National Comprehensive Cancer Network®

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Tamara Syrek Jensen, JD, Director
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

RE: Proposed Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N)

Dear Ms. Syrek Jensen:

The National Comprehensive Cancer Network® (NCCN®) is pleased to comment on the Centers for Medicare & Medicaid Services (CMS) Proposed Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N) as it relates to NCCN's mission of improving and facilitating, quality, effective, efficient, and accessible cancer care.

NCCN Member Institutions have been at the forefront of administering CAR T-cell therapy, first as clinical trial sites and, following the Food and Drug Administration (FDA) approval of two CAR T-cell products, now providing these therapies off-trial following commercialization. Both of the two commercially available CAR T-cell therapies are currently Category 2A recommendations in the NCCN Guidelines in the clinical situations outlined within the Guidelines (please see attached Appendices 1 and 2 for further information). NCCN thanks CMS for recognizing our guidelines within the proposed decision memo. NCCN would like to recommend suggested wording changes to more accurately reflect the language used in our guidelines. Additionally, NCCN has several recommendations and questions related to the implementation of the Proposed Decision Memo as it is currently written.

As an alliance of 28 leading academic cancer centers in the United States that treat hundreds of thousands of patients with cancer annually, NCCN is a developer of authoritative information regarding cancer prevention, screening, diagnosis, treatment, and supportive care that is widely used by clinical professionals and payers alike. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a comprehensive set of guidelines detailing the sequential management decisions and interventions that currently apply to 97 percent of cancers affecting patients in the United States.

NCCN Guidelines® and Library of Compendia products help ensure access to appropriate care, clinical decision-making, and assessment of quality improvement initiatives. The NCCN Drugs & Biologics Compendium (NCCN Compendium®) has been recognized by the Centers for Medicare and Medicaid Services (CMS) and clinical professionals in the commercial payer setting since 2008 as an evidence-based reference for establishment of coverage policy and coverage decisions regarding off-label use of anticancer and cancer-related medications. In 2017, the Wisconsin Physicians Service Insurance Corporation (WPS) finalized a Local Coverage Determinations (LCD) that references the NCCN Guidelines for coverage of "Chemotherapy Drugs and their Adjuncts" (L37205). Further, NCCN Guidelines and Library of Compendia products are utilized by commercial payers that represent more than 85 percent of covered lives in the United States.

NCCN imposes strict policies to shield the guidelines development processes from external influences. The "firewall" surrounding the NCCN Guidelines processes includes: financial support policies; panel participation and communication policies; guidelines disclosure policies; and policies regarding relationships to NCCN's other business development activities. The guidelines development is supported exclusively by the Member Institutions' dues and does not accept any form of industry or other external financial support for the guidelines development program.

The NCCN Guidelines are updated at least annually in an evidence-based process integrated with the expert judgment of multidisciplinary panels of expert physicians from NCCN Member Institutions. NCCN depends on the NCCN Guidelines Panel Members to reach decisions objectively, without being influenced or appearing to be influenced by conflicting interests. NCCN panel members are required to complete formal disclosures of potential financial conflicts-of-interest every 6 months. Thresholds of financial conflict, either with an individual company or in the aggregate, exclude individuals from serving on NCCN panels. Panel members with significant conflicts-of-interest are not allowed to participate in the NCCN Panel deliberations where that conflict exists. NCCN's conflict-of-interest policy is consistent with those of federal agencies and other professional medical organizations. Industry representatives are not allowed to participate in NCCN Panel meetings, and the determinations of the NCCN Panels are strictly confidential until published publicly on the NCCN website. Panel and staff disclosures are published on nccn.org for review by any user of the NCCN Guidelines.

The NCCN Guidelines are transparent, continuously updated, available free of charge online for non-commercial use and through a multitude of HIT vendors. NCCN is grateful for the opportunity to provide comment on the proposed decision memo and will focus our comments on proposed changes to NCCN related language within the proposed decision memo, areas we feel require further clarification, and suggestions for smooth implementation of the CED that will reduce administrative burden.

NCCN Categories of Evidence

NCCN is grateful to CMS for referencing the NCCN Compendium in section (A)(3)(b) of this proposed decision memo. Given the statutory use of compendia under 1861 (t)(2)(B)(ii) is fundamentally about unlabeled uses of drugs, NCCN interprets section (A)(3)(b) of this proposed decision memo to describe off-label indications of FDA approved CAR T-cell products. NCCN is grateful for the confidence that CMS places in the NCCN compendium to determine coverage for clinically appropriate indications for an FDA-approved biological when CED criteria and other requirements outlined in the memo are met.

The proposed decision memo references "the National Comprehensive Cancer Network Drugs & Biologics Compendium with grade 2 or 1." As noted in the CMS analysis section, "the NCCN guidelines apply a standard grading system, with definitions for each category of evidence grade. Specifically, grades 2 and 1 include NCCN consensus that an intervention is appropriate."

