenström's macroglobulinemia (WM), and chronic lymphocytic leukemia (CLL).

An FDA alert issued in December 2006 highlights important emerging safety information about rituximab.[350] There are at least two reported deaths associated with rituximab for systemic lupus erythematosus (SLE). The cause of death in one patient was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated John Cunningham (JC) virus. Latent JC virus is present in about 80 percent of adults.

Disease: Chronic lymphocytic leukemia. CLL is the most common form of adult leukemia, with 15,110 new cases and 4,390 deaths predicted for 2008. More than 75 percent of newly diagnosed CLL cases occur in patients over the age of 50.[351] CLL results in abnormal neoplastic proliferation of functionally incompetent B cells, which accumulate primarily in bone marrow and blood, and is characterized by the coexpression of the B-cell antigens CD19, CD20, and CD23, along with the T-cell antigen CD5. The degree of CD20 expression is often less than that seen in other lymphoma patients, frequently described as dim-CD20 positive.[352,353]

CLL has a heterogeneous natural history, with survival varying from less than 5 years to more than 25 years. The initial stage is relatively benign, and diagnosis is often incidental, occurring when routine blood tests suggest the presence of lymphocytosis. Eventually, as it progresses, CLL results in swollen lymph nodes, spleen, and liver, which may later be accompanied by anemia, thrombocytopenia, and infections, as healthy lymphocytes and other hematopoietic cells are increasingly crowded out.[354] During CLL's terminal progressive and therapeutically resistant phase, disease- and treatment-related morbidity is substantial.[355]

Decisions regarding the timing and type of treatment are currently guided by disease stage, the presence of symptoms, and disease activity.[353] Because CLL typically has a prolonged onset and occurs in an older population for whom aggressive treatment can be risky, clinicians ordinarily take a conservative approach for early-stage patients, relying on periodic observation ("watchful waiting") and treatment of symptoms.[356,357] For patients with progressing disease, various therapies may be deployed: chemotherapy, radiation, monoclonal antibodies, and bone

marrow and peripheral blood stem cell transplants.[354] However, none of these treatments exerts more than a modest impact on overall survival. New, experimental combinations of chemotherapeutic agents with purine analogs and monoclonal antibodies have led to longer progression-free intervals, but still have not demonstrably improved survival.[358]

Drug/Disease: Rituximab for Chronic Lymphocytic Leukemia. As an anti-CD20 immunoglobulin, rituximab antagonizes the CD20 surface antigens that are expressed in various densities on malignant lymphocytes in CLL. Following binding, rituximab triggers a cytotoxic immune response against CD20-positive cells and thus has been investigated in as a logical treatment option since the late 1990s.[359,360]

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded at total of 81 reports. Of these, 21 were published full reports (Table A57); 33 were published abstracts from the American Society of Hematology (ASH) 2006, ASH 2007, and American Society of Clinical Oncology (ASCO) 2007 conferences (Table A58); and 32 were additional articles considered in the horizon scan (Table A59). Five of the 21 full reports provided data used in another published report in our analysis, thereby resulting in a total of 16 different Phase I/II, non-randomized clinical trials published as full reports. There were an additional 29 Phase I/II trials published as abstracts, for a total of 45 clinical trials and four retrospective reviews when considering the full reports plus abstracts. No Phase III randomized clinical trial was identified. A case report of tumor lysis and intravascular coagulation associated with rituximab having been used for CLL appeared in the literature in 1998. In 1999, one case series and one small phase I trial were published. The first Phase II trial to appear in the literature was published in 2001.

Sample sizes for the clinical trials ranged from three to 300, with a total of 1,000 patients presented in the full reports, and 2,541 patients presented in the full reports plus abstracts. A small percentage (not quantifiable given the available information) of these patients did not have CLL or did not receive rituximab. Eligibility criteria for inclusion in the studies were generally uniform and consistent with what would be expected from studies involving patients with CLL, as defined by National Cancer Institute (NCI) 1996 guidelines. CD20-positive status was an inclusion criterion for most studies. Some studies also included patients with small lymphocytic lymphoma (SLL). Many studies included patients at any given stage of disease. Among the 16 studies represented in the fully published reports, five included only previously untreated patients, four included only treated patients, and seven included both previously treated and untreated patients. All of the studies involved adults. Patient age across the full reports ranged from 24 to 89.

The most common dosage of rituximab was 375 mg/m^2 weekly, usually for 4 weeks. Rituximab was usually used in combination with other pharmacological treatments, including fludarabine, cyclophosphamide, pentostatin, or chlorambucil.

Efficacy was reported in each of the 16 studies represented in the full reports. Nearly all of the studies assessed tumor response according to NCI-sponsored Working Group criteria. Adverse events were assessed using the NCI's Common Toxicity Criteria (CTC).

Study quality of the full published reports was almost universally poor. The frequency of the quality criteria was 6 percent for four of five criteria having been met, 75 percent for three criteria, and 13 percent for two criteria. One study (6 percent) met only one quality criterion. Most of the studies that met three or fewer quality criteria did not have an adequate followup period and did not enroll patients at a similar point in the disease process, either because many different stages of disease met inclusion criteria or not all patients had CLL, or both.

Efficacy. The range of complete response (CR) rates was 0 percent to 70 percent among the 16 fully published studies. Efficacy data were inconsistently reported in the abstracts. The range of partial response (PR) rates was 15 percent to 67 percent among the fully published studies, and 23 percent to 90 percent among the abstracts.

Adverse events. The adverse events data summarized in Table A60 were derived from the 11 full reports that reported such data. Hematologic events were the most common Grade 3/4 adverse events, followed by infection (range, 0 percent to 58 percent, reported in six studies). Neutropenia/granulocytopenia (range, 13 percent to 54 percent), thrombocytopenia (range, 4 percent to 20 percent), and anemia (range, 0 percent to 10 percent) were reported in seven studies, and eight studies reported chills or fever (range, 0 percent to 6 percent).

Horizon scan. Nearly all of the horizon scan publications were case reports or case series that reported either positive outcomes or adverse events, or both, associated with rituximab. The adverse events reported were variable across organ systems and severity. No clear pattern of the type or nature of adverse events possibly associated with rituximab use among patients with CLL was evident.

Discussion

As an anti-CD20 immunoglobulin, rituximab is theoretically well suited to treating CD20-positive CLL. Nearly all of the reports identified in this review included only patients with CLL known to have CD20-positive status. These reports provide relatively compelling evidence in support of the role of rituximab in the treatment of CLL. The quality of the studies was generally poor, and there is great variability in the clinical response rates, but in the aggregate the reports suggest some efficacy. CR and PR rates ranged from 0 percent to 70 percent and 15 percent to 67 percent, respectively, among the 16 fully published studies, and no clear pattern of the type or nature of adverse events possibly associated with rituximab use among patients with CLL was evident. Comparative effectiveness trials are needed to better determine the appropriate role of rituximab in the treatment of CLL.

Table A57: Rituximab for Chronic Lymphocytic Leukemia – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Byrd, Murphy, Howard, et al., 2001[361] AND Bannerji, Kitada, Flinn, et al., 2003[362] AND Byrd, Smith, Hackbarth, et al., 2003[363] AND Farag, Flinn, Modali, et al., 2004[364]	**Design:** Uncontrolled clinical trial Evaluate a thrice-weekly regimen of rituximab Three cohorts, each with slightly different rituximab protocols **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - CLL according to NCI WG criteria, or SLL as defined by IWF classification - Had to have failed prior treatment, but untreated pts could enroll if met certain conditions - ECOG PS 0-3 - Life expectancy > 12 wk - CD20-positive - Creatinine < 3.0	**No. in study:** 33 26 w/ CLL 7 w/ SLL **Age:** 66 (50-80) **Previous treatment:** Yes for 27/33 pts (73%) **Stage of disease:** Rai Stage: II: 9 (27%) III: 3 (9%) IV: 21 (64%) **Drug dose/day [followup]:** Three cohorts: I: Rituximab 250 mg/m^2 II: Rituximab 375 mg/m^2 III: Rituximab 375 mg/m^2 4-wk course of treatment **Outcomes sought:** Tumor response (NCI WG criteria) Clinical features predicting response to treatment	**N:** 33 (29 evaluable) 4 unevaluable: 1 died of pulmonary hemorrhage on day 3; 1 had septic arthritis; 1 died of sepsis; 1 had ITP **CR:** 1 (3%) **PR**: 14 (48%) **Stable disease:** 11 (38%) **Progressive disease:** 3 (10%)	**Survival overall (from start of treatment):** **Median survival:** Median response duration = 10 mo (3-17+) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** Median TTP for all pts = 6 mo (0-18+) **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes
Del Poeta, Del Principe, Consalvo, et al., 2005[365]	**Design:** Non-randomized trial Evaluate efficacy of adding rituximab after 6-cycle treatment with fludarabine Also identified predictors	**No. in study:** 60 (all evaluable) **Age:** 59 (37-74) **Previous treatment:** None **Stage of disease:**	**N:** 60 **CR:** 47 (78%) Induction CR of 70%, OR = 92% [this is with fludarabine] **PR:** 9 (15%) 13 pts had induction PR	**Survival overall (from start of treatment):** **Median survival:** Median followup 27 mo (no range given) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
	of response **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - CLL as defined by NCI 1996 guidelines - No prior treatment - ECOG status of 0-3 - Either: 1) required treatment for Rai Stage I-II; or 2) had Rai Stage III-IV - Exclusions: + Coombs test, active infections, major organ dysfunction	Either: 1) required treatment for Rai Stage I-II or 2) had Rai Stage III-IV Rai modified stage: Low: 5 (8%) Intermediate: 52 (87%) High: 3 (5%0 **Drug dose/day [followup]:** Fludarabine 6 cycles Then, after a median of 40 days, pts restaged to determine response Pts with stable disease or better given rituximab 375 mg/m^2 q wk x 4 wk **Outcomes sought:** Response 4-6 wk after last rituximab treatment Tumor response (NCI WG criteria) CR or PR had to be maintained for ≥ 8 wk	but later converted to CR with rituximab, for total of 9 CR **Stable disease:** 1 (2%) **Progressive disease:** 3 (5%)	**Survival (disease free):** **Median survival:** Median followup 27 mo **1 yr:** NR **3 yr:** 68% Shorter PFS in ZAP-70+ pts (25% vs. 100% at 3 yr, p = 0.00005), in CD38+ pts (18% vs. 91% at 3 yr, p = 0.00002), and in pts with more minimal residual disease (36% vs. 77% at 2.5 yr, p = 0.001)	4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes
Hainsworth, Litchy, Barton, et al., 2003[366]	**Design:** Uncontrolled clinical trial Aim: Assess toxicity of rituximab; preliminary assessment of efficacy Standard 4-wk course, plus rituximab re-treatments **Phase:** Phase II	**No. in study:** 44 39 (89%) had CLL 5 (11%) had SLL All 44 pts completed the first 4-wk course of rituximab 43 evaluable at week 6 (lost pt transferred to another MD)	**N:** 44 (43 evaluable) **CR:** 4 (9%) NOTE: These #'s represent "best response"; 6-wk followup #'s are slightly different Also, CR includes some unconfirmed CR cases **PR:** 21 (49%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** After median followup of 20 mo, 24 pts remain	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: Yes 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
		Age: 66 (38-85)		progression-free	
	Selection/ randomization: Not randomized	**Previous treatment:** None	**Stable disease:** 18 (42%)	Median PFS time is 18.6 mo	
	Eligibility criteria: - CD20+ B-cell CLL or SLL; excluded pts with other indolent lymphomas and WM - Rai Stage II, III, and IV; Stage 1 eligible if with systemic symptoms - No prior treatment for CLL/SLL - ECOG PS 0-2 - Normal LFT, RFT - No autoimmune hemolytic anemia	**Stage of disease:** Stage I: 2 (5%) II: 11 (25%) III: 7 (16%) IV: 24 (55%) 29 (66%) had malignant lymphocyte counts > 20,000/microL **Drug dose/day [followup]:** Rituximab 375 mg/ml q wk x 4 wk; some got allopurinol; routine premeds 28/43 (65%) got 1 or more re-treatment courses of rituximab **Outcomes sought:** For pts with CLL: CR = complete resolution of adenopathy/ organosplenomegaly Marrow w/ < 30% lymphs & no lymphoid nodules PR: > 50% decrease in adenopathy/organomegaly & > 50% improvement in other cytopenias Progression: > 25% increase in adenopathy/megaly	**Progressive disease:** 0 (0%)	1- &2-yr actuarial PFS rates are 62% & 49% 38 (86%) remain alive, 4 (9%) died of progressive disease, 2 (5%) died of intercurrent illness. **1 yr:** 62% **2 yr:** 49% **3 yr:** 44 (but only 43 evaluable)	

Study	Study Design	Patients	Tumor Response	Survival	Other
		Stable: Other			
Itala, Geisler, Kimby, et al., 2002[367]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Inclusion: - Age 17-75 yr - Confirmed diagnosis of CLL - Need treatment because of active disease - Life expectancy > 3 mo - ECOG grade 0-2 Exclusion: - Recent treatment with cytotoxic agents - Serious comorbidity - Uncontrolled infection - High LFTs or creatinine	**No. in study:** 24 **Age:** 57 (47-72) **Previous treatment:** No chemotherapy in past 4 wk Median number of previous treatments: 3 (1-5) **Stage of disease:** Binet A: 3 (12%) Binet B: 7 (30%) Binet C: 14 (58%) **Drug dose/day [followup]:** Rituximab 375 mg/m^2 q wk x 4 wk **Outcomes sought:** Response defined by "revised NCI criteria" PR: > 50% decrease in blood lymph count; > 50% reduction in adenopathy/ organomegaly; neutrophil count at least 1.5 x 10 to the 9th or 50% over baseline, etc. CR: Fulfillment of all CR criteria with < 30% lymphs in bone marrow	**N:** 24 (23 evaluable) **Overall Response:** 35% **CR:** 0 **PR:** 8 (35%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
Kay, Geyer, Call, et al., 2007[368] AND Shanafelt, Lin, Geyer, et al., 2007[369]	**Design:** Uncontrolled clinical trial Null hypothesis: Clinical complete response (CCR) is ≤ 25% **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Previously untreated CLL - Normal renal and hepatic function - ECOG status 0-3 - No other cancer	**No. in study:** 65 (but 1 later dropped because received concomitant treatment) **Age:** 63 (38-80) **Previous treatment:** None **Stage of disease:** Rai stage: 0: 3 1: 11 2: 16 3: 17 4: 17 **Drug dose/day [followup]:** PCR regimen Pentostatin, cyclophosphamide & rituximab 375 mg/m^2 on Day 1 21-day, 6-cycle schedule, with TIW rituximab (100 mg/m^2 on day 1 and 375 on days 3 & 5 of first wk), then rituximab at 375 for all subsequent doses Prophylbactrim & acyclovir for 1 yr Also filgrastim on day 3 **Outcomes sought:** Reponses graded according to NCI Working Group criteria with bone	**N:** 64 evaluable **CR:** 26 (41%) Overall response (CR + nodular PR + PR): 58/64 (91%) **PR:** 32 (50%) 14 (22%) had a nodular PR and 18/64 (28%) had a PR **Stable disease:** Not clear **Progressive disease:** Not clear	**Survival overall (from start of treatment):** **Median survival:** Median followup 26 mo (4-48) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Median PFS = 32.6 mo Median duration of response 34 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
		marrow collected after 2 mo of 6-cycle treatment			
Keating, O'Brien, Albitar, et al., 2005[370]	**Design:** Uncontrolled trial FCR regimen for all; no prior treatment Historical comparison, FC only **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - CLL according to NCIWG guidelines - More than 30% lymphocytes in BM - Normal LFTs and RFTs	**No. in study:** 224 **Age:** 58 (24-86) **Previous treatment:** No **Stage of disease:** Rai: 0-II: 149 (67%) III-IV: 75 (33%) **Drug dose/day [followup]:** Rituximab 375 mg/m^2 on day 1 of first cycle, given with fludarabine and cyclophosphamide Cycles 2-6: Rituximab dose 500 mg/m^2 **Outcomes sought:** As defined by NCIWG	**N:** 224 **CR:** 156 (70%) **PR:** 34 (15%) Nodular PR: 23 (10%) PR+NPR: 57 (25%) **Stable disease:** 11 (5%) didn't respond 6/11 had inadequate tumor response; 1 got Richter's; 2 died of pneumonia; 2 lost to followup and were considered treatment failures **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Compared to historical group that received FC only, FCR associated with better CR rate, number of pts w/CD5 & CD9 cells in bone marrow < 1%, time-to-treatment failure, TTP, and survival
Khouri, Lee, Saliba, et al., 2004[371]	**Design:** Non-randomized clinical trial 17 pts w/CLL refractory to fludarabine who received nonablative allogenic stem cell transplantation 10 got rituximab **Phase:** Phase II **Selection/ randomization:**	**No. in study:** 17 (only 10 got rituximab) **Age:** 54 (44-73), but not all got rituximab **Previous treatment:** Yes (all failed prior fludarabine-based chemotherapy) **Stage of disease:** Not reported **Drug dose/day**	**N:** 10/17 got rituximab **CR:** 6 (60%) **PR:** 4 (40%) 4 PR, and 2 "ongoing PR" **Stable disease:** 0 **Progressive disease:** 0	**Survival overall (from start of treatment):** Median followup 21 mo(11-84 mo) **Median survival:** **1 yr:** NR **2 yr:** 80% **3 yr:** NR **Survival (disease free):**	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: No 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:**

