



Richard H. Bagger
EVP, Corporate Affairs &
Market Access

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
Tel 908-673-9855
rbagger@celgene.com

June 15, 2018

BY ELECTRONIC DELIVERY

Tamara Syrek Jensen
Director, Evidence and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
S3-02-01
Baltimore, Maryland 21244
tamara.syrekjensen@cms.hhs.gov

Re: **National Coverage Analysis (NCA) Tracking Sheet for Chimeric Antigen Receptor (CAR) T cell Therapy for Cancers (CAG-00451N)**

Celgene Corporation (Celgene) appreciates the opportunity to provide data and input to inform the Centers for Medicare & Medicaid Services' (CMS) national coverage analysis (NCA) on CAR T cell therapies for cancer. Celgene does not believe that a National Coverage Determination (NCD) is necessary or appropriate for CAR T cell therapies. These therapies should be covered as anti-cancer regimens as provided under Medicare statute. Furthermore, if CMS proceeds with an NCD, the data demonstrating that these therapies can be safely and effectively delivered to patients are more than sufficient to support coverage without restrictions. We strongly urge the agency to preserve maximum flexibility to accommodate new therapies, indications, and patient populations. Given the novelty of CAR T cell therapy and the unique profiles of different products, we do not believe it would be reasonable or prudent to issue a decision that is specific to the earliest experience with drugs in this category.

Should CMS move forward, we encourage the agency to conduct its analysis in an efficient manner and to finalize coverage for CAR T cell therapies as quickly as possible. Patients who are candidates for CAR T cell therapies today are extremely ill and have limited or no other options for treatment. Therefore, we strongly encourage CMS to provide interim technical guidance to Medicare Administrative Contractors (MACs) and providers referencing the applicable statutory coverage provisions to ensure that appropriate beneficiaries have uninterrupted access to this care.

Celgene is a global biopharmaceutical company specializing in the discovery, development, and delivery of therapies designed to treat cancer, 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.

Since its founding, Celgene has been committed to discovering and developing treatments in disease areas with unmet need. 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.

CAR T cell technology harnesses and genetically enhances patients' own immune cells in the fight against cancer – creating a truly personalized medical treatment that has enormous potential in effectively treating both blood and solid tumor cancers.¹ As Food and Drug Administration (FDA) Commissioner Gottlieb has explained: CAR T cells open the door to “a new frontier in medical innovation with the ability to reprogram a patient’s own cells to attack a deadly cancer...[Such new] technologies...hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable diseases.”²

Celgene is at the vanguard of CAR T cell innovation. We are currently developing two CAR T cell therapies that we believe have significant clinical potential in the treatment of blood-based cancers that are under-served by existing treatment options:

- bb2121.³ 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.⁴ With an average onset 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

¹ Davila ML, Bouhassira DC, Park JH, et al. Chimeric antigen receptors for the adoptive T cell therapy of hematologic malignancies. *Int J Hematol*. 2014;99:361–371. Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4684946/pdf/nihms744119.pdf>

² FDA, *FDA Approval Brings First Gene Therapy to the United States* (Aug. 30, 2017), available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm>.

³ Efficacy and Safety Study of bb2121 in Subjects with Relapsed and Refractory Multiple Myeloma (KarMMA), available at <https://clinicaltrials.gov/ct2/show/NCT03361748>

⁴ SEER, *Cancer Stat Facts: Myeloma*, available at <https://seer.cancer.gov/statfacts/html/mulmy.html>

induce deep responses in these under-served multiple myeloma patient populations and has been granted breakthrough designation by the FDA.⁵

- JCAR017.⁶ A CD19-directed CAR T cell therapy, JCAR017 is in clinical trials for B-cell Non-Hodgkin Lymphoma (NHL). NHL is the most commonly diagnosed blood cancer in the United States and claims the lives of approximately 20,000 Americans each year.⁷ 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. JCAR017 is an innovative new CAR T cell therapy that could benefit many of these difficult-to-treat and under-served patient populations. JCAR017 also is an advancement with respect to CAR T cell technology. Unlike most CAR T cell products, JCAR017 provides modified cytotoxic (or “killer”) T cells in a 1:1 ratio 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. JCAR017 has been granted breakthrough designation by the FDA.

