CHANGING THE COURSE OF HUMAN HEALTH THROUGH BOLD PURSUITS IN SCIENCE

CAR T-cell Patient Reported Outcomes Considerations

August 22, 2018

Background / Disclosure

Karen Chung, PharmD, MS, has over 15 years of pharmaceutical/biotechnology experience in health economics and outcomes research. Experience includes developing and implementing patient reported outcomes strategy/assessments across hematology/oncology, respiratory, and cardiovascular therapeutic areas, including instrument selection, instrument development, analysis, interpretation, and communication.

Karen is employed by Celgene and owns stock in Celgene, Jazz Pharmaceuticals, Gilead Sciences, Amgen, Baxter, Shire, and Bayer Pharmaceuticals.

Legal Disclaimer

- All of Celgene's CAR T cell therapy candidates are investigational product candidates and their safety and efficacy have not been established. Celgene has not obtained marketing approval for any product, and there is no certainty that any marketing approvals will be obtained or as to the timelines on which they will be obtained.

- Any data presented pertaining to Celgene CAR T cell therapy candidates are interim data, and may include investigator-reported interim data for which Celgene has not yet independently reviewed the source data. The interim data may not be representative of the final results that may be obtained in the corresponding trial, and results from earlier trials may not be representative of results obtained in later trials or pivotal trials.

Key Points

- CAR T cell therapy has been shown to deliver promising results in patients with limited treatment options and poor prognosis, including patients who are Medicare-age
- The CAR T cell therapy evidence base spans settings of care
  - Patients are currently receiving CAR T cell therapy in clinical trials on both an inpatient and outpatient basis
- Providers and biopharmaceutical companies are learning how to anticipate and manage adverse events when they occur
  - While adverse events must be addressed quickly and completely when they occur, many patients experience lower-grade, manageable side effects
- CAR T cell patients are likely to be enrolled in rigorous long-term monitoring programs designed to assess safety and efficacy on an ongoing basis
- Collecting patient-report outcome (PRO) data from CAR T cell patients is important but complex

Celgene CAR T Cell Therapies

- Celgene is developing two CAR T-cell therapies that, if approved, we believe have the potential to significantly transform patient outcomes in the treatment of certain blood-based cancers that are **under-served** by existing treatment options
  - **JCAR017**: CD19-directed CAR T-cell therapy in clinical trials for B-cell Non-Hodgkin Lymphoma (NHL)
  - **bb2121**: a B-cell maturation antigen (BCMA)-directed CAR T-cell therapy currently in clinical trials for multiple myeloma
- Each CAR T cell therapy has a **unique target patient population**, safety profile, and manufacturing process
  - It is critically important for patients and providers to have access to the full range of CAR T cell therapies
- We strongly support the incorporation of the patient voice into clinical trials, but firmly believe PROs **should not** be a condition of coverage

Patient-Reported Outcomes Defined

- The U.S. Food and Drug Administration (FDA) defines a *patient-reported outcome* as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."†
- Patient-reported outcomes typically include information about health-related quality of life (HRQOL), symptoms, function, satisfaction with care or symptoms, adherence to prescribed medications or other therapy, and perceived value of treatment.‡
- PRO data are used to measure risks and benefits of treatments, and inform and guide patient-centered care, clinical decision-making, and health policy decisions.
- Due to the potential trade off between length of life and quality of life associated with cancer treatments, PROs have been assessed in oncology clinical trials.

† FDA Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009. Available at: http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf. Accessed May 8, 2018.
‡ Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA 2013;309:814–822.