Study	Study Design	Patients	Tumor Response	Survival	Other
	Not randomized **Eligibility criteria:** - CLL - Previously failed fludarabine-based chemotherapy - PS 0-2 - Normal organ function	**[followup]:** All got nonablative prep of fludarabine & cyclophosphamide Last 10 pts got rituximab 375 mg/m^2 q wk x 4 wk **Outcomes sought:** Actuarial survival, PFS, rate of progression, GVHD Neutrophil count recovery defined as first of 3 consecutive days that ANC > 0.5 x 10(9) Also platelet count recovery		**Median survival:** **1 yr:** NR **2 yr:** 60% (95% CI 36-85%) **3 yr:** NR	- The 10 pts treated with rituximab had much better survival curve than the 7 who were not - Treatment-related mortality (TRM) 0% at 100 days
Lamanna, Kalaycio, Maslak, et al., 2006[372]	**Design:** Uncontrolled trial PCR regimen for previously treated CLL **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - CLL - Rai class intermediate or high and met NCIWG criteria for active disease - Previously treated	**No. in study:** 46 **Age:** 62 (30-80) **Previous treatment:** Yes, for all pts Median number of previous treatments for CLL cohort = 2 (1-7) **Stage of disease:** SLL: 9 (20%) WM: 1 (2%) Follicular lymphoma: 4 (9%) CLL intermediate risk: 7 (22%) CLL high risk: 25 (78%) **Drug dose/day [followup]:** Pentostatin Cyclophosphamide	**N:** 46 (includes non-CLL pts) Among the 24 CLL responders, CR = 8, nodular response = 1, PR=15 **CR:** 9 (20%) Denominator includes 14 non-CLL pts **PR:** 22 (48%) Denominator includes 14 non-CLL pts **Stable disease:** Not reported **Progressive disease:** 8/32 pts w/CLL had SD (n = 1) or PD (n = 6) or died of infection (n = 1), but no data on the 7/14	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** For the 32 CLL pts, median duration of response = 25 mo, and median time to failure = 40 mo **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: No (heterogeneous sample) 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: Yes 5) Objective outcomes assessments?: Yes **Comments:** - Adding rituximab (to PC) may increase myelotoxicity, but not significantly - Rituximab seems to improve response duration - (Comments from Discussion section – not supported by this study)

Study	Study Design	Patients	Tumor Response	Survival	Other
		Rituximab 375 mg/m^2 **Outcomes sought:** NCIWG	nonresponders with non-CLL		
Robak, Smolewski, Cebula, et al., 2007[373]	**Design:** Non-randomized clinical trial Test feasibility, effectiveness, toxicity of rituximab + 2-CdA (RC) or RC + cyclophosphamide refractory or recurrent CLL **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Inclusion: - CLL according to NCIWG criteria - ≥ 1 prior treatment Exclusion: - Performance status 3 or 4 - Active infection - Abnormal liver or renal function - Richter syndrome - Secondary cancer	**No. in study:** 46 **Age:** 59 (40-80) **Previous treatment:** Yes (all) **Stage of disease:** Rai stage: II: 12 (26%) III: 13 (28%) IV: 21 (46%) **Drug dose/day [followup]:** Rituximab + 2-CdA (RC) or RC + cyclophosphamide Rituximab 375 mg/m^2 on day 1 only and given in 28-day cycles Treat to maximum response or intolerable toxicity **Outcomes sought:** NCIWG criteria	**N:** 46 **CR:** 3 (7%) **PR:** 31 (67%) **Stable disease:** Nonresponders (not reported SD vs. PD): 12 (28%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** Median followup 16 mo (4-54) **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** PFS derived from Kaplan-Meier curves: **1 yr:** 70% **2 yr:** 55% **3 yr:** 55%	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Discrepancy in Table 3; report 13 NR, but this should probably be 12.

Study	Study Design	Patients	Tumor Response	Survival	Other
Savage, Cohen, Hesdorffer, et al., 2003[374]	**Design:** Uncontrolled trial **Phase:** Phase I/II **Selection/ randomization:** Not randomized **Eligibility criteria:** - CD20+ low-grade lymphoma or CLL, AND creatinine < 2.5 mg/dL - Includes NHL + CLL/SLL	**No. in study:** 32 enrolled (29 evaluable) 12 (36%) of patients with CLL (rest with NHL) **Age:** 60 (26-83) **Previous treatment:** Yes (for 17 pts) **Stage of disease:** Stage III-IV: 28 (88%) No data on distribution of lower stages **Drug dose/day [followup]:** Fludarabine on days 1-4, rituximab on day 5, repeated 28 days Rituximab dose escalated, 125 to 250 to 375 mg/m^2 **Outcomes sought:** Not reported	**N:** 29 evaluable **CR:** 10 (34%) **PR:** 14 (48%) **Stable disease:** 2 (7%) **Progressive disease:** 3 (10%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: No 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes
Schulz, Klein, Rehwald, et al., 2002[375]	**Design:** Uncontrolled trial **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Inclusion: - CLL - Age 18-75 yr - Stages Binet B or C at	**No. in study:** 34 enrolled but 3 excluded for total of 31 **Age:** 59 (30-70) **Previous treatment:** No: 20 (70%) Yes: 11 (30%) **Stage of disease:** Binet stage: B: 21 (68%)	**N:** 31 **CR:** 10 (32%) Of these: 7 (23%) confirmed 3 (10%) unconfirmed **PR:** 17 (55%) **Stable disease:** 1 (3%) **Progressive disease:** 3 (9%)	**Survival overall (from start of treatment):** Median followup 54 wk **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** Median duration of response = 75 wk	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
	1st diagnosis or after treatment with chlorambucil, prednisone, or combo - > 30% of lymphs CD20+ ECOG status 0-3 Exclusion: - Prior treatment w/ fludarabine or anthracycline - + Coombs test - Richter's syndrome - Prior treatment w/ murine antibodies - Active infection - Major organ dysfunction - Pregnant or lactating	C: 10 (32%) **Drug dose/day [followup]:** 4 cycles of fludarabine and rituximab (50 mg on day 1, 150 on day 2, remainder of rituximab 375 mg/m^2 on day 3) Subsequent dose rituximab 375 mg/m^2 28-day cycles **Outcomes sought:** Outcomes measured 3-5 wk after last rituximab treatment NCIWG responses		Progression-free survival derived from Kaplan-Meier curves: **Median survival:** **1 yr:** 65% **2 yr:** NR **3 yr:** NR	
Tam, Wolf, Prince, et al., 2006[376]	**Design:** Uncontrolled clinical trial FC-R regimen **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - CLL, SLL, follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, or WM - Creatinine < 0.2 mmol/L - Bilirubin < 35 - ECOG status 0-3	**No. in study:** 77 A total of 34 (44%) had CLL **Age:** 59 (30-89) **Previous treatment:** Yes: 53 (69%) No: 24 (31%) **Stage of disease:** (many different cancers in study) **Drug dose/day [followup]:** Fludarabine, cyclophosphamide, rituximab 375 mg/m^2 4-6 cycles	**N:** 76 evaluable **(1 excluded for early death)** **CR:** 32 (42%) overall 11/34 (32%) CLL **PR:** 31 (41%) overall 22/34 (65%) CLL **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Median followup 20 mo (1-54), actuarial 3-yr PFS = 72% **1 yr:** NR **2 yr:** NR **3 yr:** 72% overall; 75% CLL **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** 48% overall; 46% CLL	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: No 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Published criteria for NHL, CLL, WM			
Tsiara, Kapsali, Chaidos, et al., 2004[377]	**Design:** Uncontrolled trial **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** Resistant/relapsing CLL	**No. in study:** 5 **Age:** 76 (57-84) **Previous treatment:** Chlorambucil-prednisolone, CHOP, and fludarabine **Stage of disease:** Binet Stage C **Drug dose/day [followup]:** Rituximab 375 mg/m^2 every other week for 4 cycles Outcomes sought: CR = disappearance of disease, resolution of symptoms, & normalization of marrow PR = > 50% reduction in lymphs in blood & marrow, 50% decrease in organomegaly, Hgb > 11, no transfusions, and platelets > 100K	**N:** 5 **CR:** 2 (40%) **PR:** 1 (20%) **Stable disease:** No response = 2 (no distinction between SD and PD) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** 19 mo (16-37) among those with CR or PR **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: No 2) Explicit eligibility criteria?: No 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
Tsimberidou, Kantarjian, Cortes, et al., 2003[378]	**Design:** Uncontrolled clinical trial, with comparison to historical control that didn't receive rituximab **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Richter's syndrome or fludarabine-refractory CLL - Age >15 - Zubrod score ≤ 3 - Normal organ function	**No. in study:** 49 **Age:** 59 (27-79) **Previous treatment:** Yes for all pts, as follows: Prior fludarabine: 42 Prior rituximab: 25 Prior campath: 11 **Stage of disease:** 30 pts had Richter's; 19 had refractory CLL **Drug dose/day [followup]:** Rituximab 375 mg/m^2 Hyper-CVXD, Ritux, GM-GSF (cycles 1, 3, 5) Alternating w/ methotrexate, Ara-C, rituximab, GM-CSF (cycles 2, 4, 6) **Outcomes sought:** CR = complete disappearance of all disease Immature marrow cells < 5% PR = reduction ≥ 50% of measurable disease Failure = all other responses	**N:** 49 **CR:** 9 (19%) Median time to CR = 2.4 mo (0.5-5.7) **PR:** 11 (22%) **Stable disease:** N - (CR + PR) = 29 **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Median followup 8.2 mo (2-15 mo) [reported for overall population only] Median survival = 8.5 mo **1 yr:** 39% **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Median CR duration: 10 mo **1 yr:** 27% **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Outcomes did not differ compared to historical control with hyper-CVXD regimen that did not include methotrexate, ara-C, rituximab or GM-CSF

Study	Study Design	Patients	Tumor Response	Survival	Other
Weide, Pandorf, Heymanns, et al., 2004[379] AND Weide, Haymanns, Gores, et al., 2002[380]	**Design:** Uncontrolled clinical trial New regimen: BMR = bendamustine, mitoxantrone, rituximab First 20 pts in a dosing study for bendamustine **Phase:** Phase I/II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Symptomatic, relapsed, or refractory indolent lymphoma or B-cell CLL - CD20+ - ECOG 0-3 - Normal LFTs and RFTs	**No. in study:** 54 **Age:** 68 (36-82) **Previous treatment:** Yes (for all pts) **Stage of disease:** 22 pts had CLL: Binet B: 4 (18%) Binet C: 1 8 (82%) **Drug dose/day [followup]:** Bendamustine Mitoxantrone Rituximab 375 mg/m^2 on day 8, 15, 22, & 29 **Outcomes sought:** Not reported	**N:** 54 **CR:** 22 (41%) overall 5/22 (23%) for CLL group **PR**: 30 (55%) overall; 16/22 (73%) for CLL group **Stable disease:** 1 (2%) overall; 1/22 (5%) for CLL group **Progressive disease:** 1 (2%) overall; 0 for CLL group	**Survival overall (from start of treatment):** **Median survival:** No median followup reported **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Median time to progression = 7.5 mo (2-31+) in secondary high grade NHL and 17 mo (1-34+) in CLL Progression-free survival for CLL derived from Kaplan-Meier curves: **1 yr**: Approx 60% **2 yr**: Approx 40% **3 yr**: Approx 20%	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: No 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes
Wierda, O'Brien, Wen, et al., 2005[381] AND Wierda, O'Brien, Faderl, et al., 2006[382]	**Design:** Non-controlled clinical trial Pts w/CLL previously treated with FC-R **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Prior treatment - Rai stage III-IV or stage 0-II w/NCIWG indication	**No. in study:** 177 **Age:** 59 (36-81) **Previous treatment:** Yes (for all pts) **Median number of previous treatments: 2 (1-10)** **Stage of disease:** Rai stages: Low-risk: 5 (3%) Intermediate risk: 84 (47%)	**N:** 177 **CR:** 45 (25%) **PR:** Nodular PR = 28 (16%) PR = 57 (32%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Median followup = 28 mo (1-50) for all pts, and 35 (1-50) for surviving pts Median survival = 42 mo (1-50 mo) **Survival derived from Kaplan-Meier curves:** **1 yr:** approx 85% **2 yr:** approx 65% **3 yr:** approx 55%	**Adverse events & tolerability:** See Table A60 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Response was predicted by elevated B2 microglobulin levels,

Study	Study Design	Patients	Tumor Response	Survival	Other
	for treatment - Adequate performance status - Adequate LFT, RFT	High: 88 (50%) **Drug dose/day [followup]:** Fludarabine Cyclophosphamide Rituximab: 375 mg/m^2 on day 1 of course 1, and rituximab 500 mg/m^2 in courses 2 to 6 **Outcomes sought:** NCIWG		**Survival (disease free):** **Median survival:** **Median time to** progression for pts w/ CR, NPR, and PR was 39, 33, and 15 mo, respectively Disease-free survival derived from Kaplan-Meier curves: **1 yr:** Approx 85% **2 yr:** Approx 60% **3 yr:** Approx 40%	cytogenetics, number of prior therapies, platelet level, hemoglobin level, and creatinine (multivariate cox models)

Abbreviations: ANC = absolute neutrophil count; BM = bone marrow; BMR = bendamustine, mitoxantrone and rituximab; CCR = clinical complete response; CHOP = cyclophosphamide, hydroxydaunomycin, oncovin (vincristine), and prednisone; CI = confidence interval; CLL = chronic lymphocytic leukemia; CR = complete response; ECOG = Eastern Collaborative Oncology Group; FC = fludarabine and cyclophosphamide; FCR = fludarabine, cyclophosphamide, and rituximab; GM-CSF = granulocyte macrophage colony-stimulating factor; GVHD = graft versus host disease; Hgb = hemoglobin; Hyper-CVXD = fractionated cyclophosphamide, vincristine, liposomal daunorubicin (Daunoxome), and dexamethasone; ITP = idiopathic thrombocytopenic purpura; LFTs = liver function tests; lymphs = lymphocytes; NCI WG = National Cancer Institute Working Group; NHL = non-Hodgkin lymphoma; NR = not reported; OR = overall response; PC = pentostatin/ cyclophosphamide; PD = progressive disease; PFS = progression-free survival; PR = partial response; PS = performance status; q = every; RFTs = renal function tests; SD = stable disease; SLL = small lymphocytic lymphoma; TIW = thrice weekly; TRM = treatment-related mortality; TTP = time to tumor progression; WM = Waldenström's macroglobulinemia;

Table A58: Rituximab for Chronic Lymphocytic Leukemia – ASH 2006, ASH 2007, and ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Del Poeta, Del Principe, Maurillo, et al., 2006[383] ASH 2006 Abstract #2824	**Disease:** CLL **Design:** **Phase:** Phase II **Selection/randomization:** Not reported **Eligibility criteria:** Symptomatic untreated CLL	**No. in study:** 75 **Age:** 60 (median) **Previous treatment:** **Stage of disease:** Low stage: 6 Intermediate stage: 66 High stage: 3 **Drug dose/day [followup]:** Fludarabine 25 mg/m^2 days 1-5 q mo x 6; *plus* Rituximab 375 mg/m^2 q wk x 4, 1 mo after completion of fludarabine. **Outcomes sought:** Response	**N:** 75 **CR:** 61 (81%) **PR:** 10 (13%) **Stable disease:** "No response" in 4 (5%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **5 yr PFS:** 67%	**Adverse events & tolerability:** Grade 3 lung infections: 3 (4%) Fatal hepatitis B reactivation: 1 (1%) Grade 3-4 hematologic toxicity: 42 (56%)
Faderl, Ferrajoli, Wierda, et al., 2006[384] ASH 2006 Abstract #2827	**Disease:** CLL **Design:** Prospective, single center **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Relapsed CLL, CD20 and CD52 positive	**No. in study:** 45 **Age:** 59 (39-78) **Previous treatment:** Median of 3 previous treatments **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab 15 mg IV by CI q d x 6, then 30 mg SC BIW x 3 wk; *plus* Rituximab 375 mg/m^2 d 1, 500 mg/m^2 days 8, 15, & 22 x 3 cycles.	**N:** 32 **CR:** 8 (25%) **PR:** 8 (25%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** CMV reactivation: 7 (22%)