NCCN Categories of Evidence and Consensus for recommendations are based on both the level of clinical evidence available and the degree of consensus within the NCCN Guidelines Panel, which considers evidence of efficacy and safety of interventions (please see Appendix 3 for additional detail). The specific definitions of the NCCN categories for recommendations are:

- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
- **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate;
- **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

NCCN reads the current proposed decision memo language to imply that Category 1, Category 2A, or Category 2B would be covered. **To avoid confusion among practitioners, NCCN respectfully recommends changing the language to include, "the National Comprehensive Cancer Network Drugs & Biologics Compendium with Category 1, Category 2A, or Category 2B."**

Clinical Environment Requirements for the Administration of CAR T

NCCN appreciates CMS' careful consideration for the management of toxicities, including neurotoxicity and cytokine release syndrome, within the proposed decision memo. As discussed in the proposed decision memo, inappropriate management of associated toxicities within the first weeks of CAR T-cell therapy infusion can result in increased chance of morbidity and mortality. In order to appropriately manage these toxicities, Section (2)(A)(B) of the proposed decision memo covers autologous CAR-T treatment in both inpatient and outpatient hospital settings if:

- Inpatient/Outpatient setting has an integrated medical team with a Clinical Program Director, Quality Manager, and at least one physician experienced in cellular therapy;
- Inpatient/Outpatient setting demonstrates that protocols, procedures, quality management, and clinical outcomes are consistent from regular interaction among all members;
- Inpatient/Outpatient setting has a designated care area that protects the patient receiving CAR-T from transmission of infectious agents and allows for appropriate patient isolation as necessary for evaluation and treatment; and
- Inpatient/Outpatient setting has written guidelines to apply when administering CAR T-cell therapy for patient communication, monitoring, and transfer to an intensive care unit.

CAR T-cell therapy is a relatively new therapeutic treatment with some variability in current evidence as to the protocols for managing toxicities and assuring patient safety. Therefore, NCCN recognizes the standardization proposed in this memo as appropriate and necessary. Further, NCCN finds these requirements to be reasonable as most hospitals experienced in cellular therapy presently meet these standards.

Clinical Study Definition

Under section (A)(3)(b) of the proposed decision memo, criteria for coverage includes patient enrollment in a "CMS-approved clinical study that consecutively enrolls patients and follows the patient for at least two years." More specifically, the Coverage with Evidence Development (CED) analysis of the memo states:

> A registry may also be considered for the evaluation of patient outcomes that we propose for off-label use of FDA-approved CAR T-cell therapy. In this case, the AHRQ has provided a guide (Gliklich et al., 2014) for researchers to apply to the analysis, interpretation, and reporting of registry data for the purposes of a controlled clinical study. Factors to be considered for this purpose are described in detail within the guide, but we emphasize here that results from a registry would be more meaningful and better interpretable when there is advanced

consideration for the prospective patient population and explicit definition of exposures, endpoints, and outcomes. We believe this proposed decision takes into consideration the range of opportunities available to study the Medicare population and answer the specific CED questions for which evidence is not currently available and generalizable to the population we serve. To this end, we would expect that patients would be enrolled in a CMS-approved clinical study that consecutively enrolls patients and follows the patient for at least two years to answer specific CED questions and collect pre-specified data elements, which would be best-served considering the AHRQ guide when a registry is submitted for this purpose.

We believe there is stakeholder confusion regarding mechanisms for data collection for the off-label use of FDA-approved CAR T-cell therapy. NCCN seeks clarification regarding whether participation in, a prospective, national, audited registry stipulated under section (A)(3)(a) of this proposed decision meets the CMS-approved clinical study criteria for coverage under section (A)(3)(b). For the off-label use of FDA-approved CAR T-cell therapy, NCCN understands the importance of CED questions for which evidence is not currently available and generalizable to the population, however, we strongly encourage CMS to consider the onerous requirements of a clinical study and expand coverage criteria to include participation in a registry under section (A)(3)(b).

Quality of Life CED Question

Under section (A)(3)(a)(ii) of the proposed decision memo CMS outlines required CED questions within the outpatient setting. The outpatient setting CED questions include an additional quality of life question not included in the inpatient setting: "*How does the patient report their symptom function health-related quality of life changes over the course of their treatment?*". NCCN recognizes the importance of collecting quality of life data but has significant concerns that collecting this in only one clinical setting will unintentionally lead to selection bias.

One example of the unintended consequences of selection bias occurred in the 1990's with the wide introduction of High-Dose Chemotherapy with Autologous Bone Marrow Transplant (HDC-ABMT) for Breast Cancer. Studies throughout the 1980's demonstrated efficacy of this treatment but failed to account for selection bias in which healthier patients would receive HDC-ABMT compared to patients receiving standard-dose chemotherapy. Medicare beneficiaries receiving CAR T-cell therapy in an outpatient setting may experience a similar selection bias of being healthier on average than Medicare beneficiaries being served in an inpatient setting. Additionally, given that currently only one of two FDA approved CAR T products is administered in the outpatient setting, this may further bias the results of the data being collected. Axicabtagene ciloleucel is currently administered exclusively in the inpatient setting,

while Tisagenlecleucel is typically administered in the inpatient or outpatient setting depending on patient and disease characteristics and treatment center. NCCN urges uniformity of CED questions across settings to reduce bias in the evidence that is received.