Celgene

The Emerging Role of Patient Reported Outcomes in the FDA

- The FDA has encouraged the use of PROs to assess three complementary but distinct areas in cancer clinical trials
  - Disease-related symptoms (e.g., pain related to metastases)
  - Physical functioning (e.g., the ability to conduct activities of daily life)
  - Symptomatic adverse events (e.g., measured by the National Cancer Institute's new PRO version of the Common Terminology Criteria for Adverse Events)
- Depending on the objectives of the study, it would **not** be appropriate to select only one of these measures if a comprehensive assessment of all relevant issues was of interest

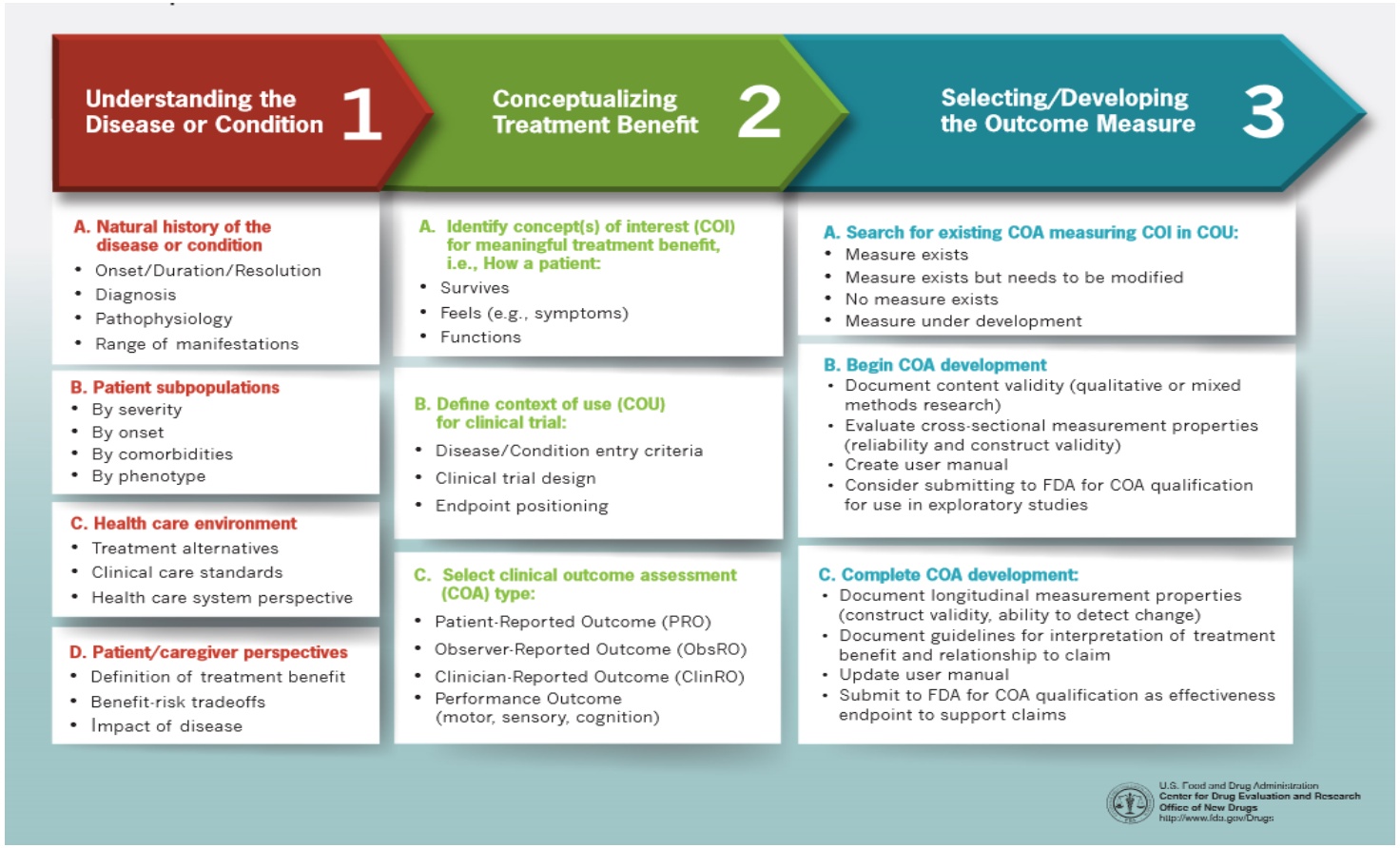
Celgene has incorporated PRO assessments in CAR T-cell clinical trials to complement clinical efficacy and safety data.