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Response, toxicity			
Faderl, Wierda, O'Brien, et al., 2006[385] ASH 2006 Abstract #2836	**Disease:** CLL **Design:** Prospective, single center **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated symptomatic CLL	**No. in study:** 31 **Age:** 57 (38-69) **Previous treatment:** **Stage of Disease:** 4 patients with Rai stage 3 or higher **Drug dose/day [followup]:** Fludarabine 25 mg/m^2 days 2-4; *plus* Cyclophosphamide 250 mg/m^2 days 2-4; *plus* Mitoxantrone 6 mg/m^2 day 2; *plus* Rituximab 375 mg/m^2 IV day 1 in first cycle then 500 mg/m^2 day 1 for 5 cycles; *plus* Pegfilgrastim 6 mg SC day 4. Above regimen repeated q 4-6 wk for 6 cycles. For cycles 2-6, FCM started on day 1 (along with R), and P on day 3. **Outcomes sought:** Response, toxicity	**N:** 29 at 3 mo 21 at 6 mo **CR:** 41% at 3 mo 33% at 6 mo **PR:** 56% at 3 mo 67% at 6 mo **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 3/21 patients did not receive full treatment due to toxicity Grade 3 or higher: Neutropenia: 77% Thrombocytopenia: 7% Anemia: 13% Infections: 45% **Comments:** Response rates appear no better than historic rates of FCR, making future use of mitoxantrone questionable

Study	Study Design	Patients	Tumor Response	Survival	Other
Kay, Geyer, Call, et al., 2006[386] ASH 2006 Abstract #35	**Disease:** CLL **Design:** Prospective, multicenter **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Previously untreated CLL	**No. in study:** 65 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** High risk: 34 (52%) **Drug dose/day [followup]:** Pentostatin 2 mg/m^2; *plus* Cyclophosphamide 600 mg/m^2; *plus* Rituximab 100 mg/m^2 d1, then 375 mg/m^2 days 3 & 5. Above regimen repeated q 21 d x 6 cycles. **Outcomes sought:** Response, toxicity	**N:** 64 **CR:** 26 (41%) **PR:** 32 (50%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival (PFS):** 32.6 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 hematologic toxicity: 38 (58%)
Klepfish, Schattner, and Kotsianidis, 2006[387] ASH 2006 Abstract #4986	**Disease:** CLL > 10 yr **Design:** Prospective, single center **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Fludarabine-resistant CLL with 2 of 3 patients rituximab-resistant	**No. in study:** 3 **Age:** 59, 70, 79 **Previous treatment:** 3 previous treatments in all, including rituximab in 2 patients **Stage of disease:** **Drug dose/day [followup]:** 2 units FFP followed by single agent 375 mg/m^2, repeated q 4-8 wk. **Outcomes sought:** OS	**N:** 3 **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** 7, 3, and 8 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** E. coli sepsis in 1 patient 4 mo after last cycle

Study	Study Design	Patients	Tumor Response	Survival	Other
Lin, Lucas, Heerema, et al., 2006[388] ASH 2006 Abstract #2841	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Relapsed CLL/SLL	**No. in study:** 36 **Age:** Not reported **Previous treatment:** Median of 2 previous treatments **Stage of disease:** Not reported **Drug dose/day [followup]:** Etanercept 25 mg SC 2x/wk x 5 wk; *plus* Rituximab 375 mg/m^2 IV 3x/wk for wk 2-5. **Outcomes sought:** Response, median PFS, toxicity	**N:** 32 **CR:** 1 (3%) **PR:** 8 (25%) **Stable disease:** 18 (56%) **Progressive disease:** 5 (16%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** 10 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 12 (33%) with Grade 4 neutropenia
Mena, Robles, Auerbach, et al., 2006[389] ASH 2006 Abstract #4978	**Disease:** CLL **Design:** Retrospective, single center **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Treated or untreated Rai stage II, III or IV CLL, PS 0-2	**No. in study:** 70 **Age:** 64 (35-83) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Pentostatin 4 mg/m^2; *plus* Cyclophosphamide 600 mg/m^2; *plus* Rituximab 375 mg/m^2 on day 1. Above regimen repeated q 21 days x 10 cycles.	**N:** 50 **CR:** 22% **PR:** 30% **Stable disease:** 46% **Progressive disease:** 2%	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 4 toxicities: Neutropenia: 2 Respiratory distress: 1 4 deaths in patients > 80 due to acute respiratory failure, MI, pulmonary edema, and sepsis

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Response, toxicity			
Pavlovsky, Pavlovsky, Pardo, et al., 2006[390] ASH 2006 Abstract #4968	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** CLL previously treated with chlorambucil or untreated	**No. in study:** 45 **Age:** 63 (34-88) **Previous treatment:** Not reported **Stage of disease:** 58% Binet C **Drug dose/day [followup]:** Fludarabine 25 mg/m^2 days 1-3; *plus* Cyclophosphamide 250 mg/m^2 days 1-3; *plus* Rituximab 375 mg/m^2 day 1. Above regimen repeated q 4 wk x 4-6 cycles. **Outcomes sought:** Response, toxicity	**N:** 41 **CR:** 69% **PR:** 22% **Stable disease:** 2% **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3-4: Neutropenia: 33% Infection requiring hospitalization: 34%
Tam, Wen, Do, et al., 2006[391] ASH 2006 Abstract #4976	**Disease:** CLL **Design:** Retrospective, single center **Phase:** n/a **Selection/randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 616 **Age:** 57 **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Not reported **Outcomes sought:**	**N:** Not reported **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Multivariate analysis shows FCR with significant improvement in survival compared to F monotherapy or FCM, except with chromosome 17 abnormality.

Study	Study Design	Patients	Tumor Response	Survival	Other
		Not reported			
Tarhini, Land, Meisner, et al., 2006[392] ASH 2006 Abstract #2844	**Disease:** CLL **Design:** Prospective, single center **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Previously untreated CLL	**No. in study:** 28 **Age:** 58 (36-85) **Previous treatment:** None **Stage of disease:** Not reported **Drug dose/day [followup]:** Fludarabine 20 mg/m^2 days 1-3 q 4 wk; *plus* Cyclophosphamide 150 mg/m^2 days 1-3 q 4 wk; *plus* Rituximab 500 mg/m^2 days 1 & 14 q 4 wk; *then* Maintenance rituximab 500 mg/m^2 q 3 mo. **Outcomes sought:** Not reported	**N:** 28 **CR:** 18 (86%) **PR:** 3 (14%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3-4 toxicities: Neutropenia: 12/154 courses given (8%) 1 episode of neutropenic fever 1 patient had pneumonia Grade 3-4 thrombocytopenia: 4 (3%) Grade 3 anemia: 2 (1%)
Tsimberidou, Wierda, O'Brien, et al., 2006[393] ASH 2006 Abstract #2825	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Transformed or fludarabine-resistant CLL	**No. in study:** 46 **Age:** 69 (41-78) transformed 57 (34-77) resistant **Previous treatment:** Median of: 3 (transformed) 4 (resistant) **Stage of disease:** 70% stage 3-4 **Drug dose/day [followup]:** Oxaliplatin up to 25 (17.5,	**N:** 37 **CR:** 3/12 transformed 1/23 resistant **PR:** 4/12 transformed 5/23 resistant **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Not reached for transformed; 4 mo for resistant **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Significant hematologic toxicity requiring platelet transfusion and RBC, but no prolonged myelosuppression Grade 3-4: Sepsis: 2 Pneumonia: 4 CMV: 2

Study	Study Design	Patients	Tumor Response	Survival	Other
		20 or 25) mg/m^2/d days 1-4; *plus* Fludarabine 30 mg/m^2 days 2-3; *plus* Cytarabine 1 g/m^2 days 2-3; *plus* Rituximab 375 mg/m^2 day 3; *plus* Pegfilgrastim 6 mg on day 6. Above regimen repeated q 4 wk x 6 cycles. **Outcomes sought:** Response, toxicity			
Wierda, O'Brien, Faderl, et al., 2006[394] ASH 2006 Abstract #31	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Pre-treated CLL	**No. in study:** 79 **Age:** 58 (39-79) **Previous treatment:** All previously treated; median of 3 lines of treatment **Stage of disease:** 40 patients high risk by Rai staging **Drug dose/day [followup]:** Cyclophosphamide 250 mg/m^2 days 3-5; *plus* Fludarabine 25 mg/m^2 days 3-5; *plus* Alemtuzumab 30 mg IV days 1, 3, & 5; *plus* Rituximab 375-500 mg/m^2 day 2. Above regimen repeated q 28 days x 6 cycles. **Outcomes sought:**	**N:** 74 **CR:** 18 (24%) **PR:** 30 (41%) **Stable disease:** Not reported **Progressive disease:** 22 (30%)	**Survival overall (from start of treatment):** **Median survival:** 19 mo overall **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** 26 mo among responders **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** CMV reactivation: 12 patients Grade 3 neutropenia: 20% of courses Grade 4 neutropenia: 39% of courses Grade 3 thrombocytopenia: 17% of courses Grade 4 thrombocytopenia: 15% of courses

Study	Study Design	Patients	Tumor Response	Survival	Other
		Response, toxicity			
Zent, Bone, Call, et al., 2006[395] ASH 2006 Abstract #2829	**Disease:** CLL **Design:** Prospective, single center **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated CLL, early stage with high-risk features	**No. in study:** 17 **Age:** 62 (29-75) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Alemtuzumab 3, 10, 30 mg on days 1-3, then 30 mg M, W, F x 4 wk; *plus* Rituximab 375 mg/m^2 IV on day 8 x 4 wk. **Outcomes sought:** Response, toxicity	**N:** 11 **CR:** 5 (4 MRD negative) **PR:** 3 nodular PR, 3 PR **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 2 serious AEs: CMV reactivation & reaction to prophylactic Bactrim Grade 3-4 toxicities: Leukopenia: 4 Neutropenia: 2 Anemia: 1 Skin reaction: 1 ALT elevation: 1
Bosch, Muntanola, Villamor, et al., 2007[396] ASH 2007 Abstract #626	**Disease:** CLL **Design:** Prospective, multicenter **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated CLL, age < 70, active disease, PS 0-2	**No. in study:** 69 **Age:** Median 59 yr **Previous treatment:** None **Stage of disease:** 83% Binet B or C **Drug dose/day [followup]:** Rituximab 500 mg/m^2 day 1, Fludarabine 25 mg/m^2 days 1-3. Cyclophosphamide 200 mg/m^2 days 1-3, Mitoxantrone 6 mg/m^2 day 1, q 4 wk x 6,	**N:** 38 **CR:** 77% **PR:** 15% **Stable disease:** Not reported **Progressive disease:**	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3-4 neutropenia: 8%

Study	Study Design	Patients	Tumor Response	Survival	Other
		Maintenance Rituximab 375 mg/m2 q 3 mo x 2 yr **Outcomes sought:** Response, toxicity			
Del Poeta, Del Principe, Maurillo, et al., 2007[397] ASH 2007 Abstract #2035	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Symptomatic, untreated CLL	**No. in study:** 82 **Age:** 61 median **Previous treatment:** Not reported **Stage of disease:** Rai low: 8 Rai intermediate: 70 Rai high: 4 **Drug dose/day [followup]:** Fludarabine 25 mg/m^2 x 5 days q 28 days x 6 cycles Rituximab 375 mg/m^2 wkly x 4 wk after fludarabine **Outcomes sought:** Response, toxicity	**N:** 82 **CR:** 66 (80%) **PR:** 12 (15%) **Stable disease:** Not reported **Progressive disease:** 4 (5%) no response or progression	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **5 yr PFS:** 68% with induction only 85% when maintenance rituximab added	**Adverse events & tolerability:** Grade 3-4 toxicities: Neutropenia: 42 Thrombocytopenia: 4
Dungarwalla, Kanagasa-bapathy, Kulkarni, et al., 2007[398] ASH 2007 Abstract #3125	**Disease:** CLL **Design:** Retrospective **Phase:** n/a **Selection/randomization:** Not reported **Eligibility criteria:** Advanced refractory CLL	**No. in study:** 14 **Age:** 62.5 (30-71) **Previous treatment:** **Stage of disease:** 9/14 with Binet stage C **Drug dose/day [followup]:** HDMP with anti-CD20 monoclone antibody & rituximab	**N:** 14 **CR:** 2 **PR:** 11 **Stable disease:** Not reported **Progressive disease:** 1	**Survival overall (from start of treatment):** **Median survival:** 20 mo **Survival (disease free):** **Median survival:** 7 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 6/14 patients developed opportunistic or viral infections resulting in 3 deaths

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Response, toxicity			
Egle, Weiss, Russ, et al., 2007[399] ASH 2007 Abstract #2045	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated B-CLL	**No. in study:** 43 **Age:** 63 (36-81) **Previous treatment:** None **Stage of disease:** Not reported **Drug dose/day [followup]:** Ind 1-FCR x 3 cycles, Ind 2 FR x 3 cycles, Maintenance rituximab q 3 mo x 2 yr **Outcomes sought:** Response, toxicity	**N:** 23 after induction 1 16 after induction 2 12 after 6 mo maintenance **CR:** 83% after induction 1 94% after induction 2 100% after 6 mo maintenance **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 25% of patients at all stages of treatment with CR, but treatment-related cytopenias Grade 3 hematologic toxicities: 28% Grade 4 hematologic toxicities: 15%, Grade 3 infectious toxicity: 13% Grade 5 herpes encephalitis: 1 10 dropped out of study due to toxicity **Comments:** Serious toxicity in 25% despite de-escalation of treatment
Faderl, Wierda, Ferrajoli, et al., 2007[400] ASH 2007 Abstract #627	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated and symptomatic CLL, age < 70	**No. in study:** 31 **Age:** 57 (38-69) **Previous treatment:** Not reported **Stage of disease:** 14% Rai stage 3 or 4 **Drug dose/day [followup]:** FCM-R Fludarabine 25 mg/m^2 days	**N:** 29 **CR:** 41% **PR:** 56% **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR	**Adverse events & tolerability:** Grade 3-4 toxicities: Neutropenia: 19 (63%) Thrombocytopenia: 2 (7%) Infectious complications: 13 (45%) 7 (23%) unable to complete treatment

Study	Study Design	Patients	Tumor Response	Survival	Other
		2-4, Cyclophosphamide 250 mg/m^2 days 2-4, Mitocantrone 6 mg/m^2 day 2, Rituximab 375 mg/m^2 day 1, X 6 cycles q 4-6 wk, with increase in rituximab to 500 mg/m^2 in cycles 2-6 **Outcomes sought:** Response, toxicity		**3 yr:** NR	
Frankfurt, Hamilton, Acharya, et al., 2007[401] ASH 2007 Abstract #2056	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated CLL	**No. in study:** 13 **Age:** 54 (29-75) **Previous treatment:** None **Stage of disease:** Rai 1: 4 Rai 2: 4 Rai 4: 5 **Drug dose/day [followup]:** Alemtuzumab 3, 10, 30 mg wk 1 days 1, 3, & 5, then 30 mg TIW x 17 wk. Rituximab 375 mg/m^2 q ow x 8 cycles starting on the 3rd wk **Outcomes sought:** Response, toxicity	**N:** 11 **CR:** 2 (18%) **PR:** 8 (73%) **Stable disease:** 1 (9%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Not Reached **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** CMV reactivation: 4 patients Grade 3-4 lymphopenia in all patients Grade 3-4 neutropenia in 5 patients
Hillmen, Pocock, Cohen, et al., 2007[402]	**Disease:** CLL **Design:** Prospective, multicenter	**No. in study:** 52 (Arm A: 26; Arm B: 26) **Age:** 65 (32-79)	**N:** 46 **(23 Arm A)** **(23 Arm B)**	**Survival overall (from start of treatment):** **Median survival:**	**Adverse events & tolerability:** FCM: 10 serious AE FCM-R: 16 serious AE

Study	Study Design	Patients	Tumor Response	Survival	Other
ASH 2007 Abstract #752	**Phase:** Phase II **Selection/randomization:** Randomization methods not reported, comparison between FCM vs. FCM-R **Eligibility criteria:** Untreated or previously treated CLL	**Previous treatment:** Median of 2 prior treatments; 31 previous treatments fludarabine based **Stage of disease:** Not reported **Drug dose/day [followup]:** Fludarabine 24 mg/m^2 days 1-5, Cyclophosphamide 150 mg/m^2 days 1-5, Mitoxantrone 6 mg/m^2 day 1, Rituximab 375 mg/m^2 day 1, then 500 mg/m^2 day 1 after cycle 1 x 6 cycles **Outcomes sought:** Response, toxicity	**CR:** FCM: 3 FCM-R: 10 **PR:** FCM: 10 FCM-R: 6 **Stable disease:** FCM: 7 FCM-R: 5 **Progressive disease:** Not reported	**1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	
Kempin, Kay, Sun, et al., 2007[403] ASH 2007 Abstract #3109	**Disease:** CLL **Design:** Prospective, multicenter, intergroup study (ECOG 2903) **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Relapsed or refractory CLL	**No. in study:** 32 **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** PCR x 6 cycles 1 mo, Campath either 4 wk or 18 wk **Outcomes sought:** Response, toxicity	**N:** 28 **CR:** Not reported **PR:** 11 (38%) **Stable disease:** Not reported **Progressive disease:** 2 (6.9%)	**Survival overall (from start of treatment):** **Median survival: 15 mo** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 4 deaths during PCR phase. CMV reactivation in 2 patients. During Campath phase, 6 patients dev'd infectious complications Grade 3 skin toxicity (q short-term patient) Grade 4 Lymphopenia **Comments:** This is a study of Campath added to PCR, which is considered a standard therapy.

