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BY ELECTRONIC DELIVERY

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

Celgene Corporation (Celgene) appreciates the opportunity to comment on the Centers for Medicare & Medicaid Services' (CMS) proposed decision memo (PDM) on CAR T cell therapies for the treatment of cancer.[1]

Celgene is a global biopharmaceutical company specializing in the discovery, development, and delivery of therapies designed to treat cancer and inflammatory and immunological conditions. Celgene strongly believes that medical innovation can lead to better health, longer life, reduced disability, and greater prosperity for patients and our nation. To this end, we seek to deliver truly innovative and life-changing therapies for the patients we serve. Presently, we are engaged in 160 clinical trials with 42 novel assets across 60 indications.

Celgene is committed to discovering and developing treatments in disease areas with significant unmet medical needs. Notably, Celgene has played a central role in the significant improvement in outcomes for patients with serious and life-threatening hematological malignancies. We believe that genetic modification of T cells with chimeric antigen receptors (CARs) represents a potential new era for the effective treatment of these cancers.

[1] Proposed Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N), Feb. 15, 2019, https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=291&bc=ACAAAAAAQAAA&.

Celgene is committed to the development of CAR T cell therapies across multiple cancer indications. This commitment to cell therapy is evidenced by our significant investment in the research and specialized manufacturing required to effectively deliver CAR T cell therapies to patients. There are currently 1,885 patients enrolled in 12 Celgene-sponsored clinical trials for CAR T cell therapies in lymphoma and multiple myeloma, and in 2018, we opened our second CAR T manufacturing site in Summit, NJ, in addition to our existing manufacturing site in Bothell, WA.

Celgene believes that CAR T cell therapy offers significant promise for patients with challenging cancer diagnoses, and we are proud of the work that we are doing to bring these innovations to patients. We currently have two CAR T cell therapies in late stage clinical development that we believe have significant clinical potential in the treatment of blood-based cancers that are under-served by existing treatment options:

Idecabtagene vicleucel (**bb2121**).[2] Developed in a collaboration between Celgene and bluebird bio, bb2121 is a B-cell maturation antigen (BCMA)-directed CAR T cell therapy currently in clinical trials for multiple myeloma. Multiple myeloma is a rare plasma cell cancer that affects approximately 125,000 Americans, including 30,000 newly diagnosed patients each year.[3] With an average onset age of 69 years, multiple myeloma uniquely and disproportionately impacts the Medicare population. Despite advances in five-year survival rates in the past two decades, this blood cancer has remained a persistent challenge to treat using traditional techniques because of its cyclical and progressive nature, as well as its ability to mutate and adapt over time. Multiple myeloma has remained an incurable disease, and heavily pretreated patients traditionally have had limited therapeutic options. Based on early clinical trial data, bb2121 has the potential to induce deep responses in these under-served multiple myeloma patient populations and has been granted breakthrough designation by the Food and Drug Administration (FDA).[4]

Lisocabtagene maraleucel (liso-cel).[5] A CD19-directed CAR T cell therapy, liso-cel is in clinical trials for B-cell Non-Hodgkin Lymphoma (NHL). Well over half a million Americans currently live with NHL, and approximately 66,000 new cases are diagnosed in any given year. The risk of developing NHL increases over time, and more than half of all NHL patients are age 65 or older. NHL also has several difficult-to-treat subsets, including diffuse large B cell lymphoma. Liso-cel has the potential to benefit many of these difficult-to-treat and under-served patient populations. Unlike most CAR T cell products, liso-cel provides modified cytotoxic (or "killer") T cells in a defined composition with modified helper T cells. This approach is anticipated to increase the efficacy of treatment and reduce the severity and frequency of adverse side-effects relative to other CAR T cell therapies. Liso-cel has

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[2] Efficacy and Safety Study of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma (KarMMa), *available at* https://clinicaltrials.gov/ct2/show/NCT03361748.

[3] SEER, *Cancer Stat Facts: Myeloma*, *available at* *https://seer.cancer.gov/statfacts/html/mulmy.html*.

[4] Celgene, *Celgene Corporation and bluebird bio Announce bb2121 Anti-BCMA CAR-T Cell Therapy Has Been Granted Breakthrough Therapy Designation from FDA and Prime Eligibility from EMA for Relapsed and Refractory Multiple Myeloma* (Nov. 16, 2017), *available from* http://ir.celgene.com/releasedetail.cfm?releaseid=1049014.