Administrative Burden

Under Section(A)(3)(B) of the proposed memo, beneficiaries administered CAR-T in inpatient and outpatient settings must be enrolled in a national, audited, CMS-approved, registry. Approved registries must consecutively enroll patients; accept all manufactured products; follow patient outcomes for at least two years; and adhere to the standards of scientific integrity and relevance to Medicare population as identified in Section (A)(4). Registries must also submit to CMS a written plan to address evidence development questions. Additionally, inpatient and Outpatient hospital settings administrating CAR T-cell therapy are tasked with addressing the above listed registry questions by tracking data at baseline, treatment, and 3 months, 6 months, 12 months, and 24 months after the treatment is administered.

NCCN firmly agrees with the principles of the registry as outlined in Section (A)(3)(B) and (A)(4). We recommend that implementation of registry and data-collection be enacted with considerable focus on reducing administrative burden and supporting patient access to innovation. While NCCN recognizes that coverage determinations are made separate and apart from reimbursement determinations, we feel it is important that CMS implement the CED with an appreciation of the current reimbursement environment. Given that most providers of CAR T-cell therapy are currently being undercompensated by several hundreds of thousands of dollars for each Medicare patient treated, and possibly more if complications arise, NCCN has concern that an overly onerous CED process could lead providers to not participate due to the additional administrative cost. In addition to the high cost of the CAR-T product, administration, and associated services, providers of CAR T-cell therapy are also tasked with maintaining REMS which require extensive and costly staff training and patient coordination. To prevent patient access issues, NCCN encourages CMS to implement CED with as minimal reporting burden as possible.

The use of a registry that is familiar to providers, like the Center for International Blood and Marrow Transplant Research registry (CIBMTR), is one method to reduce administrative burden. Additionally, requiring the collection of data elements that are already being collected may also help to ease implementation and support success of the NCD. In our early stage conversations with NCCN Member Institutions, we have heard that some providers are already collecting PROMIS data so this may be a reasonable tool to integrate into the provider work stream. NCCN encourages CMS to consider the use of a registry that is able to be operational by the enacted date of the final NCD to reduce the likelihood of patient access delays. NCCN encourages the

CMS Coverage and Analysis Group to consider NCCN member institutions as a resource. Working closely with provider groups to better understand their current processes will ensure registry and data collection requirements are integrated into hospitals with minimal interruption to clinical workflows.

NCCN appreciates the opportunity to respond to the CMS Proposed Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers. We welcome the opportunity to discuss our comments further and look forward to working together to ensure Medicare beneficiary timely access to high-quality cancer care.

Sincerely,

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Appendix 1: Selected excerpts from NCCN Guidelines for Acute Lymphoblastic Leukemia (Version 1.2018) referencing CAR T-cell Therapy

National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Acute Lymphoblastic Leukemia

Version 1.2018 — March 12, 2018

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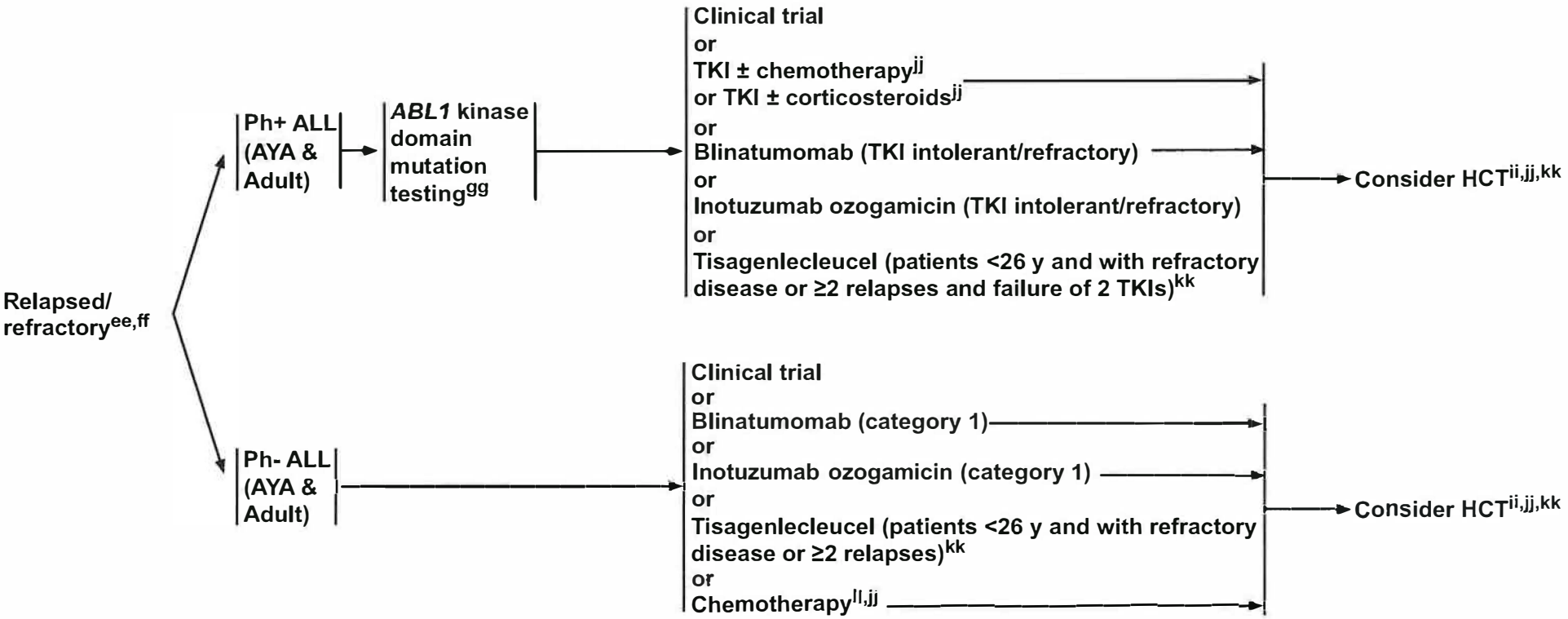
RELAPSED/REFRACTORY DISEASE **TREATMENT[hh,ii]**