Table 4 FDA-approved limited indication language on oncology/hematology product labels†

Year of approval	Project	Indication	Label language
2011	Adcetris (brentuximab)	Hodgkin's lymphoma; anaplastic large cell lymphoma	An improvement in patient-reported outcomes or survival has not been established.
2012	Afinitor Disperz (everolimus)	Advanced hormone receptor-positive, HER2-negative breast cancer; progressive neuroendocrine tumors of pancreatic origin; advanced renal cell carcinoma; renal angiomyolipoma and tuberous sclerosis complex	The effectiveness of Afinitor in the treatment of renal angiomyolipoma is based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes.
	Iclusig (ponatinib)	Chronic myeloid leukemia	There are no trials verifying an improvement in disease-related symptoms or increased survival with Iclusig.
	Kyprolis (carfilzomib)	Multiple myeloma	Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.
2013	Avastin (bevacizumab)	Metastatic carcinoma of the colon or rectum	Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy. Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
	Pomalyst (pomalidomide)	Multiple myeloma	Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.
2014	Beleodaq (belinostat)	Relapsed or refractory peripheral T-cell lymphoma	This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.
	Imbruvica (ibrutinib)	Mantle cell lymphoma and chronic lymphocytic leukemia	Approved for patients with mantle cell lymphoma who have received at least one prior therapy. Accelerated approval granted for this indication was based on overall response rate. Improvements in survival or disease-related symptoms have not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.
	Keytruda (pembrolizumab)	Unresectable or metastatic melanoma	This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
	Mekinist (trametinib)	Unresectable or metastatic melanoma with BRAF V600E or V600K mutations	Use in combination with dabrafenib is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated.
	Zydelig (idelalisib)	Relapsed chronic lymphocytic leukemia; relapsed follicular B-cell non-Hodgkin's lymphoma (FL); relapsed small lymphocytic lymphoma (SLL)	Accelerated approval was granted for FL and SLL based on overall response rate. Improvement in patient survival or disease-related symptoms has not been established. Continued approval for these indications may be contingent upon verification of clinical benefit in confirmatory trials.
	Zykadia (ceritinib)	Anaplastic lymphoma kinase-positive metastatic NSCLC	Accelerated approval was based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

† Tse J., Shingler S.L., Nixon A. The emerging role of patient-reported outcomes (PROs) in FDA hematology and oncology product labels. Value Health 18 (2015) A1–A307. https://www.ispor.org/research_pdfs/49/pdffiles/PCN119.pdf

Roadmap to patient focused outcome measurement in clinical trials



Adequate characterization of disease/condition and conceptualization of concept of treatment benefit are needed to define appropriate PRO measures

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/UCM370174.pdf

Level of Confidence regarding Validity and Generalizability of PRO Assessments to the Medicare Population

Q1. How confident are you that each of the following PRO assessments are valid and generalizable to the Medicare population? (1 = low confidence to 5 = high confidence)

Measure	Rating of Confidence	Rationale
PRO-CTCAE	4	Covers range of symptoms, developed with input from patients, items are straightforward and easy to understand, can customize so questionnaire only includes relevant items
MDASI	5	Covers range of symptoms, content has been confirmed as relevant by patients, items are straightforward and easy to understand, demonstrated reliability and validity in variety of populations
EORTC QLQ-C30	5	Frequently used in older population and in those with advanced cancer, covers many symptoms and areas of functioning, demonstrated reliability and validity in a variety of populations, many modules available
UW-QOL	2	Only relevant for head and neck cancer, unknown if patients included in development, response options are not consistent and wordy and may be confusing for an older population
PROMIS	4	Comprehensive set of item banks covering various symptoms and areas of functioning, can customize questionnaire to include only relevant items, developed and evaluated using accepted and rigorous methodology
ESRA-C	1	Not a PRO – rather a system of administering PROs
FLIC	1	Not frequently used, response options are Visual Analogue Scales – some respondents find them confusing and circle the numbers instead of putting a hash mark on the line