[5] Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-cell Non-Hodgkin Lymphoma (TRANSCEND-NHL-001), *available at* https://clinicaltrials.gov/ct2/show/NCT02631044. Liso-cel is also referred to as JCAR017.

been granted breakthrough designation and regenerative medicine advanced therapy designation by the FDA.

Summary of Our Comments

Medicare beneficiaries are disproportionately impacted by several of the cancer types currently under study for treatment with CAR T cell therapy. Therefore, CMS's final National Coverage Determination (NCD) will be critical to ensure patient access to current and future treatment options as CAR T cell therapy continues to rapidly evolve and progress. We believe that the PDM is a positive and productive first step in establishing national Medicare coverage for CAR T cell therapies. We appreciate CMS's desire to "improve access to this therapy while deepening CMS's understanding of how patients in Medicare respond to it, so the agency can ensure that it is paying for CAR T-cell therapy for cases in which the benefits outweigh the risks."[6] We are confident that data collected through the Coverage with Evidence Development (CED) framework will demonstrate the value of CAR T cell therapy for Medicare patients.

At the same time, we are mindful that NCDs focused on drugs and biologicals are rare, and that reconsidering these decisions can be resource intensive and time-consuming for CMS. As such, the final NCD should incorporate the flexibility required to reflect the rapidly evolving science of CAR T cell therapy. We want to emphasize that CAR T cell therapy as a class of medicines includes multiple therapies, diseases, and targets and that there is significant heterogeneity among both current and anticipated future CAR T treatments. We are concerned that the PDM, as currently structured, would limit CMS's flexibility to cover future CAR T therapies that could receive FDA approval within the next two years for unique patient populations or that have different characteristics (e.g., safety, dosing) than the two products currently available to patients. We are mindful that any potential inflexibility could create future limitations on patient access given the nature of the rapidly evolving science of CAR T cell therapy. Celgene's recommendations below would assist CMS in providing the required flexibility in the final decision memo to help to meet our shared objectives of patient access and evidence development.

We urge CMS to make the following changes in the final decision memo:

- **Align the patient eligibility criteria for CAR T cell therapies with FDA-approved labeling or medically accepted indications recognized in Medicare-approved compendia**, including guidance on eligible patient populations and dosing regimens. Researchers already are evaluating CAR T cell therapy's front-line potential to treat various aggressive cancer subtypes such as glioblastoma, multiple myeloma, and aggressive B-cell lymphomas.[7] Limiting coverage to relapsed and refractory cancers could have the unintended consequence of denying Medicare coverage for a therapy's FDA-approved indications.

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[6] CMS proposes Coverage with Evidence Development for Chimeric Antigen Receptor (CAR) T-cell Therapy, Feb. 15, 2019, https://www.cms.gov/newsroom/press-releases/cms-proposes-coverage-evidence-development-chimeric-antigen-receptor-car-t-cell-therapy.

[7] Clinicaltrials.gov: Study evaluating efficacy and Safety of Axicabtagene Ciloleucel as First-Line Therapy in Participants With High-Risk Large B-Cell Lymphoma, available at https://clinicaltrials.gov/ct2/show/NCT03761056?term=NCT03761056&rank=1; A study evaluating EGFRvIII CAR T Cells for Newly-Diagnosed WHO Grade IV Malignant Glioma (ExCeL), available at https://clinicaltrials.gov/ct2/show/NCT02664363?term=NCT02664363&rank=1 ; A study evaluating Up-front CART-BCMA With or Without huCART19 in High-risk Multiple Myeloma, available at https://clinicaltrials.gov/ct2/show/NCT03549442?term=NCT03549442&rank=1

Similarly, in the future, some patient populations may benefit from repeated treatment with CAR T cells. We believe that additional doses for a CAR T cell therapy should be covered when supported by that product's FDA-approved labeling or by Medicare-approved compendia.

- **Cover CAR T cell therapy under the CED framework when administered at an appropriately qualified site regardless of the site's status as a hospital.** FDA has outlined robust and appropriate safety criteria for sites through Risk Evaluation and Mitigation Strategies (REMS) that deliver CAR T cell therapy, and CMS has articulated appropriate safety- and quality-based criteria in the PDM. We encourage CMS to focus on these well-defined criteria, rather than the site's Medicare billing or legal entity status, when determining coverage.