While CAR T cell therapies share the potential to significantly improve on the existing standard of care, each CAR T cell therapy has a unique target patient population, safety profile, and manufacturing process. Thus, we believe that it is critically important for patients and providers to have access to the full range of CAR T cell therapies.

The existing data on CAR T cell therapies demonstrating the transformative potential of these therapies are robust. Further, the individual data for each CAR T cell therapy should be considered in determining the appropriate setting for administration of the product. Finally, as described in more detail below, CAR T cell therapies used for FDA-approved indications⁸ and medically-accepted indications (i.e., indications supported by recognized clinical compendia)⁹ fit the statutory definition of “drugs and biologicals” that may be covered by Medicare.

Medicare Coverage for CAR T Cell Therapy for the Treatment of Cancer

CAR T cell therapies should be covered by Medicare consistent with the Social Security Act (SSA). The SSA provides that “any drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication” are included in the definition of drugs that can be

⁵ 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>

⁶ 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>

⁷ SEER, *Cancer Stat Facts: Non-Hodgkin Lymphoma*, available at <https://seer.cancer.gov/statfacts/html/nhl.html>

⁸ Social Security Act (SSA) § 1861(t)(2)(A); SSA § 1861(t)(2)(B).

⁹ SSA § 1861(t)(2)(B)(ii).

covered under Medicare.¹⁰ Moreover, a “medically accepted indication” of a drug or biological used in an anticancer chemotherapeutic regimen is defined to include “any use which has been approved by the [FDA] for the drug.”¹¹ A “medically accepted indication” also includes a FDA-approved drug for which the “use is supported by one or more citations which are included (or approved for inclusion) in one or more” statutorily listed compendia or “determine[d], based upon guidance provided by [CMS] to carriers for determining accepted uses of drugs, that such use is medically accepted based on supportive clinical evidence in peer reviewed medical literature [approved by CMS].”¹² Essentially, a “medically accepted indication” includes the use of a FDA-approved drug described in listed compendia or approved by a MAC based on certain publications.

By recognizing these uses as “medically accepted,” Congress clearly intended for Medicare beneficiaries to have access to FDA-approved cancer therapies for any indication that is listed on the FDA-approved labeling or supported by recognized publications (e.g., approved compendia). Consistent with the statute’s language and intent, CMS traditionally has not sought to limit coverage of the FDA-approved indications of anticancer drugs through NCDs. Because CAR T cell therapies are anticancer regimens, these products should be covered like other anticancer drugs; that is, for their FDA-approved uses, as well as any other uses supported by the compendia or literature identified by CMS.

Celgene urges CMS to approve coverage for any indications listed on the FDA-approved label for a CAR T cell therapy consistent with the statute and past CMS practice. In drafting its decision, CMS should ensure that coverage for FDA-approved indications extends to any FDA-approved CAR T cell therapy, not just Kymriah® and Yescarta®, the CAR T cell therapies currently approved by the FDA. That is, any decision should be flexible enough to accommodate new products, indications, patient populations, and product safety programs. Consistent with the statute, Celgene also urges CMS to leave discretion to the MACs to determine whether any additional uses of CAR T cell therapies should be permitted as knowledge of these essential treatments evolves, consistent with current practice for other cancer treatments.

Below we provide detailed comments and data to address key elements of CMS’ analysis, including information on the efficacy and safety profiles of Celgene’s CAR T cell therapies and provider experience using CAR T cells across settings of care.

¹⁰ SSA § 1861(t)(2)(A).

¹¹ SSA § 1861(t)(2)(B)

¹² *Id.*

Safety and Efficacy Profile of CAR T Cell Therapies

Outcomes for Patients Treated with Celgene CAR T Cell Therapies

CAR T cell therapies represent a transformation in cancer care, offering new hope to patients with incurable or refractory blood cancers.¹³ The growing and evolving evidence base suggests that CAR T cell therapy can produce deep and durable responses in patients who have exhausted or not responded to other treatment options, and makes a compelling case for Medicare coverage for appropriate patients.