[ee]Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.
[ff]See NCCN Guidelines for Palliative Care.
[gg]See Treatment Options Based on *BCR-ABL1* Mutation Profile (ALL-D 3 of 6).
[hh]See Principles of Systemic Therapy (ALL-D 3 of 6 and ALL-D 4 of 6).
[ii]If second remission is achieved prior to transplant and patient has not had a prior HCT, consolidative HCT should be strongly considered.
[jj]For patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.
[kk]The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent HCT. In the global registration trial, relapse free survival was 59% at 12 months, with only 9% of patients proceeding to HCT.
[ll]For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See ALL-D 2 of 6).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SYSTEMIC THERAPY (3 of 6)

REGIMENS FOR RELAPSED OR REFRACTORY ALL[a,g]

Ph-positive ALL:

- Dasatinib[27,28]
- Imatinib[29]
- Ponatinib[30,h]
- Nilotinib[31]
- Bosutinib[32]
- Blinatumomab (for B-ALL) (TKI intolerant/refractory)[33,i]
- Inotuzumab ozogamicin (for B-ALL) (TKI intolerant/refractory)[34,j]
- The TKIs noted above may also be used in combination with any of the induction regimens noted on ALL-D 1 of 6 that were not previously given.
- Tisagenlecleucel (for B-ALL) (patients <26 y and with refractory disease or ≥2 relapses and failure of 2 TKIs)[35,k]
- MOpAD regimen (category 2B): methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease and TKI.[36]
- The regimens listed on ALL-D 4 of 6 for Ph-negative ALL may be considered for Ph-positive ALL refractory to TKIs.

TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

Mutation	Treatment Recommendation
Y253H, E255K/V, or F359V/C/I	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib

Regimens for Relapsed/Refractory Ph-Negative ALL (ALL-D 4 of 6)
References (ALL-D 5 of 6)

[a]All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

[g]The safety of relapsed/refractory regimens in older adults (≥65 years) has not been established. Please see ALL-D 6 of 6 for additional information.

[h]Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). The FDA indications are for the treatment of adult patients with T315I-positive, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) and for the treatment of adult patients with Ph+ ALL for whom no other TKI therapy is indicated. For details, see http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203469s007s008lbl.pdf.

[i]Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome and neurologic toxicities. Understanding of the risk evaluation and mitigation strategy (REMS) program and/or experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instruction for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdose and overdose. For details, see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

[j]Inotuzumab ozogamicin is associated with hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease, and increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf

[k]Tisagenlecleucel is associated with cytokine release syndrome (CRS), including fatal or life-threatening reactions. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. Neurologic toxicities, which may be severe or life-threatening, can occur following treatment, including concurrently with CRS. Monitor for neurologic events after treatment. Provide supportive care as needed. Tisagenlecleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). For details, see: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf

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PRINCIPLES OF SYSTEMIC THERAPY (4 of 6)

REGIMENS FOR RELAPSED OR REFRACTORY ALL[a,g]

Ph-negative ALL:

- **Blinatumomab (for B-ALL) (category 1)[37,i]**
- **Inotuzumab ozogamicin (for B-ALL) (category 1)[34,j]**
- **Tisagenlecleucel (for B-ALL) (patients <26 y and with refractory disease or ≥2 relapses)[35,k]**
- **Cytarabine-containing regimens: eg, high-dose cytarabine, idarubicin, IT methotrexate[38]**
- **Alkylator combination regimens: eg, etoposide, ifosfamide, mitoxantrone[39]**
- **Nelarabine (for T-ALL)[40]**
- **Augmented hyper-CVAD: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and pegaspargase; alternating with high-dose methotrexate and cytarabine[41]**
- **Vincristine sulfate liposome injection (VSLI)[42,43]**
- **Clofarabine[44]**
- **Clofarabine-containing regimens (for B-ALL): eg, clofarabine, cyclophosphamide, etoposide[45]**
- **MOpAD regimen: methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease[36]**
- **Fludarabine-based regimens**
  - **FLAG-IDA: fludarabine, cytarabine, granulocyte colony-stimulating factor, ± idarubicin[46]**
  - **FLAM: fludarabine, cytarabine, and mitoxantrone[47]**

Regimens for Relapsed/Refractory Ph-Positive ALL (ALL-D 3 of 6)
References (ALL-D 5 of 6)

[a]All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

[g]The safety of relapsed/refractory regimens in older adults (≥65 years) has not been established. Please see ALL-D 6 of 6 for additional information.