- **Ensure that the Patient Reported Outcomes (PRO) tools that are used to collect health related quality of life data are structured in a way that is consistent across care settings, preserves data integrity, and is not overly burdensome for patients or sites.**

While CAR T cell therapies share a clinical foundation and the potential to significantly improve on the existing standard of care, each CAR T cell therapy has a unique target patient population; clinical, safety, and dosing profile; and manufacturing process. With that in mind, we provide feedback below on each section of the proposed NCD Manual text in Appendix B of the PDM, including recommendations to ensure that Medicare coverage for CAR T cell therapies remains aligned with the best available clinical and scientific evidence.

Patient Eligibility Criteria

Celgene believes strongly that the final NCD should be a flexible, living document that can accommodate future innovation to meet the shared goals of patient access and data collection. The NCD's ability to evolve seamlessly with changes in science and technology is particularly critical because it will apply to all autologous CAR T cell therapies and all cancer types.

As currently written, the proposed patient eligibility criteria are not consistent with the expected future of CAR T cell therapy, including the potential to utilize CAR T therapy for non-relapsed or refractory patient populations. There are already clinical trials underway to study CAR T in the front-line treatment of aggressive cancers, such as glioblastoma, multiple myeloma, and aggressive B-cell lymphoma.[8]

We recognize that today, CAR T cell therapy is largely used to target relapsed or refractory indications. However, we believe that CAR T cell therapy will soon show promise in earlier lines of therapy – front-line studies are already underway, as demonstrated by the list of clinical trials included in the PDM as well as footnote 7 of this letter. These front-line studies focus on patients with aggressive subtypes of disease. In clinical practice, these high-risk patients are often identified based on specific factors related to underlying cancer diagnosis that may include risk stratification by molecular subtypes (aggressive B cell lymphomas with MYC and BCL2 translocations and protein-over expression; specific translocations and mutations in multiple myeloma), or advanced disease

[8] *Id*

presentation (high International Prognostic Index (IPI) or International Staging System (ISS) scores). Current standard of care treatments lead to dismal outcomes for these patients and optimization of front-line therapy with CAR T has the potential to result in clinically meaningful outcomes.

As written, there is no flexibility within this PDM to allow coverage of treatment for non-relapsed or refractory patients under any circumstances (including FDA approval or listing in Medicare approved compendia). The non-coverage section of the PDM also explicitly removes any flexibility the Medicare Administrative Contractors would have under current policy to approve claims for non-relapsed or refractory patients when treated with an FDA approved CAR T cell therapy based on new clinical data or a new FDA approved indication for front-line therapy.

Restricting coverage to patients with relapsed or refractory disease could have the unintended consequence of creating a patient access barrier as the science rapidly evolves, the FDA approves new products, and additional indications are recognized as medically accepted by the compendia.

Specifically, the limitation on patient eligibility to relapsed or refractory cancers could have the following detrimental impacts:

- Limiting patient access to FDA-approved biologics for those who may have aggressive cancers that are not relapsed or refractory disease. In a circumstance where FDA approved a CAR T cell therapy for treatment of front-line disease or use of an FDA-approved CAR T therapy for front-line disease is recognized as a medically accepted indication by one of the Medicare-approved compendia, CMS would need to reconsider this coverage decision before any Medicare beneficiary could have access to that CAR T cell therapy. At a minimum, this would cause a six to nine-month delay before Medicare beneficiaries would have access to a new, potentially lifesaving innovation.
- Creating a gap in access between Medicare beneficiaries and other patient populations, even when earlier access is supported by FDA-approved labeling or Medicare-approved compendia.
- Limiting CMS's ability to develop evidence in non-relapsed or refractory patient populations.

Celgene urges CMS to remove the proposed coverage limitation of CAR T cell therapy to those with relapsed or refractory cancers. CMS instead should cover a CAR T cell therapy for all cancer patients for its FDA-approved indication(s) or for a use that is supported by one or more citations in any of the compendia approved by CMS to identify medically accepted indications of drugs and biologicals used in anti-cancer chemotherapeutic drug regimens.[9] CMS should simply delete "relapsed or refractory" from section B.1.a of the proposed NCD Manual language. This policy would be consistent with CMS's longstanding approach to coverage of cancer therapies and would help to ensure that its coverage policy for CAR T cell therapy continues to reflect evolving evidence.