Study	Study Design	Patients	Tumor Response	Survival	Other
Lamanna, Heaney, Brentjens, et al., 2007[404] ASH 2007 Abstract #4470	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** CLL or other low-grade B neoplasia	**No. in study:** 21 17 CLL) **Age:** 62 (44-74) **Previous treatment:** **Median of 2 previous lines of treatment** **Stage of disease:** Not reported **Drug dose/day [followup]:** Pentostatin 4 mg/m^2, Cyclophosphamide 600 mg/m^2, Rituximab 375 mg/m^2 omitted in cycle 1) and mitoxantrone 6, 8, or 10 mg/m^2, All on day 1, q 18 days x 6 cycles **Outcomes sought:** Response	**N:** 16 **CR:** 4 (25%) **PR:** 11 (69%) **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported
Leupin, Schuller, Solenthaler, et al., 2007[405] ASH 2007 Abstract #2057	**Disease:** CLL **Design:** Prospective, multicenter **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated or treated with alkylating agent only, CLL	**No. in study:** 42 **Age:** 53.8 (38-65) **Previous treatment:** Not reported **Stage of disease:** Binet B: 20 Binet C: 8 **Drug dose/day [followup]:** 2-CDA 0.1 mg/kg days 1-5 cycle 1, then rituximab 375 mg/m^2 day 1 followed by 2-CDA 0.1 mg/kg q cycle 2-4 q 28 days	**N:** 40 **CR:** 9 **PR:** 17 **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 thrombocytopenia: 4% of cycles Grade 3-4 neutropenia: 27% of cycles Fever: 13 patients Infection: 9 patients

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Not reported			
Mena, Moezi, and Robles, 2007[406] ASH 2007 Abstract #1356	**Disease:** CLL **Design:** Prospective, multicenter, open-label **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated or treated stage II, III, or IV CLL	**No. in study:** 85 (61 untreated) (13 previously treated) (11 unknown treatment history) **Age:** 64 (35-83) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Pentostatin 4 mg/m^2, Cyclophosphamide 600 mg/m^2, Rituximab 375 mg/m^2 day 1, q 21 d x 8-10 cycles **Outcomes sought:** Response, toxicity	**N:** 69 **CR:** 19 (22.3%) **PR:** 29 (34%) **Stable disease:** 20 (23.5%) **Progressive disease:** 1 (1.4%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 8 deaths (1 respiratory failure, 1 carcinoma, 1 pulmonary edema, 2 sepsis, 3 unknown) Grade 3-4 toxicities: Neutropenia: 25 Anemia: 6 Thrombocytopenia: 5
Moffa, Thatikonda, Pathe, et al., 2007[407] ASH 2007 Abstract #4722	**Disease:** CLL, NHL **Design:** Retrospective **Phase:** n/a **Selection/randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 5 CLL, 3 NHL **Age:** 70 (57-83) **Previous treatment:** **FCR, FR, or PCR** **Stage of disease:** Not reported **Drug dose/day [followup]:**	**N:** Not reported **CR:** Not reported **PR:** 3/5 CLL **Stable disease:** Not reported **Progressive disease:** 2/5	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** High-dose rituximab may be beneficial in CLL that is failing standard therapy or in patients who will not tolerate standard treatment

Study	Study Design	Patients	Tumor Response	Survival	Other
		Rituximab 500 mg/m^2 TIW x 2 wk **Outcomes sought:** Response	CLL, 3/3 NHL	**2 yr:** NR **3 yr:** NR	
Quinn, Mohamedbhai, Treacey, et al., 2007[408] ASH 2007 Abstract #4719	**Disease:** CLL **Design:** Retrospective **Phase:** n/a **Selection/randomization:** **Eligibility criteria:** Pts with CLL treated with high-dose corticosteroids and Rituximab	**No. in study:** 11 **Age:** 70 (54-82) **Previous treatment:** **10 relapsed or refractory** **1 de novo** **Stage of disease:** 9 Binet stage C; median of 2 prior treatments **Drug dose/day [followup]:** 6 patients methylprednisone 1 g/m^2 days 1-5 with rituximab 375 mg/m^2 day 1 repeated q 28 days. 5 patients dexamethasone 40 mg days 1-4 with rituximab repeated q 28 days **Outcomes sought:** Response, toxicity	**N:** 11 **CR:** 1 **PR:** 7 **Stable disease:** 3 **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** 13 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 3 patients hospitalized with infectious complications of treatment; otherwise no AEs
Rieger, Witzens-Harig, Hensel, et al., 2007[409] ASH 2007 Abstract #5106	**Disease:** MCL **Design:** Retrospective **Phase:** n/a **Selection/randomization:** Not reported **Eligibility criteria:**	**No. in study:** Not reported **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:**	**N:** 34 CHOP-Cy-TBI-R, 28 R-CHOP BEAM **CR:** Not reported **PR:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **4 yr PFS:** 100% R-CHOP BEAM + rituximab maintenance	**Adverse events & tolerability:** Not reported **Comments:** Rituximab appears beneficial in autotransplant patients, but exact timing and dose remains unclear.

Study	Study Design	Patients	Tumor Response	Survival	Other
	Not reported	Not reported **Drug dose/day [followup]:** CHOP followed by cyclophosphamide-TBI-rituximab transplant vs. R-CHOP BEAM transplant with or without rituximab maintenance **Outcomes sought:** PFS	**Stable disease:** Not reported **Progressive disease:** Not reported	56% without rituximab maintenance 83% CHOP R-TBI-Cy **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	
Tarhini, Land, Pietragallo, et al., 2007[410] ASH 2007 Abstract #2037	**Disease:** CLL **Design:** Prospective, single center **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated CLL	**No. in study:** 50 **Age:** 58 (36-85) **Previous treatment:** None **Stage of disease:** "Advanced" **Drug dose/day [followup]:** Fludarabine 20 mg/m^2 days 1-3 q 4 wk, Cyclophosphamide 150 mg/m^2 days 1-3 1 4 wk, Rituximab 500 mg/m^2 days 1 & 14 q 4 wk, then rituximab 500 mg/m^2 q 3 mo until progression **Outcomes sought:** Response, toxicity	**N:** 40 **CR:** 85% **PR:** 15% **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3-4 toxicities: Neutropenia: 12% Thrombocytopenia: 3% Anemia: 2.5%

Study	Study Design	Patients	Tumor Response	Survival	Other
Wierda, O'Brien, Ferrajoli, et al., 2007[411] ASH 2007 Abstract #628	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated high risk CLL, Age < 70	**No. in study:** 40 **Age:** 63 (43-69) **Previous treatment:** **Stage of disease:** 13 Rai high risk **Drug dose/day [followup]:** Cyclophosphamide 200 mg/m^2 days 3-5, Fludarabine 20 mg/m^2 days 3-5, Alemtuzumab 30 mg days 1, 3, & 5, Rituximab 375-500 mg/m^2 day 2, All of above q 28 days x 6 cycles **Outcomes sought:** Response, toxicity	**N:** 21 **CR:** 71% **PR:** 24% **Stable disease:** Not reported **Progressive disease:** 1 non-responder	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3-4 toxicities: Neutropenia: 27% Thrombocytopenia in 7% of chemo courses FUO in 34% CMV reactivation in 4 patients, though non on valganciclovir prophylaxis
Zent, Call, Shanafelt, et al., 2007[412] ASH 2007 Abstract #2050	**Disease:** CLL **Design:** Prospective, multicenter **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** High risk CLL by FISH, IgVh, ZAP-70, or CD38	**No. in study:** 30 **Age:** 62 (29-77) **Previous treatment:** Not reported **Stage of disease:** Rai stage 0: 7 Stage I: 19 Stage II: 1 **Drug dose/day [followup]:** Alemtuzumab 3, 10, 30 mg wk 1, and then 30 mg TIW x 4 wk. Rituximab 375 mg/m^2 q wk beginning at day 8, x 4	**N:** 27 **CR:** 12 (44%) **PR:** 13 (48%) **Stable disease:** Not reported **Progressive disease:** 2 (7%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** 14.4 mo **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3-4 toxicities: CMV reactivation: 1 Drug reactions: 2

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Response, toxicity			
Bertazzoni, Laszlo, Gigli, et al., 2007[197] ASCO 2007 Abstract #7093	**Disease:** CLL/SLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 31 **Age:** 59 (31-73) **Previous treatment:** 13 (42%) previously treated **Stage of disease:** Not reported **Drug dose/day [followup]:** Rituximab 375 mg/m^2 IV d1, 2-CdA 0.1 mg/kg SQ d 2-6, q 4 wks x 4 cycles **Outcomes sought:** Response, toxicity	**N:** 24 **CR:** 10 (42%) **PR:** 13 (54%) **Stable disease:** Not reported **Progressive disease:** 1 (4%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 2 patients discontinued treatment after 2 cycles, 1 with zoster reactivation, 1 with progression of disease Major infections in 4 pts (12%) Grade 3-4 neutropenia in 4 pts (12%) **Comments:** Testing combination of rituximab with cladribine
Mena, Robles, Auerbach, et al., 2007[413] ASCO 2007 Abstract #17508	**Disease:** CLL, low grade **Design:** Prospective, multicenter, open label **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Previously treated or untreated CLL	**No. in study:** 80 **Age:** 64 (35-83) **Previous treatment:** Not reported **Stage of disease:** Stage II/III/IV CLL **Drug dose/day [followup]:** Pentostatin 4 mg/m^2 d1, Cyclophosphamide 600 mg/m^2, Rituximab 375 mg.m^2 d 1, Q 21 days, up to 10 cycles **Outcomes sought:** Not reported	**N:** 59 **CR:** 14 (23.7%) **PR:** 22 (37.3%) **Stable disease:** Not reported **Progressive disease**: Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 4 toxicities: Neutropenia: 7 Respiratory distress: 2 Anemia: 1 5 deaths during treatment (all in patients > age 70

Study	Study Design	Patients	Tumor Response	Survival	Other
Tam, O'Brien, Wierda, et al., 2007[414] ASCO 2007 Abstract #7008	**Disease:** CLL **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Age ≥ 16 yr, with untreated CLL	**No. in study:** 300 **Age:** 57 median **Previous treatment:** None **Stage of disease:** Rai intermediate risk: 61% Rai high risk: 36% **Drug dose/day [followup]:** FCR x 6 cycles **Outcomes sought:** Not reported	**N:** Not reported **CR:** Not reported **PR:** Not reported **Stable disease:** Not reported **Progressive disease**: Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** 80 mo for patients in CR, 27 mo for patients in PR **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** 5 cases of transformation 8 cases of MDS/AML

Abbreviations: AE(s) = adverse event(s); ALT = alanine transaminase; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; B-CLL = B-cell chronic lymphocytic leukemia; BEAM = bischloroethylnitrosourea, etoposide, cytarabine, and melphalan; BIW = biweekly; CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), and prednisone; CI = confidence interval; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CR = complete response; ECOG = Eastern Collaborative Oncology Group; FCM = fludarabine, cyclophosphamide, and mitoxantrone; FCM-R = fludarabine, cyclophosphamide, mitoxantrone, and rituximab; FCR = fludarabine, cyclophosphamide, and rituximab; FFP = fresh-frozen plasma; FR = fludarabine and rituximab; FUO = fever of unknown origin; IV = intravenous; MCL = mantle cell lymphoma; MDS/AML = myelodysplastic syndrome / acute myelocytic leukemia; MI = myocardial infarction; MRD = minimal residual disease; NHL = non-Hodgkin lymphoma; OS = overall survival; PFS = progression-free survival; PR = partial response; PS = performance status; q = every; R = rituximab; RBC = red blood cell(s); R-CHOP = rituximab, cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), and prednisone; SC = subcutaneous; SLL = small lymphocytic lymphoma; SQ = subcutaneous; TIW = thrice weekly;