[i]Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome and neurologic toxicities. Understanding of the risk evaluation and mitigation strategy (REMS) program and/or experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instruction for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdose and overdose. For details, see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

[j]Inotuzumab ozogamicin is associated with hepatotoxicity, including fatal and life-threatening hepatic veno-occlusive disease, and increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality. For details, see: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761040s000lbl.pdf

[k]Tisagenlecleucel is associated with cytokine release syndrome (CRS), including fatal or life-threatening reactions. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. Neurologic toxicities, which may be severe or life-threatening, can occur following treatment, including concurrently with CRS. Monitor for neurologic events after treatment. Provide supportive care as needed. Tisagenlecleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). For details, see: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf

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HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA[t]

RESPONSE TO THERAPY

CR[n,x] →
- Observation
- or
- Clinical trial
- or
- High-dose therapy with autologous stem cell rescue (HDT/ASCR) or allogeneic hematopoietic cell transplant (HCT) in selected cases ± ISRT if not previously given[j,w]

PR[n,y,z] →
- HDT/ASCR[y] or allogeneic HCT in selected cases[y] ± ISRT if not previously given[j,w]
- or
- Axicabtagene ciloleucel or tisagenlecleucel (only after ≥2 prior chemoimmunotherapy regimens)[aa,bb]
- or
- Clinical trial
- or
- Ibritumomab tiuxetan
- or
- ISRT[j] for localized residual and/or residual FDG-avid disease not previously irradiated
- or
- Observation

NR or progressive disease[n] →
- Clinical trial
- or
- Ibritumomab tiuxetan or Second-line therapy (See BCEL-C)
- or
- Axicabtagene ciloleucel or tisagenlecleucel (only after ≥2 prior chemoimmunotherapy regimens)[aa,bb]
- or
- Best supportive care

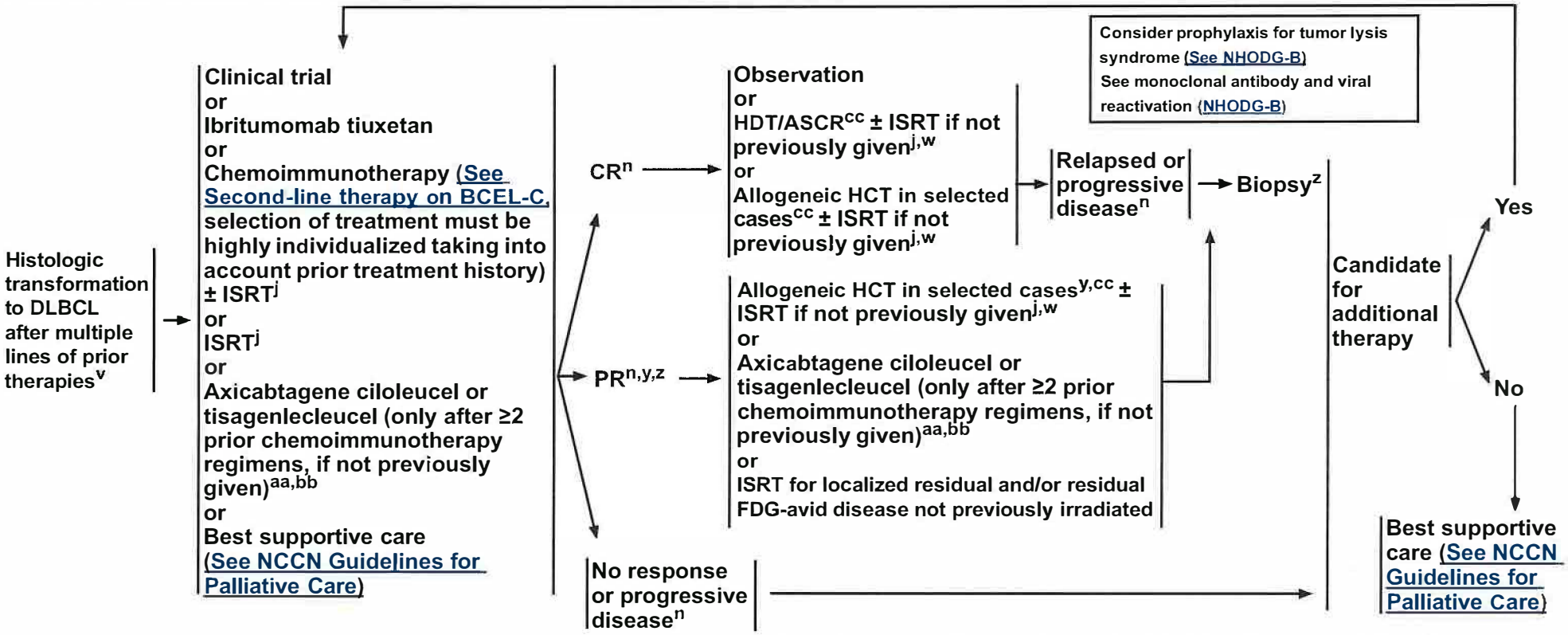
Relapsed or progressive disease[n] → **Biopsy[z]** → See Histologic Transformation to DLBCL After Multiple Prior Therapies (FOLL-8)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[j] See Principles of Radiation Therapy (NHODG-D).
[n] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).
[t] FISH for BCL2 rearrangement [t(14;18)], and *MYC* rearrangements [t(8;14) or variants, t(8;22), t(2;8)].
[u] ISRT alone or one course of single-agent therapy including rituximab.
[w] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.
[x] If transformation is co-existing with extensive FL, consider maintenance (see FOLL-5, Optional Extended Therapy).
[y] If proceeding to transplant, consider additional systemic therapy ± ISRT to induce CR prior to transplant. Axicabtagene ciloleucel or tisagenlecleucel are not appropriate treatment options for patients with a CR.
[z] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy because PET positivity may represent post-treatment inflammation. Patients with a durable response for transformed disease may recur with the original indolent lymphoma. In that case, the management should be as per FOLL-5. If biopsy negative, follow CR pathway.
[aa] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).
[bb] Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