Earlier this month, Celgene and bluebird bio reported updated results from an open-label, phase I study evaluating the preliminary safety and efficacy of bb2121 anti-BCMA CAR T cell therapy in patients with relapsed or refractory multiple myeloma.¹⁴ Patients were treated with increasing dose of CAR T cells. Patients were heavily pre-treated, with a median of seven prior myeloma treatment regimens in the dose escalation cohort and eight prior regimens in the dose expansion cohort. In the dose expansion cohort, more than 90 % of patients had received prior treatment with two IMiD® therapies, two proteasome inhibitors, daratumumab and an autologous stem cell transplant.

Forty-three patients had been enrolled and dosed in the two study cohorts as of March 29, 2018. As illustrated below, patient responses were significant across all dose levels. Patients who received a dose of greater than 150 million CAR T cells showed a response in more than 90% of cases. This included a complete response in 50 % of the patients. Additionally, more than 35% of patients had a very good partial response as defined by IMWG criteria (reduction of involved protein by 90% or higher).

Measure	50 x 10 ⁶ (n=3), median follow-up 84 days (59,94)	150 x 10 ⁶ (n=14), median follow-up 87 days (36,638)	> 150 x 10 ⁶ (n=22), median follow-up 194 days (46, 556)
Overall response (ORR)	33.3%	57.1%	95.5%
Complete response (CR)	0%	42.9%	50%
Very good partial response (VGPR)	0%	7.1%	36.4%
Median duration of response mDOR	1.9 months	Not estimable	10.8 months

*Patients with ≥2 months of response data or PD/death within < 2 months

¹³ Lim WA, June CH. The Principles of Engineering Immune Cells to Treat Cancer. *Cell*. 2017;168(4):724-740. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5553442/pdf/nihms890678.pdf>

¹⁴ All bb2121 data presented in this section available at <http://ir.celgene.com/releasedetail.cfm?ReleaseID=1069096>. "Updated Results of Ongoing Multicenter Phase I Study of bb2121 anti-BCMA CAR T Cell Therapy Continue to Demonstrate Deep and Durable Responses in Patients with Late-Stage Relapsed/Refractory Multiple Myeloma at ASCO Annual Meeting."

Additionally, Celgene reported updated results from an open-label, phase I seamless pivotal study evaluating the preliminary safety and efficacy of JCAR017 anti-CD19 CAR T cell therapy (lisocabtogene maraleucel) in patients with relapsed or refractory aggressive NHL.¹⁵ Patients in the study were heavily pre-treated, with a median of three prior lymphoma treatment regimens. Seventy percent were chemorefractory, and nearly 50% had never been in a complete remission. Patients 65 years of age or older constituted 36% of the treated patient population.

Over 100 patients had been treated as of May 4, 2018. As illustrated below, patient responses were significant with a high rate of durable complete response. Among the patient population moving forward into the registrational trial (CORE population), more than 75% of patients had either a complete response or a partial response, with approximately half of patients still in remission at 6 months at the dose going forward into the pivotal trial (100 x 10⁶ CAR T cells).

	All Treated (n=102)	CORE population		
		Total (n=73)	50 x 10 ⁶ CAR T cells (n=33),	100 x 10 ⁶ CAR T cells (n=37),
Overall response (ORR)	75%	80%	79%	78%
Complete response (CR)	55%	59%	55%	62%
3 month ORR	51%	59%	52%	65%
3 month CR	38%	45%	36%	51%
6 month ORR	40%	47%	42%	49%
6 month CR	34%	41%	33%	46%

Median duration of follow-up, 8 months

Potential Side Effects of Treatment with CAR T Cells

We share CMS's goal of ensuring that all Medicare beneficiaries receive safe, effective, and appropriate care. Like many innovative and novel therapies, treatment with CAR T cells poses a risk of side effects including cytokine release syndrome (CRS) and neurotoxicity.¹⁶ The side effects can be serious and must be quickly and fully addressed when they occur. However, each CAR T cell therapy presents a distinct safety profile.