Table A59: Rituximab for Chronic Lymphocytic Leukemia – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Berkahn, Simpson, Raptis, et al., 2002[415]	Pilot study	375 mg/m^2	5	Used rituximab as in vivo purging step following cyclophosphamide 4 mg/m^2 and granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor mobilization therapy for pts with advanced-stage CLL undergoing autologous stem cell transplantation. No regimen-related mortality was seen. Authors conclude that purging with rituximab 48 hr prior to stem cell collection was able to reduce significantly (but not eliminate) the % of CLL cells in the leukaphereses.
Borthakur, O'Brien, Wierda, et al., 2007[416]	Retrospective analysis of pts enrolled prospectively in a clinical trial of therapy with FCR	Day 1 of 1st cycle = 375 mg/m^2 of rituximab Day 1 of subsequent cycles = 500 mg/m^2 rituximab	300	Rituximab treatment was followed in each cycle with 3 days of fludarabine 25 mg/m^2/d and cyclophosphamide 250 mg/m^2/d IV. Authors state data may indicate a reduced incidence of AIHA in pts treated with chemoimmunotherapy that includes rituximab and cyclophosphamide. The incidence of IA among pts with CLL being treated with FCR as first-line treatment is comparable with historical rates. An FCR front-line treatment alone or with other immune manipulations can produce resolution of pre-existing IA in some pts with CLL.
Byrd, Gribben, Peterson, et al., 2006[417] CALGB 9712	Subset of a completed, randomized Phase II trial, these pts had at least 1 cryo-preserved vial of tissue available for analysis		88	All pts included here were derived from a completed, randomized Phase II trial of fludarabine and rituximab that yielded positive results in terms of CR rate, ORR, PFS, and OS as compared with a previously completed U.S. intergroup trial with similar eligibility in which pts received fludarabine alone. Seemed more a processing of tissue for prognosis than study of pts receiving rituximab as treatment.
Byrd, Rai, Peterson, et al., 2005[418] CALGB 9712 & 9011	Retrospective comparison of treatment outcome with pts of similar clinical characteristics in 2 multi-center clinical trials		104 rituximab + fludara-bine; 178 fludara-bine alone	Combination treatment had significantly better PFS and OS than pts receiving fludarabine alone. 2-yr PFS probabilities were 0.67 vs. 0.45, and 2-yr OS probabilities were 0.93 vs. 0.81. Infectious toxicity was similar between groups. Note the retrospective data could be confounded by differences in supportive care or dissimilar enrollment of genetic subsets on each trial.
Byrd, Waselenko, Maneatis, et al., 1999[419]	Case series; observations collected from physician-submitted reports of AEs in pts	375 mg/m^2	5 (only 2 with CLL)	Rituximab administration in pts who have a high number of tumor cells in the blood may have an increased likelihood of severe initial infusion-related reactions.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Cohen, Da'as, Libster, et al., 2002[420]	Case reports		9 (5 received rituximab + fludara-bine in sequence; only 2/5 with CLL)	Reports of 9 pts with previously-treated indolent LPD in whom the onset of large-cell transformation occurred during or shortly after the initiation of regimens containing rituximab and fludarabine before the transformation occurred. Authors thought this was more than just a chance relationship; however, there was no conclusive evidence to prove their hypothesis.
Dereure, Navarro, Rossi, et al., 2001[421]	Case report	700 mg rituximab in 1st infusion	1	44-y/o man with h/o treatment with fludarabine for conventional B-cell CLL with only PR. 2 days after 1st infusion (700 mg rituximab) pt developed systemic symptoms with lower limb pain, fever, shivers, rapidly followed by onset of inflammatory skin lesions on the ankles, legs, and knees. These soon spread to thighs and abdomen turning into purpuric lesions with sometimes an annular pattern.
Garypidou, Perifanis, Tziomalos, et al., 2004[422]	Case report	375 mg/m^2 weekly x 4 consecutive weeks	1	71-y/o male diagnosed with B-CLL 5 yr earlier. 4 hr after 1st infusion began, pt developed substernal pain radiating in neck and left arm, along with palpitations. Infusion interrupted. 2 hr later infusion restarted and 30 min later pt developed identical pain which stopped as infusion was stopped. Rituximab was discontinued.
Harrer, Geissdorfer, Schoerner, et al., 2007[423]	Case report		1	63 y/o male developed a seronegative Lyme neuroborreliosis complicating chemotherapy for CLL. Authors state when dealing with complications on chemotherapy, oncologists should be aware that Lyme borreliosis may mimic an opportunistic infection, and should be included in the diagnostic workup of pts with neuropathic and rheumatological symptoms.
Herold, Schulze, Hartwig, et al., 2000[424]	Case reports	375 mg/m^2 weekly	2	Both pts suffered from severe thrombocytopenia requiring platelet transfusions over several months. Neither chemotherapy nor immunosuppressive agents were effective. After rituximab, both pts recovered within a few weeks to partial remission.
Jensen, Winkler, Manzke, et al., 1998[360]	Case report	375 mg/m^2	1	26 y/o female with progressive low-grade B-cell lymphoma. After treatment for initial reactions, full doses were given on days 8, 15, and 22 without clinical problems. Author states when treating pts with CLL and marked lymphocytosis with rituximab, clinicians need to be aware of risk of hitherto unreported acute tumor lysis and intravascular coagulation.
Jourdan, Topart, Richard, et al., 2003[425]	Case report	375 mg/m^2 q wk x 4 wk	1	64 y/o male had been treated with no response after 6 courses. Rituximab was administered for 4 wk with PR. Pt died suddenly 3 mo later of severe ischemic colitis, which was considered independent of hematological malignancy.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Kanelli, Ansell, Habermann, et al., 2001[426]	Retrospective review	375 mg/m^2 q wk x 4 wk	27 (only 12 had CLL)	Study evaluated the AEs in pts with malignant B-cell lymphocytosis who received rituximab. Authors state prospective trials should define guidelines for the safe delivery of monoclonal antibodies to pts with circulating malignant cells.
Klepfish, Schattner, Ghoti, et al., 2007[427]	Case report	400 mg/m^2 on day 1, 270 mg/m^2 on day 2; given for 4 cycles	1	59 y/o female with CLL had been treated with chlorambucil pulses followed by 10 cycles of cyclophosphamide for 5 yr. Some PR was noted. CLL progressed. Disease was resistant to CHOP-R. After marked PR for 3 mo, pt developed sudden sepsis from Escherichia coli and died.
Kunzmann, Ruediger, Hallek, et al., 2001[428]	Case report	42.5 mg total dose of rituximab given	1	65 y/o male with heavily pre-treated CLL was treated with rituximab. Pt had marked AEs. Rituximab was discontinued. Clinical condition of pt deteriorated. Despite inotropic support, pt died from cardiopulmonary failure 13 hr after initiation of rituximab infusion. Authors state tumor cell agglutination could be responsible for severe infusion-related AEs during rituximab treatment.
Ladetto, Bergui, Ricca, et al., 2000[429]	Phase I	375 mg/m^2 q wk x 4 wk	7	Mild (5) or severe (1) AEs were observed during first hours of rituximab infusion, almost exclusively on first course. Symptoms rapidly subsided with temporary drug withdrawal and low-dose steroids. Authors state rituximab in CLL pts is feasible and has an accepted toxicity. Rituximab was shown to induce marked, though transient, responses at PB level.
Lim, Koh, and Tan, 1999[430]	Case report	375 mg/m^2	1	71 y/o female with CLL pre-treated with chlorambucil and subsequently with fludarabine. AEs apparent in 2nd hr.
Nabhan, Patton, Gordon, et al., 2004[431]	Phase I	Rituximab 375 mg/m^2 wk 1, 3, 4, & 5; CAM 3 mg tiw (n = 3), 10 mg tiw (n = 3) & 30 mg tiw (n = 6)	12 (divided into 3 cohorts: n = 3, 3, & 6)	Study examined if combining rituximab with alemtuzumab is safe in refractory CLL. Authors state the combination was proven to be safe, not toxic, feasible, and active. 1 pt attained PR with other pts had SD lasting median of 101.5 days. All pts normalized their peripheral lymphocytosis within a median of 23.5 days. No treatment-related mortality was identified. No CMV reactivation occurred.
Narayan, Bandyo-padhyay, Schmidt, et al., 2005[432]	Case report		1	83 y/o male diagnosed with CLL 6 yr ago. Pt received 8 courses of 21-day cycle of CHOP-R and achieved radiological and immunophenotypic CR that persists 13 mo after end of treatment. There are no guidelines on the management of pts with CLL complicated by a large osteolytic lesion and hypercalcaemia. Aggressive antibody-chemotherapy is effective for quick tumor debulking. Significant osteolytic lesions in the weight bearing bones also warrant prophylactic orthopedic intervention to prevent pathological fracture.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Nieto, Bearman, Shpall, et al., 2001[433]	Case report		1	51 y/o male was pretreated with no response. Treatment with cyclophosphamide, paclitaxel, doxorubicin, solumedrol, and rituximab from days +11 to +14 produced a rapid response.
Niscola, Del Principe, Maurillo, et al., 2005[434]	Case report	375 mg/m^2 q wk x 4 wk	1	51 y/o male presented stable disease for 3 yr from diagnosis. Fludarabine was started because of progressive disease. A good PR was obtained so the pt received 4 weekly standard doses of rituximab, achieving a CR. Close f/u for 2 yr until a disease recurrence when rituximab was given again. After 4 weekly doses and a GPR, 6 monthly courses (150 mg/m^2) given as maintenance treatment. Pt developed acute hepatitis, hepatic function did not recover, and pt died 32 days post-admission.
O'Brien, Kantarjian, Thomas, et al., 2001[435]	Phase I (dose-escalation trial)	375 mg/m^2 as 1st dose; then escalated	50 (40 with CLL)	Study was designed to define the MTD, evaluate first-dose reactions in pts with high circulating lymphocyte counts, and assess efficacy at higher vs. lower doses. 6 pts had severe toxicity with first dose. Toxicity on subsequent doses was minimal until a dose of 2,250 mg/m^2 was achieved. Dose escalation was stopped when significant toxicity was seen on subsequent doses. Grade 3/4 toxicity was low in CLL pts (1/40).
Robak, Gora-Tybor, Tybor, et al., 2004[436]	Case report	375 mg/m^2 on day 1 and 2-CdA on days 2-6	1	60 y/o female diagnosed with B-cell CLL. Pt enrolled in Phase II trial evaluating a combination of 2-CdA, mitoxantrone, and cyclophosphamide repeated q 28 days, up to 4 courses. Pt remained in PR 50 mo. In 2003, enrolled in trial to evaluate 2-CdA combined with rituximab. PR was achieved after 2nd mo. Complications arose which were treated with surgeries and f/u treatment.
Sarrecchia, Cappelli, and Aiello, 2005[437]	Case report	300 mg/mo	1	51 (53 in another place of report) y/o male treated for B-cell CLL in 2002. In 2004 was treated with rituximab for leukemia reactivation. Pt died on day 27 of hepatic failure with hepatorenal syndrome.
Scaramucci, Miscola, Buffolino, et al., 2004[438]	Case reports		3	3 pts (48, 54, and 59 y/o) were given sequential immunotherapy with rituximab aimed to prolong the duration of the response. 1 CR and 2 PR were achieved. No neutropenic fever, transfusions, or admissions were recorded.
Sokol and Agosti, 2004[439]	Case report		1	83 y/o male diagnosed with simultaneous CLL and HCL. Pt developed severe anemia. Pt was treated with 8 weekly cycles of rituximab which resulted in rapid resolution of anemia. Pt was stable for last 8 mo.
Tinhofer, Steurer, Leitinger, et al., 2006[440]	Phase I		14	Study investigated tumor cell apoptosis *in vivo* in 14 heavily-pretreated pts with B-cell chronic lymphocytic leukemia undergoing rituximab monotherapy. Apoptosis induction was more pronounced in pts with mutated IgVH genes than in those with unmutated IgVH genes. Results suggest an association between IgVH gene mutational status and rituximab-induced apoptosis.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Voog, Morsch-hauser, and Solal-Celigny, 2003[441]	Case reports		1/8 had CLL	Only one 54 y/o male had CLL, and was treated with 4 weekly courses of rituximab in addition to chlorambucil, CAP, fludarabine, autologous stem-cell transplantation (with cyclophosphamide + total body irradiation), as well as interferon. CLL in CR at 9 mo.
Watanabe, Takahashi, Sugimoto, et al., 2005[442]	Case report	375 mg/m^2 q wk for 4 wk x 4 cycles	1	70 y/o female diagnosed with B-CLL began rituximab treatment after other drugs failed to achieve response. Rituximab treatment elicited AEs (fever, chills, severe neutropenia), but the regimen elicited a CR.
Williams, Densmore, Pawlucz-kowycz, et al., 2006[443]	Phase I	Pts 1, 2, 3, 10, 11, & 12 received 20 mg/m^2 tiw; other 6 pts received 60 mg/m^2 tiw	12	Pilot clinical study to determine if more frequent, lower doses of rituximab could reduce shaving and still provide adequate targeting and clearance of circulating CD20$^+$ B lymphocytes. Both low doses promoted lymphocyte clearance during the first infusion. Infusions of 20 mg/m^2 tiw better preserved the CD20 target. Authors state these low doses promoted substantial and rapid clearance of circulating CD20$^+$ cell in CLL pts.
Winkler, Jensen, Manzke, et al., 1999[359]	Phase I	375 mg/m^2 q wk x 4 wk	10/11 had B-CLL	Because of severe AEs with 1st pt, remaining pts were given 50 mg rituximab on day 1, 150 mg rituximab on day 2, and 400-500 mg on day 3 of the first infusion cycle. Pts were retrospectively stratified into 2 groups according to peripheral lymphocyte counts at baseline. 9/10 CLL pts were evaluable (1 pt removed from trial due to severe AEs during 1st infusion). Authors state incidence and severity of AEs during 1st infusion are dependent on number of circulating CD20$^+$ tumor cells. Reducing the numbers of circulating tumor cells to counts below 50.0 x 10^9/L by using chemotherapeutic regimens seems reasonable before treatment with rituximab.
Yang, Rosove, and Figlin, 1999[444]	Case reports	375 mg/m^2	1/2 had CLL	76 y/o female with B-CLL for 19 yr. Had good response with fludarabine, but developed autoimmune hemolysis that failed to respond to corticosteroids and splenectomy but stabilized with IV immunoglobulin. 12 hr after single dose of rituximab, TLS was diagnosed, and hemodialysis was started. Her overall condition continued to deteriorate, and she died of sepsis 7 days after rituximab treatment.

Abbreviations: AE(s) = adverse events; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CR = complete response; d = day(s); FCR = fludarabine, cyclophosphamide, and rituximab; f/u = followup; GPR = good partial response; HCL = hairy cell leukemia; h/o = history of; IA = immune anemia; IV = intravenous; MTD = maximum tolerated dose; ORR = overall response rate; OS = overall survival; PB = peripheral blood; PFS = progression-free survival; PR = partial response; q = every; SD = stable disease; tiw = thrice weekly ; TLS= tumor lysis syndrome.

Table A60.1: Rituximab for Chronic Lymphocytic Leukemia – Adverse Events (Grade 3/4+ Events Only) – Part 1

Study	Superficial edema	Anemia	Neutropenia/ granulocytopenia	Leukopenia	Thrombocytopenia	Diarrhea	Nausea	Vomiting	Dermatitis or rash	Fatigue	Headache	Pain	Chills/fever	Dyspnea	Myalgia or musculoskeletal pain
Byrd et al., 2001[361]	0%	3%	18%	-	9%	0%	0%	0%	-	0%	-	0%	0%	3%	-
Del Poeta et al., 2005[365]	-	0%	48%	-	5%	-	-	-	-	-	-	-	-	-	-
Hainsworth et al., 2002[445]	0%	0%	-	0%	-	-	0%	0%	-	0%	0%	-	2%	-	-
Hainsworth et al., 2003[366]	-	-	-	-	-	-	0%	0%	0%	2%	2%	-	0%	-	0%
Itala et al., 2002[367]	-	-	-	-	-	-	0%	-	-	0%	0%	-	0%	-	4%
Kay et al., 2007[368]	-	2%	41%	8%	20%	-	9%	6%	2%	2%	-	2%	6%	3%	2%
Keating et al., 2005[370]	-	-	-	-	-	-	0%	0%	0%	-	0%	-	1%	0%	0%
Robak et al., 2007[373]	-	9%	13%	-	9%	-	-	-	-	-	-	-	-	-	-
Schulz et al., 2002[375]	0%	10%	42%	26%	9%	0%	0%	-	0%	0%	0%	3%	3%	-	-
Tam et al., 2006[376]	-	-	52%	-	4%	-	1%	-	-	-	-	-	-	-	-
Weide et al., 2004[379]	-	7%	54%	50%	15%	-	-	-	-	-	-	-	0%	-	-

Table A60.2: Rituximab for Chronic Lymphocytic Leukemia – Adverse Events (Grade 3/4+ Events Only) – Part 2

Study	Infection	Neutropenic fever	Upper respiratory tract infection	Hypotension	Pulmonary	Low serum Ca	Hemorrhage	Secondary malignancy	Neurosensory	Neuralgia	Autoimmune disorder	Ischemia/infarction	Hypersensitivity	Other
Byrd et al., 2001[361]	12%	-	-	3%	6%	3%	3%	-	-	-	-	-	-	3%
Del Poeta et al., 2005[365]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hainsworth et al., 2002[445]	-	-	-	0%	-	-	-	-	-	-	-	-	-	2%
Hainsworth et al., 2003[366]	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Itala et al., 2002[367]	-	-	-	4%	-	-	-	-	-	-	-	-	-	-
Kay et al., 2007[368]	9%	-	-	5%	-	-	-	2%	2%	2%	2%	2%	-	6%
Keating et al., 2005[370]	-	-	-	1%	-	-	-	-	-	-	-	-	-	-
Robak et al., 2007[373]	28%	-	17%	-	-	-	-	-	-	-	-	-	36%	-
Schulz et al., 2002[375]	58%	13%	32%	-	-	-	-	-	-	-	-	-	-	3%
Tam et al., 2006[376]	12%	-	-		-	-	-	-	-	-	-	-	-	-
Weide et al., 2004[379]	0%	-	-	-	-	-	-	-	-	-	-	-	0%	-

Rituximab for Nodular Lymphocyte Predominant Hodgkin Disease

Background

Drug: Rituximab (Rituxan®). Rituximab is a humanized monoclonal antibody that binds to the CD20 protein, which is expressed on pre-B and mature B lymphocytes but not on hematopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissues. Possible mechanisms of action include induction of antibody dependent cell-mediated cytotoxicity; complement mediated lysis, phagocytosis of antibody-coupled tumor cells, and induction of apoptosis.

In November 1997, rituximab received FDA approval as a treatment for relapsed or refractory non-Hodgkins lymphoma. Rituximab then received FDA approval in February 2006 for first-line treatment of diffuse large B-cell, CD20-positive non-Hodgkin lymphoma, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or other anthracycline-based chemotherapy regimens. In September 2006, the FDA approved two rituximab supplemental applications for the first-line treatment of patients with low grade or follicular B-cell, CD20-positive non-Hodgkin lymphoma: first, for use in combination with cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; second, for use following CVP chemotherapy. Rituximab has been evaluated for off-label use in nodular lymphocyte predominant Hodgkin disease (NLPHD), Waldenström's macroglobulinemia (WM), and chronic lymphocytic leukemia (CLL).

An FDA alert issued in December 2006 highlights important emerging safety information about rituximab.[350] There are at least two reported deaths associated with rituximab for systemic lupus erythematosus (SLE). The cause of death in one patient was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated John Cunningham (JC) virus. Latent JC virus is present in about 80 percent of adults.

Disease: Nodular lymphocyte predominant Hodgkin disease. NLPHD is a rare type of Hodgkin lymphoma characterized by the presence of CD20-positive "popcorn" cells, which are different from the typical Reed-Sternberg cells (RSC) found in classical Hodgkin lymphoma. Affecting about 5 percent of all Hodgkin disease patients, NLPHD is a clinically indolent condition that typically presents in its early stages with localized lymphadenopathy. Overall survival is excellent, ranging from 70 percent to 94 percent at the 10-year mark.[446,447]

Standard Hodgkin disease protocols using radiotherapy or chemotherapy result in complete remission for more than 95 percent of patients with NLPHD.[447] However, these patients tend to relapse continuously over time, with relapses often occurring more than a decade after initial remission. Retrospective studies suggest that freedom from relapse and overall survival do not improve significantly with intensification of radiotherapy or chemotherapy.[447,448] Furthermore, both treatments result in late toxic repercussions,[449] including secondary malignancies, with mortality rates comparable to NLPHD itself.[447] While the fact that iatrogenic complications represent a major cause of death among NLPHD patients may suggest overtreatment,[450] NLPHD can, if left untreated, transform into diffuse large B-cell lymphoma, an aggressive form of non-Hodgkin lymphoma.[451] The generally benign nature of NLPHD relapses, along with the risks posed by treatment-related toxicity, suggest that patients could benefit from novel targeted therapies that are better tolerated.