HISTOLOGIC TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA



[j] See Principles of Radiation Therapy (NHODG-D).

[n] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five Point Scale (FPS).

[v] This includes ≥2 of chemoimmunotherapy regimens for indolent or transformed disease. For example, prior treatment with BR and RCHOP.

[w] Consider ISRT for localized presentations, bulky disease, and/or limited osseous disease.

[y] If proceeding to transplant, consider additional systemic therapy ± ISRT to induce CR prior to transplant. Axicabtagene ciloleucel or tisagenlecleucel are not appropriate treatment options for patients with a CR.

[z] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy because PET positivity may represent post-treatment inflammation. Patients with a durable response for transformed disease may recur with the original indolent lymphoma. In that case, the management should be as per FOLL-5. If biopsy negative, follow CR pathway.

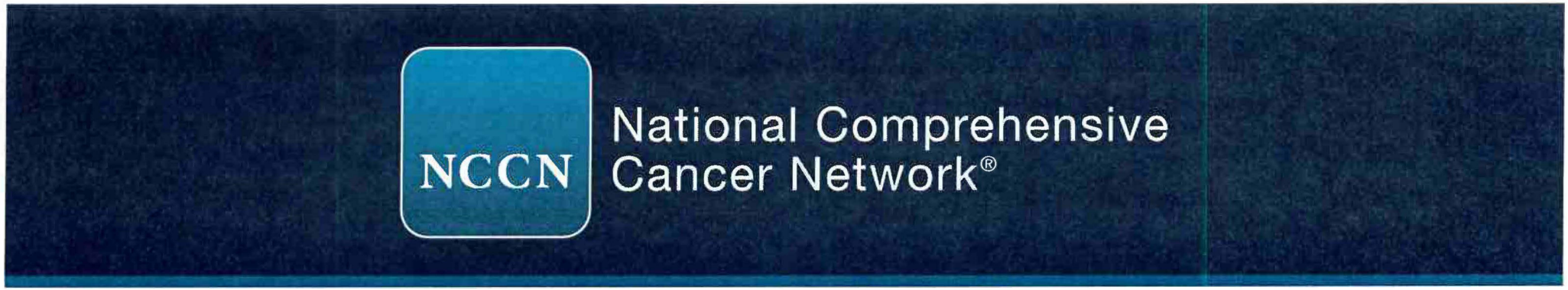
[aa] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).

[bb] Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.

[cc] Data on transplant after treatment with axicabtagene ciloleucel or tisagenlecleucel are not available. HDT/ASCR is not recommended after axicabtagene ciloleucel. Allogeneic HCT could be considered but remains investigational.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Appendix 2: Selected excerpts from NCCN Guidelines for B-Cell Lymphomas Guideline (Version 2.2019) referencing CAR T-cell Therapy



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

B-Cell Lymphomas

Version 2.2019 — March 6, 2019

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RELAPSE/ REFRACTORY DISEASE | **ADDITIONAL THERAPY** | **RESPONSE #2** | **CONSOLIDATION/ADDITIONAL THERAPY**

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Relapsed/ refractory disease

- For patients with intention to proceed to transplant → Second-line therapy See Suggested Regimens (BCEL-C)
  - Complete response[v] → High-dose therapy with autologous stem cell rescue (category 1) ± ISRT[p,cc] or Clinical trial or Allogeneic hematopoietic cell transplant in selected cases[dd] ± ISRT[p,cc]
  - Partial response[v,bb] → Axicabtagene ciloleucel or tisagenlecleucel[ee,ff] or High-dose therapy with autologous stem cell rescue ± ISRT[p,cc] or Clinical trial or Allogeneic hematopoietic cell transplant in selected cases[dd] ± ISRT[p,cc]
  - No response or progressive disease[v] → See Relapse #2 or greater (BCEL-8)
- Non-candidates for transplant → Clinical trial or Second-line therapy See Suggested Regimens (BCEL-C) or Palliative ISRT[p] or Best supportive care
  - Complete response[v] → See Follow-up (BCEL-8)
  - Partial response[v,gg] → See Relapse #2 or greater (BCEL-8)
  - No response or progressive disease[v] → See Relapse #2 or greater (BCEL-8)