Assessment of Supporting Evidence of Combined PRO Measures

Q2 Considering all PRO assessments in question 1 with greater than or equal to score 2.5 (i.e., PRO-CTCAE, MDASI, EORTC QLQ-C30, PROMIS), please vote whether or not those PRO assessments combined have available supporting evidence on each of the following desired characteristics.

	Yes/No
A. Breadth of measures in emotional, social, and physical well-being	Yes (Agree)
B. Quick throughput to apply to clinical study	Yes (Agree)
C. Transferable to community practice settings	Yes (Agree)
D. Measures are not sensitive to differences in age	No (Disagree)
E. Measures are not sensitive to line of therapy	No (Disagree)
F. Measures are not sensitive to comorbidities	No (Disagree)
G. Measures are generalizable to study of combinations of therapies	Yes (Agree)
H. Used in net benefit analysis based on symptom burden and well-being	Unknown

NOTE: The EORTC-QLQ-C30 and PROMIS are both measures of functioning and well being. The PRO-CTCAE contains symptomatic toxicities, and the MDASI focuses on symptoms and symptom interference. Therefore, depending on the objectives of the study, it would **not** be appropriate to select only one of these measures if a comprehensive assessment of all relevant issues was of interest.

Barriers to PRO Assessment in the Real World

PRO assessment in the real world is challenging due to several factors:

- Healthcare provider burden (e.g., follow-up, management)
- Additional FTE(s) necessary to coordinate administration and data collection
- Lack of consensus regarding appropriate PRO instruments (e.g., by tumor type, stage of disease)
- Lack of expertise / experience
  - Instruments
  - Scoring
  - Analyses
  - Interpretation
- Completion rates / adherence
- Patient fatigue
- Cost of electronic PRO data capture
- Technology barriers (particularly in the Medicare population)

Conclusion

- Patient reported outcomes are key measures in hematology/oncology clinical trials, including trials involving CAR T-cell therapies. Important foundational considerations include:
  - Range of tumor types / stage
  - Areas of patient reported outcomes impact / interest
    - Physical functioning
    - Disease / toxicity related symptoms
    - Adverse events
    - Health-related quality of life
- Due to the diverse nature (including disease presentation) and range of symptoms across and within tumor types and administrative burden, assessing patient reported outcomes with validated instruments is complex
- Celgene has incorporated relevant PRO assessments in CAR T-cell clinical trials to complement clinical efficacy and safety data
- While PRO assessments are important, they should not be a condition of coverage




Back Up

Patient-reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE)

Objective	Evaluate symptomatic toxicity in patients on cancer clinical trials
Year Developed	2009-2015
Patient input in development	“Created with substantial input from patients, clinicians and PRO methodologists, and underwent refinement through cognitive interviews with patients to establish content validity”
Description/ Domains	124 items representing 78 symptomatic toxicities drawn from CTCAE evaluating occurrence, frequency, severity, and interference
Recall Period	Past 7 days
Use in populations of those 65+	Limited use in Cancer Population Populations include HPV-associated oropharyngeal squamous cell carcinoma (Mavroidiset et al., 2017, Chera et al., 2015), oropharyngeal carcinoma (Talchook et al., 2016), adult women in the US (Craig and Mitchell, 2016), adults undergoing hematopoietic cell transplant (Bennett et al., 2016), adults with cancer undergoing chemotherapy or radiation therapy (Duek et al., 2015)
Misc Aspects	Developed by the National Cancer Institute Considered a promising tool to provide standard yet flexible method to assess symptomatic AEs from patient perspective Generally used via web-based platform or IVR interface Moderate amount of data available regarding its reliability, validity, and sensitivity to change, with additional studies underway