Drug/Disease: Rituximab for NLPHD. Because rituximab is an anti-CD20 immunoglobulin that antagonizes the high-density CD20 surface antigens characteristic of the malignant cell population of NLPHD patients, it has emerged as a promising treatment option since its first off-label use in 1999 for a patient with difficult refractory NLPHD.[452] Early research suggests that rituximab is both effective in the short term and well tolerated, but the duration of response appears to be limited.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded at total of 11 reports; two of these were published full reports (Table A61), two were published abstracts from the American Society of Hematology (ASH) 2006 and 2007 conferences (Table A62), and seven were additional articles considered in the horizon scan (Table A63). Study designs included three Phase II non-randomized clinical trials, one case series, and seven case reports. The first case report, which was published in 1999, reported almost complete tumor regression and disease remission associated with rituximab in a 45-year-old male who had not responded to prior treatment. The next reports of rituximab in the treatment of NLPHD appeared in the literature in 2003, when the two full reports were published.

Sample sizes for the three clinical trials ranged from 14 to 23, with a total of 36 patients presented in the full reports, and 59 patients presented in the full reports plus the abstract. Eligibility criteria for inclusion in the studies included either untreated or previously treated CD20+ NLPHD. Twelve (33 percent) of the patients in the fully published trials had not been previously treated. Patients in stages I–IV were included. All of the studies involved adults. Patient age across the three clinical trials ranged from 17 to 71.

The dosage of rituximab was 375 mg/m^2 weekly for 4 weeks in all three clinical trials, but in one study, additional doses of rituximab were administered every 6 months for up to 2 years in 16 patients (27 percent). Rituximab was used as monotherapy in one study; in combination with bortezomib in another; and in combination with high-dose cyclophosphamide, cytarabine (Ara-C), then stem cell transplant with melphalan and either doxorubicin or cisplatin in a study published as an abstract.

Efficacy was reported in the two studies represented in the full reports. Tumor response according to National Cancer Institute (NCI)-sponsored Working Group criteria was the clinical outcome assessed. Adverse events were assessed using the NCI's Common Toxicity Criteria (CTC).

Both fully published reports met three of five quality criteria. Neither study had a sufficiently long followup period, nor neither included patients who were at a similar stage in their disease progression at time of enrollment.

Efficacy. The range of complete response (CR) rates was 45 percent to 69 percent among the three clinical trials. The range of partial response (PR) rates was 28 percent to 54 percent.

Survival. Survival data were sparsely reported in the full studies. Estimated 10- and 20-year overall survival rates were 97 percent and 85 percent, respectively, in the study published as an abstract. Median disease-free survival was 24 months among patients who received four doses of rituximab, and was not reached among patients who continued to receive rituximab at 6-month intervals.

Adverse events. Only one of the two full reports provided data on Grade 3/4 adverse events.[450] In this study, hypotension and chills or fever were reported in a single patient (7 percent).

Horizon scan. Five of the seven horizon scan publications were case reports and two were small case series, representing a total of 13 patients treated with rituximab. All but one reported some degree of clinical response with few or now adverse events.

Discussion

Because rituximab is an anti-CD20 immunoglobulin that antagonizes the high-density CD20 surface antigens characteristic of the malignant cell population of NLPHD patients, it has emerged as a promising treatment option since its first off-label use in 1999 for a patient with difficult refractory NLPHD.[452] Subsequent case reports and Phase II studies identified in this review provide further evidence that rituximab appears to be both effective in the short term and well tolerated, but that the duration of response may be limited. The observed CR and PR rates of 45 percent to 69 percent and 28 percent to 54 percent, respectively, compare favorably to existing treatment options, as do the estimated 10- and 20-year overall survival rates of 97 percent and 85 percent reported in a published abstract. The ASH 2006 and 2007 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates. Only one out of 14 patients (7 percent) experienced a Grade 3/4 adverse event in the single study that reported adverse events.

Table A61: Rituximab for Nodular Lymphocyte Predominant Hodgkin Disease – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Ekstrand, Lucas, Horwitz, et al., 2003[453]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - NLPHD, either untreated or previously treated - CD20+, CD15-, CD30-, and morph features of NLPHD - Age 3-70 yr - ECOG 0-2 - Measurable disease - ANC > 1500 - Platelet > 50K - Normal RFT, LFT	**No. in study:** 22 **Age:** 45 (18-63) **Previous treatment:** Yes: 10/22 (45%) No: 12/22 (55%) **Stage of disease:** I: 7/22 (32%) II: 7/22 (32%) III: 8/22 (36%) **Drug dose/day [followup]:** Rituximab 375 mg/m^2 qwk x 4 wk **Outcomes sought:** NCI WG criteria	**N:** 22 **CR:** 9 (41%) Unconfirmed CR: 1 (5%) Total CR: 10/22 (45%) **PR:** 12 (54%) **Stable disease:** 0 **Progressive disease:** 0	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** 9 mo (6-14); at 10.2 months 52% were free of progression (± SE 13%) Freedom from progression estimated from Kaplan-Meier curves: **1 yr:** Approx 40% **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Not reported **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes
Rehwald, Schulz, Reiser, et al., 2003[450]	**Design:** Uncontrolled clinical trial Feasibility of standard-dose rituximab in pts w/NLPHD **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - CD20+ Hodgkin	**No. in study:** 14 **Age:** 40 (18-51) **Previous treatment:** Yes, including 2 cases with prior stem cell transplant Median prior treatments: 2 (1-3) **Stage of disease**: Ann Arbor Stage: I: 3/14 (21%)	**N:** 14 **CR:** 8 (57%) **PR:** 4 (29%) **Stable disease:** 0 **Progressive disease:** 2 (14%)	**Survival overall (from start of treatment):** Median followup 12 mo **Median survival:** Median duration of response not yet reached at 20+ mo **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** Mean duration of response: 20 mo (95% CI	**Adverse events & tolerability:** Hypotension and chills or fever were reported in a single patient (7%). **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes

Study	Study Design	Patients	Tumor Response	Survival	Other
	lymphoma at first or higher relapse or progressive disease after at least one standard treatment - NLPHD and CD20+ classical HDz or transformed HDz included - Measurable disease - WHO PS 0-2 - Age ≥ 18 yr - Not pregnant or lactating - Life expectancy ≥ 3 mo	II: 5/14 (36%) III: 1/14 (7%) IV: 5/14 (36%) **Drug dose/day [followup]:** Rituximab 375 mg/m^2 q wk x 4 wk **Outcomes sought:** Criteria for non-Hodgkin lymphomas according to NCI-WG		15-25 mo) Duration of response estimated from Kaplan-Meier curves: **1 yr:** Approx 70% **2 yr:** NR **3 yr:** NR	

Abbreviations: ANC =absolute neutrophil count; CI = confidence interval; CR = complete response; ECOG = Eastern Collaborative Oncology Group; LFT = liver function tests; NCI = National Cancer Institute; NCI-WG = National Cancer Institute-sponsored Working Group; NLPHD = nodular lymphocyte predominant Hodgkin disease; PR = partial response; PS = performance status; q = every; RFT = renal function tests; WHO = World Health Organization.

Table A62: Rituximab for Nodular Lymphocyte Predominant Hodgkin Disease – ASH 2006 and 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Genadieva-Stavrik, Ivkovski, and Pivkova, 2006[454] ASH 2006 Abstract #4696	**Disease:** Lymphocyte predominant Hodgkin lymphoma **Design:** Case report **Phase:** Case report **Selection/randomization:** Non-randomized **Eligibility criteria:** Not reported	**No. in study:** 1 **Age:** 46 **Previous treatment:** None **Stage of disease:** IIB **Drug dose/day [followup]:** ABVD day 2; *plus* Rituximab 375 mg/m^2 day 1. Above regimen repeated x 6 cycles. **Outcomes sought:** Not reported	**N:** 1 **CR:** 1 **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** 1 (100%) **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** 1 (100%) **3 yr:** NR	**Adverse events & tolerability:** Not reported **Comments:** Authors state case report suggests that rituximab is both safe and effective in patients with CD20+ NLPHD
Horning, Bartlett, Breslin, et al., 2007[455] ASH 2007 Abstract #644	**Disease:** Nodular lymphocyte predominant Hodgkin disease **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated or relapsed CD20+ NLPHD	**No. in study:** 23 – 4 wkly doses rituximab 16 – wkly doses rituximab q 6 mo for 2 yr **Age:** 44 (17-71) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Rituximab 375 mg/m^2 q wk x 4 doses (limited) Rituximab 375 mg/m^2 q wk x 4 doses q 6 mo x 2 yr (extended)	**N:** Not reported **CR:** 27 (69%) **PR:** 11 (28%) **Stable disease:** 1 (3%) **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR Estimated 10-yr survival: 97% Estimated 20 yr survival: 85% **Survival (disease free):** **Median survival:** 24 mo with 4 doses rituximab; not reached with rituximab maintenance **1 yr:** NR **2 yr:** NR	**Adverse events & tolerability:** No Grade 3-4 toxicities 4 transformations to large cell lymphoma **Comments:** Extended treatment regimen prolongs FFP

Study	Study Design	Patients	Tumor Response	Survival	Other
				3 yr: NR	
		Outcomes sought: Not reported			

Abbreviations: ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; ASH = American Society of Hematology; CR = complete response; FFP = fresh frozen plasma; NLPHD = nodular lymphocyte predominant Hodgkin disease; PR = partial response; q = every.

Table A63: Rituximab for Nodular Lymphocyte Predominant Hodgkin Disease – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Boulanger, Meignin, Leverger, et al., 2003[456]	Case report	375 mg/m^2 weekly x 4 wk	1	16 y/o boy had splenectomy, refused chemotherapy, so was treated with rituximab. Had a tumor response, but then progressive disease.
Culic, Armanda, Kuljis, et al., 2006[457]	Case report	375 mg/m^2 weekly x 4 wk	1	10 y/o girl treated with rituximab and ABVD. CR and 2-yr remission after 6 cycles. No AEs.
Ibom, Prosnitz, Gong, et al., 2003[458]	Case series	375 mg/m^2 weekly x 4 wk	6	Pts treated with either radiation therapy or chlorambucil after 4 weekly treatments with rituximab. No disease progression, median f/u 12.5 mo (range, 6-39).
Keilholz, Szelenyi, Siehl, et al., 1999[459]	Case report	375 mg/m^2 weekly x 4 wk, then q 3 wk	1	45 y/o male, relapsed after COPP/ABVD, then later DexaBEAM and then DIZE. 10 wk after rituximab treatment, almost complete tumor regression, with remission ongoing 6 mo later.
Lush, Jones, and Haynes, 2001[452]	Case report	375 mg/m^2 weekly x 4 wk	1	52 y/o male, stage IIA, treated with radiation therapy and ChIVPP/PBIOE, then salvage IVE chemotherapy. After recurrence, he was treated with rituximab with subsequent remission. No AEs from rituximab.
Rose, Forsythe, and Maloney, 2003[460]	Case report	375 mg/m^2 weekly x 2 wk	1	46 y/o male, stage IV, treated with rituximab on days 30 and 37 after PR from chemotherapy. On day 122, had agranulocytosis, which was attributed by authors to rituximab.
Unal, Sari, Deniz, et al., 2005[461]	Case series	375 mg/m^2	2	Mother (age 48) and son (age 30) treated with CHOP-R. Chemotherapy well tolerated, both achieved CR for 34 and 40 mo. No AEs.

Abbreviations: AE(s) = adverse events; CR = complete response; DexaBEAM = dexamethasone, carmustine, etoposide, arabinoside C, and melphalan; PR = partial response; q = every.

Rituximab for Waldenström's Macroglobulinemia

Background

Drug: Rituximab (Rituxan®). Rituximab is a humanized monoclonal antibody that binds to the CD20 protein, which is expressed on pre-B and mature B lymphocytes but not on hematopoietic stem cells, pro-B-cells, normal plasma cells, or other normal tissues. Possible mechanisms of action include induction of antibody dependent cell-mediated cytotoxicity, complement mediated lysis, phagocytosis of antibody-coupled tumor cells, and induction of apoptosis.

In November 1997, rituximab received FDA approval as a treatment for relapsed or refractory non-Hodgkins lymphoma. Rituximab then received FDA approval in February 2006 for first-line treatment of diffuse large B-cell, CD20-positive non-Hodgkin lymphoma, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or other anthracycline-based chemotherapy regimens. In September 2006, the FDA approved two rituximab supplemental applications for the first-line treatment of patients with low grade or follicular B-cell, CD20-positive non-Hodgkin lymphoma: first, for use in combination with cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy; second, for use following CVP chemotherapy. Rituximab has been evaluated for off-label use in nodular lymphocyte predominant Hodgkin disease (NLPHD), Waldenström's macroglobulinemia (WM), and chronic lymphocytic leukemia (CLL). The FDA subsequently approved rituximab for relapsed or refractory WM.

An FDA alert issued in December 2006 highlights important emerging safety information about rituximab.[350] There are at least two reported deaths associated with rituximab for systemic lupus erythematosus (SLE). The cause of death in one patient was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated John Cunningham (JC) virus. Latent JC virus is present in about 80 percent of adults.

Disease: Waldenström's macroglobulinemia. A rare, indolent non-Hodgkin lymphoma, WM originates in B lymphocytes. WM is characterized by the proliferation of abnormal lymphoplasmacytic cells (B cells that are in the process of maturing into plasma cells), which produces large amounts of monoclonal immunoglobulin M (IgM) antibody. High levels of IgM in the blood cause hyperviscosity, leading to many of the symptoms of WM.[462] The cause of WM is unknown, and there is no known cure.

About 1,500 new cases occur annually in the United States, with a median survival of 5 to 10 years. Incidence substantially increases with age, the median age at diagnosis being 63.[463] Asymptomatic patients are monitored without treatment, and they often remain asymptomatic for many years.[462] Patients who present with symptoms are usually treated with chemotherapy, but may also receive biological therapy, combination chemotherapy, or chemoimmunotherapy.[464] No clinical data suggest that any one of these protocols is more effective than the others, with overall response rates hovering around 50 percent to 60 percent.[465-467] For patients who fail to respond to primary treatments, high-dose therapy with autologous bone marrow transplantation may be warranted.[465] Patients with high levels of IgM and hyperviscosity syndrome may also undergo plasmapheresis, which will temporarily reduce IgM levels.[462,464]

Drug/Disease: Rituximab for WM. Because rituximab is an anti-CD20 immunoglobulin that targets the CD20 surface antigens that are expressed on malignant lymphocytes in WM, investigations of this antibody as an alternative/complementary treatment option began in the late

1990s.[467] It is currently recognized as an acceptable off-label treatment for WM.

Methods

The systematic review was conducted using the methodology and search strategy described in the Introduction to this report.

Results

Studies identified. The search strategy yielded at total of 40 reports. Eight of these were published full reports (Table A64); nine were published abstracts from the American Society of Hematology (ASH) 2006, ASH 2007, and American Society of Clinical Oncology (ASCO) 2007 conferences (Table A65); and 23 were additional articles considered in the horizon scan (Table A66). Three of the eight full reports provided data used in another published report in our analysis, thereby resulting in a total of five different clinical trials. There were an additional eight Phase II trials published as abstracts, for a total of 13 Phase II clinical trials, one retrospective review, and one case series when considering the full reports plus abstracts. One of the clinical trials randomized patients to weekly vs. biweekly dosing of bortezomib while keeping the rituximab dosage constant. The other 12 trials were all non-randomized Phase II studies. Case reports of rituximab having been used for WM began appearing in the literature in 1999. The first clinical trial was published in 2002; this study started accruing patients in 1999.

Sample sizes for the clinical trials range from 20 to 94, with a total of 213 patients described in the full reports, and 399 in the full reports plus abstracts. Eligibility criteria for inclusion in the studies were generally uniform and consistent with what would be expected from studies involving patients with a clinicopathological diagnosis of WM. Among the fully published reports, 102 patients (48 percent) had been previously treated for WM, and 111 patients (52 percent) were previously untreated. All of the studies involved adults. Patient age across the full reports ranged from 29 to 90.

The majority of studies used rituximab in combination with other therapies, including bortezomib, cyclophosphamide, dexamethasone, fludarabine, cladribine, or thalidomide. The dosage of rituximab studied was almost universally 375 mg/m^2 given either weekly or every 2 or 3 weeks.