[p] See Principles of Radiation Therapy (NHODG-D).
[v] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[bb] Some NCCN Member Institutions require a complete metabolic response in order to proceed to high-dose therapy with autologous stem cell rescue.
[cc] Additional RT can be given before or after transplant to sites of previous positive disease.
[dd] Selected cases include mobilization failures and persistent bone marrow involvement.
[ee] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).
[ff] Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
[gg] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOLLOW-UP

RELAPSE #2 OR GREATER

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Follow-up after treatment for relapsed/refractory disease →

- **Clinical: H&P and labs, every 3–6 mo for 5 y and then yearly or as clinically indicated**
- **Imaging: C/A/P CT scan with contrast no more often than every 6 mo for 2 y after completion of treatment, then only as clinically indicated**

→ **Partial response[gg] or Relapse or Progression of disease[v]** →

Axicabtagene ciloleucel or tisagenlecleucel (if not previously given)[ee,ff] or Clinical trial or Alternative second-line therapy[hh] (See BCEL-C) or Palliative ISRT[p] or Best supportive care

[p] See Principles of Radiation Therapy (NHODG-D).
[v] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[ee] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (BCEL-D).
[ff] Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma.
[gg] Repeat biopsy should be strongly considered if PET-positive prior to additional therapy, because PET positivity may represent post-treatment inflammation. If biopsy negative, follow CR pathway.
[hh] Patients who progress after three successive regimens are unlikely to derive additional benefit from currently utilized combination chemotherapy regimens, except for patients with a long disease-free interval.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

GUIDANCE FOR TREATMENT OF PATIENTS WITH CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY

Axicabtagene ciloleucel[a]

- Patient selection
  - Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL, NOS; primary mediastinal large B-cell lymphoma; high grade B-cell lymphoma; and DLBCL arising from follicular lymphoma.[a]
  - Health care facilities that dispense and administer axicabtagene ciloleucel must be enrolled and comply with the Risk Evaluation and Mitigation Strategies (REMS) requirements.[a] See REMS for axicabtagene ciloleucel.
- Cytokine release syndrome (CRS) management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Neurologic toxicity management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Prolonged cytopenias
  - Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and axicabtagene ciloleucel infusion.
- Hypogammaglobulinemia
  - B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with axicabtagene ciloleucel.

Tisagenlecleucel[b]

- Patient selection
  - Tisagenlecleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, NOS and high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.[b]
  - Health care facilities that dispense and administer tisagenlecleucel must be enrolled and comply with the REMS requirements.[b] See REMS for tisagenlecleucel.
- CRS management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Neurologic toxicity management - See CAR T-Cell-Related Toxicities in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities
- Prolonged cytopenias
  - Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and tisagenlecleucel infusion.
- Hypogammaglobulinemia
  - B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after tisagenlecleucel infusion.

[a]Prescribing information for axicabtagene ciloleucel is available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM581226.pdf.
[b]Prescribing information for tisagenlecleucel is available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Appendix 3: NCCN Categories of Evidence and Consensus

- NCCN Categories of Evidence and Consensus for recommendations are based on both the level of clinical evidence available and the degree of consensus within the NCCN Guidelines Panel, which considers evidence of efficacy and safety of interventions.
- The specific definitions of the NCCN categories for recommendations are:
  - **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
  - **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate;
  - **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate;
  - **Category 3**: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.
- All recommendations are category 2A unless otherwise indicated.

Appendix 4: Listings of Axicabtagene ciloleucel and Tisagenlecleucel in the NCCN Drugs & Biologics Compendium (NCCN Compendium®)

NCCN Drugs & Biologics Compendium®

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	Follicular Lymphoma (grade 1-2)
Agent:	Axicabtagene ciloleucel
FDA Indication:	Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Brand:	Yescarta™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Treatment of histologic transformation to diffuse large B-cell lymphoma (DLBCL) in patients who have received • minimal or no chemotherapy prior to histologic transformation to DLBCL and have partial response, no response, or progressive disease after treatment with ≥2 chemoimmunotherapy regimens which included at least one anthracycline or anthracenedione-based regimen, unless contraindicated • multiple lines of prior therapies (not including axicabtagene ciloleucel or tisagenlecleucel) for indolent or transformed disease (only after treatment with ≥2 chemoimmunotherapy regimens which included at least one anthracycline or anthracenedione-based regimen, unless contraindicated)
ICD10:	C83.30-C83.39, C85.20-C85.29
Billing Code:	Q2041

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	Diffuse Large B-Cell Lymphoma
Agent:	Axicabtagene ciloleucel
FDA Indication:	Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Brand:	Yescarta™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Used for diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma as • additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease • treatment (if tisagenlecleucel or axicabtagene ciloleucel was not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for relapsed or refractory disease
ICD10:	C83.30-C83.39, C85.20-C85.29
Billing Code:	Q2041