¹⁵ 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 non-Hodgkin Lymphoma at ASCO"

¹⁶ Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-95. Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4093680/?report=printable>

The latest bb2121 data show that most patients who experience CRS or neurotoxicity have Grade 1 and 2 effects that respond to symptomatic treatment or moderate intervention.¹⁷ Among the 43 infused patients in the dose escalation study, 63% had cytokine release syndrome (CRS).¹⁸ Of these, two patients experienced Grade 3 CRS with the remainder experiencing Grades 1 or 2. The median duration of CRS was 6 days. Fourteen patients experienced neurotoxicity, with one patient experiencing a grade 3 or higher event. Other frequent Grade 3 or 4 adverse events included cytopenias commonly associated with lymphodepleting chemotherapy, such as neutropenia (79%), thrombocytopenia (51%) and anemia (44%), as well as infection of any grade (61%).

The latest JCAR017 data show that the majority of patients (57%), including those over age 65, do not experience CRS or neurotoxicity. When 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).

	All Treated (n=102)	CORE population		
		Total (n=73)	50 x 10 ⁶ CAR T cells (n=33),	100 x 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%

CRS, cytokine release syndrome; sCRS, severe CRS; NT, neurotoxicity; sNT, severe NT

The emerging safety profile of Celgene's CAR T cell therapies suggests that some CAR T cell products, in certain patient populations, have low rates of CAR T cell side effects. As experience with CAR T cells increases, we anticipate that toxicity management algorithms will become more established, and the side effect profiles of each product more defined. Further, we expect our CAR T cell products to be subject to strict and robust Risk Evaluation and Mitigation Strategies (REMS) programs that will assure appropriate oversight and management of any patient risks. Celgene has

¹⁷ For more detailed information about the grading of CRS, see Lee et al. "Current concepts in the diagnosis and management of cytokine release syndrome." *Blood*. 2014; 124(2): 188–195.

¹⁸ All bb2121 data presented in this section available at <http://ir.celgene.com/releasedetail.cfm?ReleaseID=1069096>. "Updated Results of Ongoing Multicenter Phase I Study of bb2121 anti-BCMA CAR T Cell Therapy Continue to Demonstrate Deep and Durable Responses in Patients with Late-Stage Relapsed/Refractory Multiple Myeloma at ASCO Annual Meeting."

substantial REMS experience, and we will apply our industry-leading expertise to our CAR T cell programs.

Maximizing Access to CAR T Cell Therapies

We believe that all Medicare beneficiaries who need CAR T cell therapy should be able to access care in the setting that is most appropriate for their treatment. While academic medical centers and other hospitals will play an important role in delivering CAR T cell therapies for many patients, not all patients who could benefit from CAR T cell therapy will be able to be treated in an inpatient setting – either because of distance, inability to travel, or because patients with their condition most often receive care in the community.

In its announcement, CMS notes that the existing data on CAR T cell therapy come from the inpatient setting. In fact, providers are currently delivering CAR T cell therapies on an outpatient basis in clinical trials. Patient outcomes at this stage suggest that these therapies can be delivered safely and effectively in the outpatient setting.

We strongly believe that care models including outpatient administration of cellular therapies, such as at sophisticated hospitals within community oncology networks, will be an important option for some patients. For example, outpatient administration in clinics affiliated with hospitals that are qualified to manage the side effects of CAR T cells could provide important access for patients who live in rural areas. In addition, outpatient administration and monitoring may allow patients to remain with their trusted providers, promote continuity and coordination of care, and allow patients to rely fully on their social support networks at a clinically critical time.

Several academic centers have championed outpatient administration of CAR T cells, including the Fred Hutchinson Cancer Research Center (FHCRC), and Seattle Children's hospital. Over 200 patients with CD19-positive leukemia and lymphomas have been infused as outpatients at the FHCRC,¹⁹ with 30% of patients with NHL at the target dose of CAR T cells remaining outpatient without need for hospitalization in the month after CAR T cell administration. Over 100 pediatric patients with CD19-positive ALL have been treated at Seattle Children's hospital,²⁰ with over 90% infused as outpatients. Patients infused as outpatients are monitored closely, consistent with current best practices for all cancer patients, and those who develop fevers are admitted for management of possible CRS.