Similarly, Celgene asks CMS to clarify the co-morbid conditions that may preclude a patient from benefiting from CAR T therapy. In section VIII of the PDM, CMS states: *"We believe, based on limitations on FDA indications, contraindications, and the inclusion and exclusion criteria of*

[9] Social Security Act (SSA) § 1861(s)(2). Medicare Benefit Policy Manual, ch. 12, § 50.4.5.

published studies, that these limitations include examples such as primary central nervous system lymphoma, Burkitt lymphoma, HIV/AIDS, active Hepatitis B or C, active uncontrolled infection, any autoimmune disease currently requiring immune suppression, and active grade 2 to 4 graft-versus-host disease."

Celgene recognizes that this is a representative list of comorbid conditions based upon the FDA labels for the two current FDA-approved CAR T cell therapies. The comorbid conditions that may preclude a patient from benefiting from future CAR T cell therapies will be different based upon the FDA-approved labeling for those therapies and the patient's underlying disease. Celgene recommends that CMS modify the statement about relevant comorbid conditions in section B.1.b of the proposed NCD Manual language to read "is *not currently experiencing any comorbidity that would otherwise preclude patient benefit as identified in the FDA-approved label of the prescribed CAR T-cell therapy."*

In summary, CMS should ensure that the patient eligibility criteria in the final decision provide sufficient flexibility for future CAR T innovations. We recommend CMS do this by aligning all of the criteria, including the comorbid condition exclusions, with the FDA label or indications supported by one or more of the Medicare-approved compendia for each FDA-approved CAR T cell therapy.

Criteria for Sites Administering CAR T Cell Therapy

Celgene strongly supports CMS's proposal to cover CAR T cell therapy in both inpatient and outpatient settings of care. We are conducting clinical trials to demonstrate that, depending upon the characteristics of the individual patient, his or her underlying disease, and the profile of the CAR T cell therapy itself, patients can safely and effectively receive CAR T cells as outpatients.[10]

Celgene agrees with CMS that important patient safeguards should be put in place for managing adverse events for CAR T cell therapies. Sites with which Celgene chooses to partner to deliver CAR T cell therapy will need to meet robust safety standards, including but not limited to FDA Risk Evaluation and Management System (REMS) requirements and additional infrastructure requirements for patient monitoring, quality management and procedures for a patient's admission to an intensive care unit (ICU) when necessary.

Among the most important safety criteria that should be in place for the delivery of CAR T cell therapy is an integrated medical team of physicians, nurses, and care coordinators who will comprise the CAR T cell care management team. Consistent with CMS's proposal, this CAR T cell care management team should have a documented protocol to ensure 24/7 communication and logistics for patient care coverage by members of the designated care team and provide continual oversight of the patient by the primary CAR T cell physician.

Aligned with our comments above, Celgene urges CMS to establish site requirements that can adapt to rapidly evolving scientific advances in CAR T cell therapy, including the development of

[10] Clinicaltrials.gov: A Safety Trial of Lisocabtagene Maraleucel (JCAR017) for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL) in the Outpatient Setting, available at https://clinicaltrials.gov/ct2/results?cond=&term=NCT03744676&cntry=&state=&city=&dist=; Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-NHL-006), available at https://clinicaltrials.gov/ct2/show/NCT03483103?term=NCT03483103&rank=1

therapies with different profiles than the currently approved CAR T cell therapies. In particular, Celgene urges CMS to not limit provision of CAR T cell therapies to "hospitals" in the final decision memo and use a more generic term such as "site." Using "site" instead of "hospital" would allow Medicare to cover CAR T cell therapies in any appropriate site of care as these technologies and treatment regimens evolve. Celgene believes strongly that the safety criteria outlined in the PDM should drive the determination of appropriate sites where CAR T cell therapy is available, rather than the legal or billing distinction as a hospital. CMS should cover CAR T cell therapies in any setting of care that meets the proposed requirements of section B.3 of the Proposed NCD Manual language, regardless of whether that site meets CMS's definition of hospital in this context.

The emerging safety profile of Celgene's CAR T cell therapies suggests that some CAR T cell therapies, in certain patient populations, have low rates of CAR T cell side effects or late onset of side effects that make immediate hospitalization at time of infusion unnecessary. As experience with CAR T cells increases, and cell therapy evolves, we anticipate that toxicity management algorithms will become more established, and the side effect profiles of each therapy more defined, potentially allowing use in more settings of care.

We highlight the latest liso-cel investigational data below to demonstrate the substantial variation in safety profile that can occur across CAR T cell therapies. These data show that the majority of patients (57%), including those over age 65, do not experience cytokine release syndrome (CRS) or neurotoxicity. Notably, only 1% of liso-cel patients experienced grade 3 or 4 CRS.