Efficacy was reported in each of the six studies described in the full reports. Reduction or elimination of monoclonal IgM and resolution of adenopathy were the most common a priori definitions of clinical response to treatment. Surprisingly, interpretable adverse events data were provided in only three of the six fully published trials. Adverse events were assessed using the National Cancer Institute's Common Toxicity Criteria.

Study quality of the fully published reports was generally good, with 67 percent of studies meeting four of five quality criteria, and 33 percent meeting three of five criteria. Most frequently, the missing quality criteria were sufficiently long followup period and patients entering in the study at a similar point in their disease progression.

Efficacy. The range of complete response (CR) rates was 0 percent to 18 percent in the six fully published studies. Four of these studies reported a CR of 0 percent. Among the five abstracts that provided data on CR, two reported a CR rate of 0 percent and three reported rates ranging from 4 percent to 8 percent.

The range of partial response (PR) rates was 44 percent to 73 percent among the fully published studies, and 23 percent to 90 percent among the abstracts.

Adverse events. The adverse events data summarized in Table A67 were derived from three of the full reports. No single adverse event was reported in all three studies. Grade 3/4 anemia (range, 13 percent to 25 percent), leucopenia (range, 6 percent to 25 percent), and thrombocytopenia (range, 6 percent to 19 percent) were reported in two studies. These data suggest that the most common adverse events among patients with WM treated with rituximab are hematologic in nature.

Horizon scan. The horizon scan identified reports that suggest that rituximab for WM:

- May be generally well tolerated;
- Was not effective in treating pleural effusion associated with WM;
- May have caused a pro-inflammatory syndrome resulting in synovitis;
- May have clinical activity in heavily pre-treated patients with WM;
- Seems to have facilitated wound healing in a patient with vasculitis;
- May encounter resistance, possibly caused by autoantibodies;
- Was associated with improvement in neurological function;
- Was associated with worsening of neuropathy;
- Appears to induce remission and facilitates hematologic recovery;
- May result in severe adverse events secondary to abrupt rise in IgM levels;
- Is active with the CHOP regimen and spares circulating effector cells;
- Contributed to complete resolution of a tremor and arm paresis;

Discussion

Rituximab, an anti-CD20 immunoglobulin that targets the CD20 surface antigens that are expressed on malignant lymphocytes in WM, has been used as an off-label treatment for WM since the late 1990s. This review identified 13 published Phase II reports suggesting some efficacy, with one reported CR rate reaching 18 percent and PR rates ranging as high as 90 percent. Historically, single and combination chemotherapies for advanced disease have had variable response rates and short median survivals. In Phase II reports, rituximab was generally well-tolerated, and it compares favorably to these existing treatment options. The ASH 2006, ASH 2007, and ASCO 2007 abstracts and horizon scan did not suggest any major modifications in the dosing schedule, planned combinations with other drugs, or anticipated response rates.

Table A64: Rituximab for Waldenström's Macroglobulinemia – Full Reports

Study	Study Design	Patients	Tumor Response	Survival	Other
Dimopoulos, Anagnostopoulos, Zervas, et al., 2005[468] AND Dimopoulos, Alexian, Gika, et al., 2004[464]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not randomized; all eligible pts received same treatment protocol **Eligibility criteria:** - Diagnosis of WM - Monoclonal IgM in serum and LL bone marrow infiltration	**No. in study:** 54 **Age:** 72 (39-85) **Previous treatment:** Yes: 30 No: 24 **Stage of disease:** Not reported **Drug dose/day [followup]:** 375 mg/m^2 rituximab q wk x 4 wk, then q 3 mo in pts w/o progressive disease **Outcomes sought:** Not defined	**N:** 54 **CR:** 0 **PR:** 24 (44%) **Stable disease:** 19 (35%) **Progressive disease:** 11 (20%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Median time to response 3.8 mo (1.4-10.3) Median TTP for all pts 14 mo (no range given) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A67 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: No 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: No **Comments:** - Objective response in 44% of pts - "We conclude that patients with low levels of monoclonal protein and normal albumin are the best candidates for treatment with rituximab."
Dimopoulos, Zervas, Zomas, et al., 2002[469] AND Dimopoulos, Zervas, Zomas, et al., 2002[470]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not randomized; consecutive pts **Eligibility criteria:** - WM - Monoclonal IgM in serum and marrow with small lymphs, plasmacytoid lymphs, and plasma cells - CD20+ tumor cells	**No. in study:** 27 **Age:** 72 (39-85) **Previous treatment:** Yes: 12 2 were primary refractory (i.e., didn't respond to any prior treatments), 8 relapsed during chemotherapy, and 2 relapsed after completed prior treatment Previously untreated: 15 **Stage of disease:** Not reported	**N:** 27 **CR:** 0 **PR:** 12 (44%) **Stable disease:** 10 (37%) **Progressive disease:** 5 (19%)	**Survival overall (from start of treatment):** **Median survival:** Median followup 16 mo (9-32+) **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Median TTP for all pts 16 mo (95% CI 6.7-24.7 mo) **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A67 **Quality assessment:** 1) Representative sample from a relevant population?: Yes (consecutive pt series) 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** "Rituximab is well tolerated and active in WM"

Study	Study Design	Patients	Tumor Response	Survival	Other
		Drug dose/day [followup]: 375 mg/m^2 rituximab q wk x 4 wk Dose held if Grade 3 or 4 toxic event **Outcomes sought:** CR: Disappearance of IgM, resolution of lymphadenopathy and hepatosplenomegaly, and < 20% lymphs in marrow PR: > 50% decrease in IgG for 2 mos, and > 50% decrease in tumor infiltrate Stable: IgM decrease of 0-50%			
Gertz, Rue, Blood, et al., 2004[471] AND Ghobrial, Fonesca, Greipp, et al., 2004[472]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - WM - Bone marrow with > 10% lymphoplasmacytic cells or aggregates/sheets of cells - Monoclonal IgM > 1,000 mg/dL - Evidence of impaired BM function with hemoglobin < 11 g/dL or hyperviscosity	**No. in study:** 72 (3 ineligible, for final n = 69) **Age:** 69 (45-89) **Previous treatment:** Yes: 35 No: 34 **Stage of disease:** Not reported **Drug dose/day** [followup]: 375 mg/m^2 rituximab weekly x 4 wk **Outcomes sought:** CR: Negative immunofixation (serum and urine) and < 5% lymphs and plasma cells	**N:** 69 (but 3 were unevaluable – died without evidence of progression – for total of 66) **CR:** 0 **PR:** 36 (55%) (19 "objective" and 17 "minor" response) **Stable disease:** 22 (33%) **Progressive disease:** 8 (12%)	**Survival overall (from start of treatment):** **Median survival:** Overall survival derived from Kaplan-Meier curves (numbers are approximate): **1 yr:** No prior treatment: 100% Prior treatment: 80% **2 yr:** No prior treatment: 95% Prior treatment: 75% **3 yr:** NR **Survival (disease free):** **Median survival:**	**Adverse events & tolerability:** See Table A67 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** Rituximab produced objective or minor response in 52%, with Grade 4 toxicity rate of 11%

Study	Study Design	Patients	Tumor Response	Survival	Other
	- No more than 2 prior treatments and no prior rituximab - Adequate RFT, LFTs - ECOG 0-3	in marrow. Objective response: 50% reduction in IgM and 50% decrease in urine light chain excretion Minor response: > 25% but < 50% decrease in IgM Progression: 25% increase in IgM or required apheresis All others considered "stable disease"		Disease-free survival of responders derived from Kaplan-Meier curves (numbers are approximate): **1 yr:** 80% **2 yr:** 65% **3 yr:** NR	
Hensel, Villalobos, Kornacker, et al., 2005[473]	**Design:** Uncontrolled clinical trial **Phase:** Phase II **Selection/ randomization:** Not randomized Pentostatin w/ & w/o rituximab First 9 pts got pentostatin w/o rituximab; next 8 got rituximab Pts who had at least partial response were given rituximab every 3 mo **Eligibility criteria:** - WM or lymphoplasmacytic lymphoma - Bone marrow Dx, plus symptoms: fever,	**No. in study:** 17 9 got PC (pentostatin/cyclo-phosphamide) and 8 got PC + rituximab All pts with at least partial response then got rituximab as maintenance **Age:** 62 (29-79) **Previous treatment:** Yes (8 pts) **Stage of disease:** Not reported **Drug dose/day [followup]:** 375 mg/m^2 Rituximab q 3 wk Pts with at least PR then got 375 mg/m^2 rituximab q 3 mo	**N:** 13 got rituximab initially (n = 8) or in maintenance phase (n = 5) 4 did not receive rituximab **CR:** With rituximab: 2/13 (15%) Without rituximab: 0/4 (0%) **PR:** With rituximab: 8/13 (62%) Without rituximab: 2/4 (50%) **Stable disease:** With rituximab: 2/13 (15%) Without rituximab: 2/4 (50%) [these data are inconsistent in the report] **Progressive disease:**	**Survival overall (from start of treatment):** Median followup 13 mo (2-48 mo) **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** See Table A67 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** PC-R followed by rituximab maintenance is effective in pretreated and untreated pts with WM/LL

Study	Study Design	Patients	Tumor Response	Survival	Other
	sweats, fatigue from anemia, weight loss, lymphedema or splenomegaly, anemia platelets < 100K, hyperviscosity syndrome	**Outcomes sought:** CR: Disappearance of monoclonal IgM, resolution of adenopathy, disappearance of all signs of WM PR: ≥ 50% reduction in above-stated outcomes	With rituximab: 0 Without rituximab: 0		
Treon, Emmanouilides, Kimby, et al., 2005[474]	**Design:** Uncontrolled clinical trial Objective: To evaluate the efficacy and safety of extended rituximab treatment **Phase:** Phase II **Selection/ randomization:** Not randomized **Eligibility criteria:** - Clinicopathological diagnosis of WM - CD20+ - No more than 2 prior therapies - Must have been symptomatic and in need of therapy	**No. in study:** 29 **Age:** 65 (43-90) **Previous treatment:** Yes: 17 (59%) No: 12 (41%) **Stage of disease:** Not reported **Drug dose/day [followup]:** 375 mg/m^2 rituximab weekly x 4 wk and then repeat at 12 wk **Outcomes sought:** CR: Resolution of all symptoms, normalization of IgM with complete disappearance of IgM paraprotein, and resolution of adenopathy or splenomegaly PR and minor response: ≥ 50% and > 25% reduction in IgM Stable disease: Change in IgM in absence of new signs/symptoms	**N:** 26 **CR:** 0 **PR:** 19 (73%) (14 had partial response. 5 had minor response) **Stable disease:** 3 (12%) **Progressive disease:** 4 (15%)	**Survival overall (from start of treatment):** Median followup 29 mo (12-36+ mo) **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** Median TTP for all pts 14 mo (no range given) **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse Events & Tolerability:** See Table A67 **Quality assessment:** 1) Representative sample from a relevant population?: Yes 2) Explicit eligibility criteria?: Yes 3) Patients entered at similar point in disease progression?: No 4) Adequate followup period?: No 5) Objective outcomes assessments?: Yes **Comments:** - Extended rituximab is active, and may lead to more major responses than standard dose rituximab in WM - IgM levels (serum) of < 6000 mg/dl predicts benefit from extended therapy

Abbreviations: BM = bone marrow; CI = confidence interval; CR = complete response; Dx = diagnosis; ECOG = Eastern Collaborative Oncology Group; g = gram(s); IgG = immunoglobulin G; IgM = immunoglobulin M; LFT(s) = liver function test(s); LL = lymphoplasmacytoid lymphoma; m = meter; PC = pentostatin / cyclophosphamide; PC-R = pentostatin / cyclophosphamide + rituximab; PR = partial response; q = every; RFT(s) = renal function test(s); TTP = time to tumor progression; WM = Waldenström's macroglobulinemia.

Table A65: Rituximab for Waldenström's Macroglobulinemia – ASH 2006, ASH 2007, and ASCO 2007 Abstracts

Study	Study Design	Patients	Tumor Response	Survival	Other
Dimopoulos, Anagnostopoulos, Kyrtsonis, et al., 2006[475] ASH 2006 Abstract #128	**Disease:** Waldenström's macroglobulinemia **Design:** Prospective, multicenter **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Previously untreated WM	**No. in study:** 70 **Age:** 71 (33-89) **Previous treatment:** None **Stage of disease:** Not reported **Drug dose/day [followup]:** Dexamethasone 20 mg IV day 1; *plus* Rituximab 375 mg/m^2 IV day 1; *plus* Cyclophosphamide 100 mg/m^2 PO BID days 1-5. Above regimen repeated q 21 days x 6 cycles. **Outcomes sought:** Response	**N:** Not reported **CR:** 7% **PR:** 70% (with 50% reduction in IgM) **Stable disease:** 20% (with < 50% reduction in IgM) **Progressive disease:** 10%	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** 60% **3 yr:** NR	**Adverse events & tolerability:** 1 patient died of interstitial pneumonia 20% Grade 3-4 neutropenia
Treon, Soumerai, Patterson, et al., 2006[166] ASH 2006 Abstract #2765	**Disease:** Waldenström's macroglobulinemia **Design:** Prospective, single center **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Diagnosis of WM	**No. in study:** Not reported **Age:** Not reported **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.3 mg/m^2 days 1, 4, 8, & 11; *plus* Dexamethasone 40 mg IV days 1, 4, 8, & 11; *plus*	**N:** 10 evaluable **CR:** 5 major response 5 minor response (major vs. minor is > or < 50% IgM reduction) **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3-4 toxicities: Sepsis: 1 Pneumonia: 1 Thrombocytopenia: 1 Zoster infection: 4

Study	Study Design	Patients	Tumor Response	Survival	Other
		Rituximab 375 mg/m^2 day 11. Above regimen repeated x 4 cycles, then 4 more cycles q 3 mo. **Outcomes sought:** Not reported			
Vargaftig, Pegourie-Bandelier, Mahe, et al., 2006[476] ASH 2006 Abstract #4727	**Disease:** Waldenström's macroglobulinemia **Design:** Retrospective, multicenter **Phase:** n/a **Selection/randomization:** Non-randomized **Eligibility criteria:** Previous treatment of WM with FCR	**No. in study:** 21 **Age:** 65 (40–77) **Previous treatment:** 19/21 previously treated with median 2 lines of treatment **Stage of disease:** Not reported **Drug dose/day [followup]:** Rituximab 375 mg/m^2 d 1; *plus* Fludarabine 40 mg/m^2 PO days 1-3; *plus* Cyclophosphamide 250 mg PO days 1-3. Above regimen repeated q 4 wk x 2-6 cycles. **Outcomes sought:** Response, toxicity	**N:** 21 **CR:** 1 (5%) **Minor response:** 5 (24%) **PR:** 10 (48%) **Stable disease:** 5 (24%) **Progressive disease:** None	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3-4 toxicities: Neutropenia: 10 (only 1 with infectious episode) Thrombocytopenia: 5 Anemia: 2

Study	Study Design	Patients	Tumor Response	Survival	Other
Abonour, Zhang, Rajkumar, et al., 2007[477] ASH 2007 Abstract #3616	**Disease:** Waldenström's macroglobulinemia **Design:** Prospective, multicenter **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Previously untreated WM	**No. in study:** 16 **Age:** 60 (44-79) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Standard R-CHOP **Outcomes sought:** Response, toxicity	**N:** 11 **CR:** 10 objective responses, 1 minor response **PR:** Not reported **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median survival:** Not Reached **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Not Reached **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 4 neutropenia: 8 Grade 3 lymphopenia: 8 **Comments:** ECOG study closed due to poor accrual
Agathocleous, Rule, Johnson, et al., 2007[169] ASH 2007 Abstract #2559	**Disease:** MCL, Waldenström's macroglobulinemia **Design:** Prospective, multicenter **Phase:** Phase I/II **Selection/randomization:** Randomization not described, randomized between once or twice weekly bortezomib **Eligibility criteria:** Recurrent CD20+ MCL, or WM (or other histology not of interest to target therapy)	**No. in study:** 45 (18 MCL, 10 WM) **Age:** 60 (45-79) **Previous treatment:** Median of 2 previous treatments **Stage of disease:** Not reported **Drug dose/day [followup]:** Arm A: Bortezomib 1.3 mg/m^2 days 1, 4, 8, & 11; *plus* Rituximab 375 mg/m^2 day 1, q 21 days x 8 cycles Arm B: Bortezomib 1.6 mg/m^2 days 1, 8, 15, & 22 q 35 days; *plus* Rituximab 375 mg/m^2 days 1, 8, 15, & 22 on cycles 1 & 4 x 6 cycles.	**N:** Unclear how many patients with each histology available for analysis **CR:** Not reported **PR:** Overall response rate: 46% in MCL 90% in WM **Stable disease:** Not reported **Progressive disease:** Not reported	**Survival overall (from start of treatment):** **Median Survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3: Neurotoxicity: 2 patients Neutropenia: 25% Thrombocytopenia: 22% **Comments:** Dosing schedules did not influence response rate, thus weekly bortezomib is advocated