In the phase 1 trial of JCAR017, 19 patients have been infused as outpatients to date. At this time, as of the data cutoff for presentations at the 2017 Conference of the American Society of

¹⁹ *Immunotherapeutic Approaches for B-Cell Acute Lymphocytic Leukemia* (Nov. 10 2017), available at <https://ascopost.com/issues/november-10-2017/immunotherapeutic-approaches-for-b-cell-acute-lymphocytic-leukemia/>

²⁰ Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. *Blood*. 2017;129(25):3322-3331. Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5482103/?report=printable>

Hematologists,²¹ data have been disclosed on 8 patients who were infused in the outpatient setting of care. Among those who required hospitalization, the median day of hospitalization was day 5, with a range from day 4 to day 22. The mean number of days spent in the hospital was 40% lower (16 days to 9 days) in patients infused as outpatients, with no increase in severe CRS or neurotoxicity, no admissions to the intensive care unit, and no increase in interventions for CRS or neurotoxicity. Similarly, outpatient administration in 18 of 68 (27%) of patients with aggressive NHL treated with Kymriah® was reported.²²

Current and future clinical trials with JCAR017 will allow for outpatient administration with appropriate monitoring for side effects. These trials will test the safety of JCAR017 at non-academic centers that have intensive care and specialty capabilities, and will include selected sites in large cancer networks such as US Oncology, Tennessee Oncology, and Florida Cancer Specialists.

Celgene will launch and oversee a rigorous provider certification program with the goal of ensuring safe and effective delivery of CAR T cells irrespective of where those providers administer our products. We do not believe that CMS should require additional provider certification criteria, which could significantly jeopardize access for some patients without a corresponding benefit to patient safety.

We expect that any CAR T cell therapy, administered in any setting, will be subject to intense oversight and monitoring by the therapy's manufacturer and the FDA. This oversight and monitoring will encompass each CAR T cell's manufacturing process. We also expect all CAR T cell therapies to have robust REMS programs that will ensure appropriate provider certification and patient education; long-term monitoring; and analysis of patient outcomes, including any side effects. Should CMS believe that any additional data on CAR T cell therapies need to be collected, we strongly encourage the agency to leverage product REMS programs to the fullest extent possible in lieu of separate and potentially duplicative reporting.

Conclusion and Recommendations

CMS should continue to cover CAR T cell therapies for FDA-approved indications and to allow for coverage of other indications that are well supported by evidence and current standards for

²¹ Maloney DG, Abramson JS, Palomba ML, et al. Preliminary Safety Profile of the CD19-Directed Defined Composition CAR T Cell Product JCAR017 in Relapsed/Refractory Aggressive B-NHL Patients: Potential for Outpatient Administration. *Blood*. 2017;130:1552. Available at, http://www.bloodjournal.org/content/130/Suppl_1/1552

²² Novartis, Kymriah® (tisagenlecleucel), first-in-class CAR-T therapy from Novartis, receives second FDA approval to treat appropriate r/r patients with large B-cell lymphoma (May 1, 2018), available from <https://www.novartis.com/news/media-releases/kymriah-r-tisagenlecleucel-first-class-car-t-therapy-from-novartis-receives-second-fda-approval-treat-appropriate-rr-patients-large-b-cell-lymphoma>

anticancer therapies. Further, CMS should permit providers to determine the appropriate setting of care for each CAR T cell patient.

We urge CMS to confirm current coverage of CAR T cell therapies for FDA-approved indications through interim guidance to Medicare Administrative Contractors and healthcare providers. Absent such guidance, we are very concerned that confusion about the NCA will jeopardize access to care for patients who cannot afford to wait.

Thank you for your consideration of our comments.

Sincerely,

A handwritten signature in black ink that reads "Rich Bagger". The signature is written in a cursive, flowing style.

Richard H. Bagger

Executive Vice President, Corporate Affairs and Market Access