		CORE population[11]		
	All Treated (n=102)	Total (n=73)	50×10^6 CAR T cells (n=33),	100×10^6 CAR T cells (n=37),
CRS, any grade	37%	37%	42%	30%
CRS, grade 1-2	36%	36%	39%	30%
CRS, grade 3-4 (sCRS)	1%	1%	3%	0%
NT, any grade	23%	25%	24%	24%
NT, grade 1-2	10%	10%	3%	16%
NT, grade 3-4 (sNT)	13%	15%	21%	8%
Any CRS or NT	43%	44%	45%	41%
Any sCRS or sNT	13%	15%	21%	8%

[11] All JCAR017 data presented in this section available at http://ir.celgene.com/releasedetail.cfm?ReleaseID=1069109 "Celgene Announces Updated Safety and Efficacy Data from the TRANSCEND Trial of liso-cel (JCAR017) in Patients with Relapsed or Refractory B-cell

When these side effects occurred, patients typically experience them late in the first week or into the second week after treatment (median of 5 and 10 days, respectively).

Celgene is currently conducting multiple studies in outpatient sites of care, including sites that do not bill as hospitals. The OUTREACH[12] study is designed to test the safety of liso-cel in outpatient sites of care in order to safely expand access of care to qualified oncology care sites that can support CAR T cell administration and management. PILOT[13]is a study in second-line, transplant non-eligible patients. This patient population is treated predominantly at non-academic centers that also have a predominantly outpatient site of care model.

Both trials will contribute significantly to our experience and data around administering CAR T cells safely in the outpatient setting in sites that may or may not meet the definition of hospital intended by CMS in the PDM. These sites have several defining characteristics. First, they have demonstrated one of the following core capabilities: Transplant capability, phase 1 hematology/oncology trial experience, or CAR T experience with currently marketed CAR T cell therapies. Second, they work in a coordinated care model that includes cross functional CAR T cell therapy medical teams. Lastly, they are able to function seamlessly across the various disciplines and include oncologists, nurse coordinators, specialists such as neurologists and ICU physicians, apheresis centers, emergency room, infusion centers, and inpatient hospital staff to care for each patient.

In addition to the emerging safety data that support greater utilization and administration of CAR T cell therapies in an outpatient setting of care, Medicare policies that blur the line between hospitals and non-hospital settings reinforce why coverage of CAR T cell therapies should be available across appropriate sites of care. In the PDM, CMS says the benefit categories for CAR T cell therapies include Social Security Act (SSA) §§ 1861(b) ("inpatient hospital services") and 1861(s)(2)(B) ("hospital services (including drugs and biologicals which are not usually self-administered by the patient) incident to physicians' services rendered to outpatients and partial hospitalization services incident to such services)." These benefit categories do not align neatly with either the statutory definition of a "hospital"[14] or the definition of "covered outpatient department services."[15] A provider can be a "hospital" under one part of the statute but not have its services paid as hospital services under another part of the statute. Moreover, the safety requirements that CMS proposes for delivery of CAR T cell therapies can be fulfilled by a site regardless of whether it meets the statutory definition of a hospital or whether its services are payable as "covered outpatient department services". In light of this fact, Celgene recommends that CMS remove the term "hospital" from the final decision and instead allow "sites" to administer CAR T cell therapy that meet the standards outlined in section B.3 of the proposed NCD Manual text.

Treatment Criteria

[12] Clinicaltrials.gov: A Safety Trial of Lisocabtagene Maraleucel (JCAR017) for Relapsed and Refractory (R/R) B-cell Non-Hodgkin Lymphoma (NHL) in the Outpatient Setting, available at https://clinicaltrials.gov/ct2/results?cond=&term=NCT03744676&cntry=&state=&city=&dist=

[13] Clinicaltrials.gov: Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-NHL-006), available at https://clinicaltrials.gov/ct2/show/NCT03483103?term=NCT03483103&rank=1

[14] SSA § 1861(e).

[15] SSA § 1833(t)(1)(B)(v).

Celgene understands CMS's desire for additional clinical data on CAR T cell therapy for the Medicare population, and we support the collection of these additional data which we believe will demonstrate the transformative potential of CAR T therapies in treating multiple forms of cancer. At the same time, we strongly believe that any evidence development requirements must be implemented in the least burdensome manner to ensure that the NCD achieves CMS's goal of appropriately expanding access to CAR T cell therapies. As discussed above, Medicare's coverage requirements for CAR T cell therapies also should be aligned with FDA-approved labeling or Medicare-approved compendia.