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	High-Grade B-Cell Lymphomas
Agent:	Axicabtagene ciloleucel
FDA Indication:	Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Brand:	Yescarta™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Used for high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) or high-grade B-cell lymphomas, not otherwise specified as • additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease • treatment (if tisagenlecleucel or axicabtagene ciloleucel was not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for relapsed or refractory disease
ICD10:	C83.30-C83.39, C85.10 - C85.19
Billing Code:	Q2041

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	AIDS-Related B-Cell Lymphomas
Agent:	Axicabtagene ciloleucel
FDA Indication:	Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Brand:	Yescarta™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Used for relapsed AIDS-related diffuse large B-cell lymphoma and HHV8-positive diffuse large B-cell lymphoma, not otherwise specific (NOS) as • additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease • treatment (if not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for relapsed or refractory disease
ICD10:	B20, C83.30-C83.39, C85.80-C85.89
Billing Code:	Q2041

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	Post-Transplant Lymphoproliferative Disorders
Agent:	Axicabtagene ciloleucel
FDA Indication:	Axicabtagene ciloleucel is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Brand:	Yescarta™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Treatment for monomorphic PTLD (B-cell type) as • additional therapy for patients with intention to proceed to transplant who have partial response following second-line chemoimmunotherapy for relapsed or refractory disease • treatment of disease in second relapse or greater (if not previously given)
ICD10:	C83.30-C83.39, C85.80-C85.89
Billing Code:	Q2041

Disease Information	
Guideline Name:	Acute Lymphoblastic Leukemia 1.2018
Disease:	Acute Lymphoblastic Leukemia
Agent:	Tisagenlecleucel
FDA Indication:	Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.
Brand:	Kymriah™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Single-agent therapy for • relapsed/refractory Philadelphia chromosome-positive B-ALL in patients < 26 years and with refractory disease or ≥ 2 relapses and failure of 2 TKIs • relapsed/refractory Philadelphia chromosome-negative B-ALL in patients < 26 years and with refractory disease or ≥ 2 relapses
ICD10:	C91.00, C91.02
Billing Code:	Q2042

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	Follicular Lymphoma (grade 1-2)
Agent:	Tisagenlecleucel
FDA Indication:	Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.
Brand:	Kymriah™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Treatment of histologic transformation to diffuse large B-cell lymphoma (DLBCL) in patients who have received • minimal or no chemotherapy prior to histologic transformation to DLBCL and have partial response, no response, or progressive disease after treatment with ≥2 chemoimmunotherapy regimens which included at least one anthracycline or anthracenedione-based regimen, unless contraindicated • multiple lines of prior therapies (not including axicabtagene ciloleucel or tisagenlecleucel) for indolent or transformed disease (only after treatment with ≥2 chemoimmunotherapy regimens which included at least one anthracycline or anthracenedione-based regimen, unless contraindicated)
ICD10:	C83.30-C83.39, C85.20-C85.29
Billing Code:	Q2042

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	Diffuse Large B-Cell Lymphoma
Agent:	Tisagenlecleucel
FDA Indication:	Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.
Brand:	Kymriah™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Used for diffuse large B-cell lymphoma or primary mediastinal large B-cell lymphoma as • additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease • treatment (if tisagenlecleucel or axicabtagene ciloleucel was not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for relapsed or refractory disease
ICD10:	C83.30-C83.39, C85.20-C85.29
Billing Code:	Q2042

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	High-Grade B-Cell Lymphomas
Agent:	Tisagenlecleucel
FDA Indication:	Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.
Brand:	Kymriah™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Used for high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) or high-grade B-cell lymphomas, not otherwise specified as • additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease • treatment (if tisagenlecleucel or axicabtagene ciloleucel was not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for relapsed or refractory disease
ICD10:	C83.30-C83.39, C85.10 - C85.19
Billing Code:	Q2042

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	AIDS-Related B-Cell Lymphomas
Agent:	Tisagenlecleucel
FDA Indication:	Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.
Brand:	Kymriah™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Used for relapsed AIDS-related diffuse large B-cell lymphoma and HHV8-positive diffuse large B-cell lymphoma, not otherwise specific (NOS) as • additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease • treatment (if not previously given) of disease in second relapse or greater in patients with partial response, no response, or progressive disease following therapy for relapsed or refractory disease
ICD10:	B20, C83.30-C83.39, C83.80-C83.89, C83.90-C83.99, C85.80-C85.89
Billing Code:	Q2042

Disease Information	
Guideline Name:	B-Cell Lymphomas 2.2019
Disease:	Post-Transplant Lymphoproliferative Disorders
Agent:	Tisagenlecleucel
FDA Indication:	Tisagenlecleucel is indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.
Brand:	Kymriah™
Category of Evidence:	2A
Pharmacologic Class:	CD19-directed genetically modified autologous T cell immunotherapy
Route:	IV
Recommended:	Treatment for monomorphic PTLD (B-cell type) as • additional therapy for patients with intention to proceed to transplant who have partial response following second-line chemoimmunotherapy for relapsed or refractory disease • treatment of disease in second relapse or greater (if not previously given)
ICD10:	D47.Z1
Billing Code:	Q2042