MD Anderson Symptom Inventory (MDASI)

Objective	Assess severity of symptoms and impact on daily functioning (can be supplemented with modules unique to population)
Year Developed	2000
Patient input in development	Focus groups, clinician review, and cognitive debriefing used in its development; continuous validation of the core items and modules still underway
Description/ Domains	Severity assessed for 13 core symptom items (pain, fatigue, nausea, disturbed sleep, distress (emotional), shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling) 6 interference items [general activity, walking ability, normal work (activity sub-dimension) and relations with other people, mood and enjoyment of life (affective sub-dimension)]
Recall Period	Past 24 hours
Use in populations of those 65+	Moderate use in Cancer Population Populations include Oropharyngeal cancer (MD Anderson Head and Neck Cancer Symptom Working Group et al. 2017), metastatic prostate cancer (Bergin et al., 2017), pancreatic cancer (Fogelman et al., 2017), chronic lymphocytic leukemia (Jain et al., 2017), cervical cancer (Wang et al., 2017), advanced cancer (Georgia et al., 2016), lung cancer (Shi et al., 2016), gynecologic cancer (Brown et al., 2016), non-small cell lung cancer (Wang et al., 2016), colorectal cancer (Wang et al., 2016), breast cancer (Ochayon et al., 2014)
Misc Aspects	Assesses both symptom severity and interference Detailed User Guide available which contains details on its validation Available in all modes of administration including paper, IVR and web-based Large amount of data available regarding its reliability, validity, and sensitivity to change

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (Core; EORTC QLQ-C30)

Objective	Evaluate QoL in cancer patients (can be supplemented with cancer-specific modules)
Year Developed	Initial version 1987, current version 1997
Patient input in development	346 patients with lung cancer participated in an international field study to evaluate the practicality, reliability and validity of the measure. In general, patients found the questionnaire to be acceptable
Description/ Domains	Contains 30 items related to Functioning (Physical, Role, Emotional, Cognitive, Social), Symptoms (Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea), Financial Difficulties and Global Health Status
Recall Period	Past week
Use in populations of those 65+	Widely used in Cancer Population Populations Include breast cancer (Kawahara et al., 2018), esophageal squamous cell carcinoma (Chen et al., 2017), glioblastoma (Zhu et al., 2017, Field et al., 2017), metastatic colorectal cancer (Winther et al., 2017, Palesh et al., 2017), advanced cancer (Grotmol et al., 2017, Paulsen et al., 2017), cancer pain (Lam et al., 2017), spine metastases (Bernard et al., 2017), prostate cancer (van Die et al., 2017), melanoma (Coens et al., 2017)
Misc Aspects	One of the most widely used cancer-specific PROs available Detailed User Guide available which contains information on validation as well as reference values for variety of cancer types Module available specific for elderly patients Very large amount of data available regarding its reliability, validity, and sensitivity to change

University of Washington Quality of Life (UW-QOL)

Objective	Evaluate changes in HRQOL specific to head and neck cancer
Year Developed	1993 (original version)
Patient input during Development	Unknown
Description/ Domains	Version 4 contains 12 items related to chewing, swallowing, speech, taste, saliva, appearance (physical subscale) and anxiety, mood, pain, activity, recreation, shoulder pain (social-emotional subscale); 1 item asking patients to choose up to 3 of most important of these items, and 3 global questions (how they feel relative to before diagnosis, overall health-related QOL, and overall QOL) (note: Version 4.1 includes 1 item on intimacy and 1 item on fear of recurrence) For item assessing most important domain, results presented as % of patients choosing each domain and also in rank order. All items can be scored as single items or as subscales.
Recall Period	Past 7 days
Use in populations of those 65+	Moderate use in cancer population Populations include Head and neck cancer (Mucke et al., 2015, Roe et al., 2014, Chen et al., 2014, Cardoso et al., 2015), oropharyngeal cancer (Rogers et al., 2016, Chen et al., 2015), squamous cell carcinoma in oral cavity (Iriya et al., 2017)
Misc Aspects	Simplicity in scoring is appealing Only relevant for head and neck cancers Moderate amount of data available regarding its reliability, validity, and sensitivity to change