Additional Doses of CAR T Cell Therapies Should Be Covered Consistent with FDA label or Medicare-Approved Compendia

Celgene notes that the limitation outlined in the treatment criteria under section B.3.a. of the proposed NCD Manual language which limits a Medicare beneficiary's coverage of CAR T cell treatment to a single dose of an FDA approved biological unless a new primary cancer diagnosis is made may not be consistent with the FDA approved labels or Medicare-approved compendia as CAR T cell treatment paradigms evolve. Celgene urges CMS to cover additional doses as described in the FDA label or the Medicare-approved compendia so that patients may receive coverage for additional doses as supported by the clinical evidence.

CMS Should Clarify How Registries Should Address the Proposed Questions

We appreciate the proposal that additional clinical data be collected via a registry mechanism because many sites administering CAR T cell therapy will be familiar with this approach, and it would limit hurdles for providers and patients. Several biopharmaceutical companies have already committed to the collection of long-term outcomes and safety data for CAR T cell therapies and are partnering with organizations like the Center for International Blood and Marrow Transplant Research (CIBMTR) that have experience with the collection of this type of data.

Celgene agrees with the questions posed of the CED registry and the types of data for collection as long-term real-world evidence is of utmost importance in a new and rapidly evolving treatment landscape. Celgene urges CMS to consider the following changes to maximize value of the evidence collected through the CED registry:

- Clarify the approach to CED questions that are not addressable through the data variables to be collected (i.e. efficacy relative to a standard of care control, outcomes relative to clinical trial results)
- Provide greater guidance and specificity regarding the data collection time points, specifically what constitutes "baseline" measurement for CAR T cell treatment (i.e. post apheresis, but pre-lymphodepletion). In the relapsed or refractory cancer setting, there is a time interval between when a patient's disease progresses and when they receive CAR T cell therapy. During this time, a patient's quality of life may rapidly change. Without clear guidance of what constitutes baseline, there may be inaccurate representation of the baseline for patients receiving therapy.

CMS Should Revise the Proposed Requirements for Collection of PRO Data

Celgene shares CMS's interest in addressing the patient's health related quality of life. PROs are important to understanding health-related quality of life (HRQOL) and symptom impacts associated with treatments such as CAR T cell therapy. Celgene has long had a commitment to assessing PROs in the context of clinical trials and in the real world. We believe this information should be collected regardless of whether the patient is treated in the inpatient or outpatient setting, and should be encouraged, but not required, for coverage of CAR T cell therapies.

In pivotal trials for both liso-cel and bb2121, Celgene is utilizing the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30), an integrated system for assessing the Health-Related Quality of Life (HRQOL) of patients with cancer, and EQ-5D-5L, a measure of patients' well-being and perceived health status. In addition, the myeloma-specific subscale of the EORTC QLQ-C30 has been included in the bb2121 clinical program. Celgene intends to collect PROs for at least two years for liso-cel and up to five years for bb2121 after initial administration. Celgene is also conducting individual patient interviews in a subset of trials in order to capture additional patient experience data.

Celgene believes collecting PRO data from patients receiving CAR T cell therapy is important. However, we know from direct experience that the data collection, analyses, and interpretation for PROs can be complex and logistically challenging. We are concerned that the PRO requirements in the PDM could create barriers to patient access in the near term as the infrastructure to collect PRO data from patients through registries is largely underdeveloped. As noted above, Celgene has experience with PROs both in a clinical trial setting and through the continued real-world collection of patient outcomes via Celgene Connect® Registries. As a result of this experience, Celgene urges CMS to consider the following changes to the way that the PRO collection is structured within the coverage decision:

- Implement a single measure, the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS®), with specific domains for assessment, to evaluate symptom impact, functional well-being, and HRQOL as PROMIS represents a comprehensive and robust patient reported outcome measure.
- Collect PRO data across inpatient and outpatient settings and adjust the time intervals for data collection to provide increased granularity around schedule of assessments and consider a single "baseline" assessment to maximize consistency and minimize patient burden.
- Rather than require providers to submit PRO data as a condition of coverage, allow providers to submit PRO data voluntarily until additional experience and insight is gained through CIBMTR's electronic PRO (ePRO) pilot.