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Not reported			
Ghobrial, Padmanabhan, Badros, et al., 2007[478] ASH 2007 Abstract #4494	**Disease:** Waldenström's macroglobulinemia **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Relapsed or refractory WM	**No. in study:** 17 **Age:** 62 (43-81) **Previous treatment:** Median of 3 lines previous treatment **Stage of disease:** Not reported **Drug dose/day [followup]:** Bortezomib 1.6 mg/m^2 days 1, 8, & 15 q 28 days x 6 cycles, Rituximab 375 mg/m^2 days 1, 8, 15, & 22 with cycles 1 & 4 **Outcomes sought:** Response, toxicity	**N:** 17 **CR:** 1 (8%) **PR:** 3 (23%) **Stable disease:** 9 (69%) **Progressive disease:** 0	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** Not Reached **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** Grade 3 toxicities: Neuropathy: 1 Neutropenia: 3 Anemia and hyponatremia: 1
Laszlo, Rabascio, Andreola, et al., 2007[479] ASH 2007 Abstract #1357	**Disease:** Waldenström's macroglobulinemia **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Untreated or pre-treated CLL	**No. in study:** 29 **Age:** 64 (36-75) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** 2-CDA 0.1 mg/kg days 1-5, Rituximab 375 mg/m^2 day 1, q 28 days x 4 cycles	**N:** 29 **CR:** 17 CR/PR **PR:** **Stable disease:** 8 MR/SD **Progressive disease:** 4	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR	**Adverse events & tolerability:** Grade 3 neutropenia: 3 patients Rituximab cardiac toxicity: 3 patients

Study	Study Design	Patients	Tumor Response	Survival	Other
		Outcomes sought: Response, toxicity		**3 yr:** NR	
Tedeschi, Moqueluiz, Ricci, et al., 2007[480] ASH 2007 Abstract #1290	**Disease:** Waldenström's macroglobulinemia **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** Symptomatic WM, previously treated or untreated	**No. in study:** 19 **Age:** 57 median **Previous treatment:** Median of 2 lines of treatment in 14 previously treated patients **Stage of disease:** Not reported **Drug dose/day [followup]:** Fludarabine 25 mg/m^2 days 2-4, Rituximab 375 mg/m^2 day 1, Cyclophosphamide 250 mg/m^2 days 2-4, q 4 wk **Outcomes sought:** Response, toxicity	**N:** 19 **CR:** **PR:** 15 (79%) **Stable disease:** 3 (16%) **Progressive disease:** 1 (5%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR	**Adverse events & tolerability:** No IgM flare Neutropenia in 82% of courses 2 FUO 1 pneumonia aspergillosis resulting in death
Soumerai, Branagan, Patterson, et al., 2007[481] ASCO 2007 Abstract #8017	**Disease:** Waldenström's macroglobulinemia **Design:** Prospective **Phase:** Phase II **Selection/randomization:** Non-randomized **Eligibility criteria:** WM, no previous rituximab or thalidomide exposure	**No. in study:** 25 **Age:** 63 (44-86) **Previous treatment:** Not reported **Stage of disease:** Not reported **Drug dose/day [followup]:** Rituximab 375 mg/m^2/wk x 4, wk 2 & 13.	**N:** 23 **CR:** 1 (4%) **PR:** 15 (65%) **Minimal response:** 2 (9%) **Stable disease:** 1 (4%) **Progressive disease:** 9 (39%)	**Survival overall (from start of treatment):** **Median survival:** **1 yr:** NR **2 yr:** NR **3 yr:** NR **Survival (disease free):** **Median survival:** **1 yr:** NR **2 yr:** NR	**Adverse events & tolerability:** Neuropathy: 11 Somnolence: 3 Confusion: 3 Rash: 2 Tremors: 2 Bradycardia: 2 Palpitation: 1 **Comments:** Thalidomide discontinuation in 11, dose reduction in all

Study	Study Design	Patients	Tumor Response	Survival	Other
		Thalidomide 200 mg PO qhs x 2 wk, then 400 mg PO qhs x 50 wk **Outcomes sought:** Response, toxicity		**3 yr:** NR	

Abbreviations: 2-CDA = 2-chlorodeoxyadenosine (cladribine); ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; BID = twice daily; CLL = chronic lymphocytic leukemia; CR = complete response; ECOG = Eastern Collaborative Oncology Group; FCR = fludarabine, cyclophosphamide, and rituximab; FUO = fever of unknown origin; IgM = immunoglobulin M; IV = intravenous; MCL = mantle cell lymphoma; PO = orally; PR = partial response; q = every; qhs = at bedtime; R-CHOP = rituximab, cyclophosphamide, hydroxydaunomycin, Oncovin (vincristine), and prednisone; SD = stable disease; WM = Waldenström's macroglobulinemia.

Table A66: Rituximab for Waldenström's Macroglobulinemia – Horizon Scan

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Amin and Rabinowitz, 2005[482]	Case report		1	77 y/o female with h/o WM. Diagnosed with left pleural effusion (uncommon pulmonary involvement). Treatment with rituximab decreased pt's serum IgM levels, but pleural effusions never improved.
Bertazzoni, Andreola, Laszio, et al., 2006[483]	Case report	375 mg/m^2	1	61 y/o male referred for investigation of IgM gammopathy. Performance status was limited by a severe peripheral neuropathy. Pt was given rituximab on day 1 and cladribine (0.1 mg/kg, SC injection) for 5 consecutive days. Treatment was administered 4 x q 4 wk. Treatment was well tolerated and toxicity was mild.
Buda-Okreglak, Drabick, and Delaney, 2004[484]	Case report	Initial dose of 100 mg, followed by 375 mg/m^2 3 x weekly for 4 wk	1	58 y/o male presented with novel proinflammatory syndrome associated with rituximab. He had no h/o rheumatoid arthritis. Each time he finished a course of treatment, he experienced AEs of acute swelling and pain which responded to prednisone. Authors state rituximab played a pathogenetic role in his acute synovitis. While the precise mechanism of action remains unknown, genetic polymorphisms associated with B-cell depletion with rituximab may play a role in the response of some pts in non-Hodgkin lymphomas and similar variation in polymorphisms may predispose some pts to acute synovitis with treatment with rituximab.
Byrd, White, Link, et al., 1999[466]	Examined clinical and lab data from pts with WM treated on IDEC Pharma-ceutical trials or at WRAMC	375 mg/m^2	7 (5 from serial trials, and 1 from WRAMC)	All were symptomatic pts with WM. 6 were treated with 4 weekly infusions of rituximab; 1 pt received 8 weekly infusions. Pts had received a median of 3 prior treatments (range 1-4) which included alkylator treatment in all (5 pts refractory) and fludarabine in 4 (all refractory). Treatment was well tolerated in all pts without decrement in cellular immune function or significant infectious morbidity. PRs were noted in 3 pts, including 2 with fludarabine-refractory disease. Median PFS was 6.6 mo (range, 2.2 to 29+ mo). Data suggest rituximab has clinical activity in heavily pretreated pts with WM.
Ghobrial, Uslan, Call, et al., 2004[485]	Case report	375 mg/m^2	1	75 y/o female with 7-yr h/o small vessel vasculitis identified as type II cryoglobulinemia. Treated for 2 mo with prednisone, wound care, and debridement, the lesions extended revealing viable tendons and muscle tissue. Treatment with chlorambucil (4 mg/day) was initiated with no improvement. Weekly IV rituximab treatment was given for 8 wk. With continued wound care, pt had viable granulation tissue and complete resolution of the ulcer without use of skin grafts. When published, pt had 19+ mo remission.
Gironi, Saresella, Ceresa, et al., 2006[486]	Case report	375 mg/m^2	1	64 y/o female with WM and a neuropathy associated with anti-MAG IgM/k antibodies. Rituximab was injected once weekly x 4 wk. 3 mo post-treatment a severe worsening of all neurological signs and specifically of the tremor occurred. Rituximab treatment was stopped, and after 6 mo lab values returned to previous levels, but pt continued to worsen. Authors state these data may suggest that the auto-antibodies are secreted by a cell population clearly insensitive to rituximab. An explanation for the clinical and immunological worsening could be the disruption of idiotype-anti-idiotype network.
Iyer, Mathur,	Case report	375 mg/m^2	1	60 y/o male with 11 yr h/o WM. Pt had no response from chlorambucil treatment, so was

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Deepak, et al., 2006[487]				given 8 weekly doses of rituximab. After 5 mo hiatus, pt was given multiple doses of fludarabine and chlorambucil, resulting in pancytopenia. Pt was given 3 more doses of weekly rituximab. 2 mo later, pt was given 5 monthly doses of rituximab plus prednisone, combined with intermittent treatment of vincristine and cytoxan. Final dose of rituximab was given 3 wk prior to death, combined with single dose of thalidomide. Total rituximab dosage was 11,200 mg.
Kanelli, Ansell, Haberman, et al., 2001[426]	Review of pt lab records	375 mg/m^2	27 (only 1 had WM)	Pts were pretreated with acetaminophen and diphenhydramine. This study was designed to examine the toxicity in this pt population, and not to assess the OR to rituximab.
Khaled and Hanbali, 2007[488]	Case report		1	32 y/o female with WM and positive serology for HB surface antigen in whom rituximab treatment was associated with active hepatitis B viral replication despite prophylactic administration of adefovir for 2 mo after the end of rituximab treatment.
Liberato, Riethmuller, Comenzo, et al., 2003[489]	Case report	375 mg/m^2	1	65 y/o male with diagnosis of WM. Pt was given oral prednisone and cyclophosphamide with minimal improvement. Later treated with 6 courses of plasmapheresis, pulse dexamethasone, and 1 dose of intrathecal methotrexate with improvement in confusion, but no response in neurological function. Treatment with once weekly rituximab was started with dramatic improvement in neurological function. After 16 doses of rituximab pt has normal leg strength and although slow, can walk unassisted, can drive, and has returned to work.
Mohammad, Aboukameel, Nabha, et al., 2002[490]	Case report	Rituximab day 1, 375 mg/m^2; cyclophos-phamide day 2, 750 mg/m^2; and dexa-methasone 12 mg orally days 1-7	1	57 y/o female diagnosed with WM was treated with RCD showing PR for 7 mo. Treatment well tolerated.
Mori, Tamaru, and Kondo, 2002[491]	Case report	375 mg/m^2	1	69 y/o male received 4 cycles of rituximab at weekly intervals. 3 mo after treatment, pt achieved remission with disappearance of constitutional symptoms.
Mori, Tamaru, Sumi, et al., 2002[492]	Case report	375 mg/m^2 weekly for 4 wk	1	52 y/o male diagnosed with LPL was successfully treated with rituximab.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Noronha, Fynan, and Duffy, 2006[493]	Case report		1	72 y/o male with h/o peripheral neuropathy leading to diagnosis of WM. Prednisone and fludarabine in combination with rituximab treatment. Pt had dramatic worsening of neuropathy after rituximab treatment, returning to baseline levels after 1 mo.
Pearlman, Fechner, and Constanti-nides, 2006[494]	Case report		1	72 y/o male developed acute and extensive necrosis of nasal skin and soft-tissue envelope while undergoing chemo for WM. Pt refused surgery. At 12 wk, nose had healed completely without scarring. Author states conservative management of even extensive nasal skin loss should be considered when clinically acceptable.
Treon, Agus, Link, et al., 2001[495]	Retrospective study	375 mg/m^2	30	27% of treated pts had PR and 33% had MR with median TTF of 8.0 mo. An additional 30% of pts demonstrated SD with median TTF of 5.0 mo. Authors state rituximab induces remission and facilitates hematologic recovery in pts with WM.
Treon, Branagan, Hunter, et al., 2004[496]		375 mg/m^2 weekly x 4 wk	11	10/11 (91%) demonstrated abrupt rise in IgM levels following treatment. 3 pts experienced severe AEs due to IgM levels and increasing serum viscosity. Authors state careful clinical and laboratory monitoring is warranted.
Treon, Hunter, and Branagan, 2005[497]		375 mg/m^2	13	Intended treatment was 6 cycles of CHOP, along with 6 infusions of rituximab that were each administered on day 1 of CHOP. 9/13 completed the intended treatment. 11/13 (85%) demonstrated at least PR following CHOP-R treatment. 8 exhibited PR, while 3 exhibited CR. 1/13 had minor response, while another pt exhibited SD. Author states the CHOP-R regimen is active in pts with WM and spares circulating effector cells, including natural killer cells. The overall response rate of CHOP-R appears to be on par with rituximab-based regimens containing nucleoside analogues.
Treon, Shima, Preffer, et al., 1999[498]	Case report	375 mg/m^2 weekly x 4 wk	2 (1 with WM)	WM pt is 69 y/o male treated with chlorambucil, dexamethasone, and clarithromycin. After rituximab treatment, pt made rapid recovery with ongoing response at 19+ mo. Authors state use of serotherapy to treat PCDs represents a promising approach to treatment of WM.
Weber , Dimopoulos, Delasalle, et al., 2003[499]		375 mg/m^2	90 (17 treated with rituximab)	90 consecutive, previously untreated pts with symptomatic WM were treated using either 2-CdA alone or in combination with other agents (including rituximab). The observations support the potential role of 2-CdA regimens as the treatment of choice for previously untreated WM.
Weide, Heymanns, and Koppler, 1999[467]	Case report	375 mg/m^2 weekly x 4 wk	1	70 y/o male diagnosed with WM. Rituximab-based treatment was tolerated well. 3 wk after last treatment, pt's performance status and hematological parameters recovered to normal with no evidence of residual CD20-positive cells in the bone marrow. Authors state excellent response suggests that rituximab may be a very effective new treatment modality for pts with WM.

Study	Study Design	Drug Dose Per Day	Sample Size	Comments
Weide, Heymanns, and Koppler, 2000[500]	Case report	375 mg/m^2 weekly x 4 wk	1	50 y/o male diagnosed with WM. Pt received chemo with PR of arm tremor. Subsequently treated with rituximab leading to complete resolution of the tremor and the paresis of the arm. Additionally, his headache and imbalance disappeared. 15+ mo later he remained free of any neurological symptoms. Author states this shows WM-associated polyneuropathy can be treated effectively with a comb of chemotherapy and rituximab.
Zinzani, Tani, Alinari, et al., 2003[501]	Case report		1	45 y/o male diagnosed with lymphoplasmacytoid lymphoma/immunocytoma. Discusses 10 different courses of chemotherapy, and gives little to no data.

Abbreviations: 2-CdA = 2-chlorodeoxyadenosine (cladribine); AE(s) = adverse event(s); CHOP = cyclophosphamide, hydroxydaunomycin, Oncovin®, and prednisone; CR = complete response; h/o = history of; IgM = immunoglobulin M; IV = intravenous; OR = overall response; PCDs = plasma cell dyscrasias; PFS = progression-free survival; PR = partial response; q = every; RCD = rituximab, cyclophosphamide, and dexamethasone; SC = subcutaneous; SD = stable disease; TTF =time to treatment failure; WM = Waldenström's macroglobulinemia; WRAMC = Walter Reed Army Medical Center.

Table A67.1: Rituximab for Waldenström's Macroglobulinemia – Adverse Events (Grade 3/4+ Events Only) – Part 1

Article	Anemia	Neutropenia/ granulocytopenia	Leukopenia	Thrombocytopenia	Lymphopenia	Transfusion	Hemorrhage, other	Diarrhea	Nausea	Dermatitis or rash	Fatigue	Headache	Arthralgia	Chills/fever	Myalgia or musculoskeletal pain	Infection	Allergic reaction
Dimopoulos et al., 2002[469]	-	0%	-	0%	-	-	-	-	0%	-	-	0%	-	0%	-	0%	-
Gertz, et al., 2004[471]	13%	11%	6%	6%	10%	6%	1%	0%	0%	0%	3%	1%	1%	3%	3%	0%	3%
Hensel, et al., 2005[473]	25%	-	25%	19%	-	-	-	-	0%	-	-	-	-	-	-	13%	-

Table A67.2: Rituximab for Waldenström's Macroglobulinemia – Adverse Events (Grade 3/4+ Events Only) – Part 2

Article	Sinus tachycardia	Hypertension	Hypotension	Hypercalcemia	Hyperglycemia	Hyperkalemia	Hypermagnesemia	Hypernatremia	Hypocalcemia	Hypoglycemia	Hypokalemia	Hypomagnesemia	Hyponatremia	Neuropathy, sensory	Pneumonia	Septicemia	Other
Dimopoulos et al., 2002[469]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Gertz, et al., 2004[471]	1%	1%	1%	6%	10%	8%	6%	4%	3%	3%	3%	3%	6%	1%	-	-	3%
Hensel, et al., 2005[473]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6%	6%	-