Patient-reported Outcome Measurement Information System (PROMIS)

Objective	Assess functioning, symptoms, behaviors, and feelings
Year Developed	2004-2014
Patient input in development	“review of the items by experts and patients”
Description/ Domains	Includes 300+ measures of physical, mental, and social health for use with general population and individuals living with chronic conditions (1,839 items for adults)
Recall Period	Past 7 days (most items)
Use in populations of those 65+	Moderate use in Cancer Population Populations include Prostate cancer (Wang et al., 2017, Quach et al., 2916), lung cancer (Khullar et al., 2017), malignant brain tumor (McCarty et al., 2017, Romero et al., 2015), sacral tumor (van Wulfften et al., 2017), lower extremity bone metastases (Janssen et al., 2016), metastatic bone disease (van der Vliet et al., 2017), breast cancer (Junghaenel et al., 2015, Seliktar et al., 2015), head and neck cancer (Stachler et al., 2014), cancer patients in general (Jensen et al., 2017, Pergolotti et al., 2017, Cessna et al., 2015, Jensen et al., 2015), neuroendocrine tumors (Pearman et al., 2016)
Misc Aspects	Relevant for general population and individuals with chronic conditions; Available in multiple formats; Preference-based scoring available Moderate amount of data available regarding its reliability, validity, and sensitivity to change, with additional studies underway

Electronic Self-report – Cancer (ESRA-C)

Objective	Evaluate changes in HRQOL specific to head and neck cancer
Year Developed	1993 (original version)
Patient input during Development	Unknown
Description/ Domains	Version 4 contains 12 items related to chewing, swallowing, speech, taste, saliva, appearance (physical subscale) and anxiety, mood, pain, activity, recreation, shoulder pain (social-emotional subscale); 1 item asking patients to choose up to 3 of most important of these items, and 3 global questions (how they feel relative to before diagnosis, overall health-related QOL, and overall QOL) (note: Version 4.1 includes 1 item on intimacy and 1 item on fear of recurrence) For item assessing most important domain, results presented as % of patients choosing each domain and also in rank order. All items can be scored as single items or as subscales.
Recall Period	Past 7 days
Use in populations of those 65+	Moderate use in cancer population Populations include Head and neck cancer (Mucke et al., 2015, Roe et al., 2014, Chen et al., 2014, Cardoso et al., 2015), oropharyngeal cancer (Rogers et al., 2016, Chen et al., 2015), squamous cell carcinoma in oral cavity (Iriya et al., 2017)
Misc Aspects	Has only been implemented in a few studies, with a small number of PROs Reliability, validity and sensitivity not relevant since it's a web-based program

Functional Living Index – Cancer (FLIC)

Objective	Assess QoL in cancer patients
Year Developed	1984
Patient input in development	“Items selected from previous instruments by a panel of patients and health professionals”
Description/ Domains	22 items - Physical Well-Being and Ability, Emotional/Psychological State, Sociability, Family Situation, Nausea
Recall Period	Past 2 weeks/currently
Use in populations of those 65+	Limited used in cancer population Populations include Lung cancer (Hintistan et al. 2017), gynecological cancer Akkuzu et al., 2014), breast cancer (Colby et al., 2013, Mallinckrodt et al., 2012), patients receiving intensive chemotherapy (Luthie et al., 2012)
Misc Aspects	One of the first cancer-specific PROs developed Briefer version containing 11 items available (Quick-FLIC) Minimal amount of data available regarding its reliability, validity, and sensitivity to change

Morrow GR, Lindke J, Black P. Measurement of Quality of Life in Patients : Psychometric Analyses of the Functional Living Index - Cancer (FLIC). Quality of Life Research 1992;1:287-296