Providers Should Collect PRO Data Using a Single Tool

PRO data differ from objective clinical data, in that the data must be collected prospectively and directly from the patient, requiring the need for a tool that can be used in diverse circumstances that are convenient and efficient for the site, healthcare provider, and patient, while also ensuring that the data collected are accurate. As noted in our testimony at the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting, collecting PROs in a real-world

setting can present unique challenges for patients and providers, particularly if those PROs are expected to be collected two years post treatment administration.

Requiring institutions with limited experience with PRO measures to select between the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO CTCAE™) and PROMIS (as well as specific adverse events and symptom impact, functional well-being, and HRQOL, respectively) may lead to inconsistent assessments and a data set that is difficult to analyze. Celgene recommends that CMS limit the PRO collection to the PROMIS tool, which would address CMS's objective of capturing "symptom function health-related quality of life changes over the course of their treatment". PROMIS is the more appropriate tool as it measures functions, symptoms, behaviors, and feelings, while the focus of the PRO-CTCAE is the evaluation of symptomatic adverse events (frequency, severity and/or interference), which may be impacted by non-CAR T-cell treatments (e.g., lymphodepletion, treatments following progression).[16] Celgene specifically recommends the Physical Function, Global Health, Pain Interference and Fatigue modules to best assess symptoms, function, and HRQoL in patients receiving CAR T cell therapy.

Providers Should Collect a Consistent Set of Data Across Settings of Care

Celgene also urges CMS to consider the collection of PRO data across both the inpatient and outpatient settings of care in order to maximize the value of evidence collected. We believe that PRO data could be informative and valuable for patients treated across settings of care. In addition, patients may initiate care in one setting and transition across multiple sites of care, thereby undermining CMS' goal to collect HRQOL data for those beneficiaries treated as outpatients.

PRO Data Will Provide Additional Insights if Collected Soon After Treatment with CAR T cell Therapy

In addition, Celgene recommends considering the collection of data via PROMIS at one month after CAR T cell administration, in addition to collection of data at baseline, treatment, and follow-up at 3 months, 6 months, and 12 months. We believe that collecting data after one month will increase the credibility and validity of the data, as patients will be better positioned to report their recent post-CAR T cell infusion experience. Celgene also recommends CMS limit the follow-up period to one year and provide more flexibility around data collection time points (e.g., 3 months ± 2 weeks).

CMS Should Leverage the Ongoing CIBMTR Pilot Before Implementing a PRO Requirement

CIBMTR began a pilot program during the summer of 2018 using PROMIS as an ePRO. In addition, CIBMTR formed a multidisciplinary working group to devise a strategy for the collection of late effects of patients contributing to the CIBMTR registry. Given the unique challenges of PRO data collection in the real world, Celgene strongly recommends that PRO data collection not be a condition of coverage, and that such data collection be a recommendation rather than a requirement. Celgene urges CMS to allow the CIBMTR ePRO PROMIS pilot program to be completed, such that the learning and insights can be used to mitigate the unique challenges of collecting PRO evidence and position CMS, patients, and providers for success.

[16] National Cancer Institute, PRO-CTCAE available at https://healthcaredelivery.cancer.gov/pro-ctcae/; Health Measures, PROMIS, available at http://www.healthmeasures.net/explore-measurement-systems/promis.

Nationally Non-Covered Indications

Celgene recommends that CMS make changes to section C of the proposed NCD Manual text. CMS should delete the second sentence of this section, which currently refers to the relapsed and refractory indications specified in the draft patient criteria section of the proposed NCD manual text. We note that the references to the sections of the NCD Manual in section C also do not appear to be correct and should be updated in the final decision.

Conclusion

Celgene is committed to developing CAR T cell therapies in areas of significant unmet medical need, and we are supportive of the framework for this coverage decision. We look forward to continuing to collaborate with CMS to ensure that Medicare beneficiaries can obtain access to these novel therapies as the science in this therapeutic class continues to rapidly evolve.

We appreciate CMS' attention to and investment in CAR T cell therapies and the agency's desire to ensure appropriate access for Medicare patients. To further that goal, we urge CMS to make targeted revisions to the PDM to ensure that Medicare's final coverage policy for CAR T cell therapies can accommodate future evidence-based changes in where, how, and for whom these exciting medicines show promise.

Sincerely,

Richard H. Bagger
Executive Vice President, Corporate Affairs and Market Access