bacteria,'' which play a role in protecting the body from infection. Antibiotics can kill these good bacteria and allow the *C-diff* bacteria to multiply and release toxins that damage the cells lining the intestinal wall, resulting in a CDI. CDI is a leading cause of hospital-associated gastrointestinal illnesses. Persons at increased risk for CDI include people who are treated with current or recent antibiotic use, people who have encountered current or recent hospitalization, people who are older than 65 years, immunocompromised patients, and people who have recently had a diagnosis of CDI. CDI symptoms include, but are not limited to, diarrhea, abdominal pain, and fever. CDI symptoms range in severity from mild (abdominal discomfort, loose stools) to severe (profuse, watery diarrhea, severe pain, and high fevers). Severe CDI can be life-threatening and, in rare cases, can cause bowel rupture, sepsis and organ failure. CDI is responsible for 14,000 deaths per year in the United States.

C-diff produces two virulent, pro-inflammatory toxins, Toxin A and Toxin B, which target host colonocytes (that is, large intestine endothelial cells) by binding to endothelial cell surface receptors via combined repetitive oligopeptide (CROP) domains. These toxins cause the release of inflammatory cytokines leading to intestinal fluid secretion and intestinal inflammation. The applicant asserted that ZINPLAVA™ targets Toxin B sites within the CROP domain rather than the *C-diff* organism itself. According to the applicant, by targeting *C-diff* Toxin B, ZINPLAVA™ neutralizes Toxin B, prevents large intestine endothelial cell inflammation, symptoms associated with CDI, and reduces the recurrence of CDI.

ZINPLAVA™ received FDA approval on October 21, 2016, for reduction of recurrence of CDI in patients receiving antibacterial drug treatment for CDI and who are at high risk of CDI recurrence. ZINPLAVA™ became commercially available on February 10, 2017. Therefore, the newness period for ZINPLAVA™ began on February 10, 2017. The applicant submitted a request for a unique ICD–10–PCS procedure code and was granted approval for the following procedure codes: XW033A3 (Introduction of bezlotoxumab monoclonal antibody, into peripheral vein, percutaneous approach, new technology group 3) and XW043A3 (Introduction of bezlotoxumab monoclonal antibody, into central vein, percutaneous approach, new technology group 3).

After evaluation of the newness, costs, and substantial clinical improvement criteria for new technology add-on payments for ZINPLAVA™ and consideration of the public comments we received in response to the FY 2018 IPPS/LTCH PPS proposed rule, we approved ZINPLAVA™ for new technology add-on payments for FY 2018 (82 FR 38119). With the new technology add-on payment application, the applicant estimated that the average Medicare beneficiary would require a dosage of 10 mg/kg of ZINPLAVA™ administered as an IV infusion over 60 minutes as a single dose. According to the applicant, the WAC for one dose is $3,800. Under § 412.88(a)(2), we limit new technology add-on payments to the lesser of 50 percent of the average cost of the technology or 50 percent of the costs in excess of the MS–DRG payment for the case. As a result, the maximum new technology add-on payment amount for a case involving the use of ZINPLAVA™ is $1,900.

With regard to the newness criterion for ZINPLAVA™, we considered the beginning of the newness period to commence on February 10, 2017. Because the 3-year anniversary date of the entry of ZINPLAVA™ onto the U.S. market (February 10, 2020) will occur after FY 2019, we are proposing to continue new technology add-on payments for this technology for FY 2019. We are proposing that the maximum payment for a case involving ZINPLAVA™ would remain at $1,900 for FY 2019. We are inviting public comments on our proposal to continue new technology add-on payments for ZINPLAVA™ for FY 2019.

5. FY 2019 Applications for New Technology Add-On Payments

We received 15 applications for new technology add-on payments for FY 2019. In accordance with the regulations under § 412.87(c), applicants for new technology add-on payments must have FDA approval or clearance by July 1 of the year prior to the beginning of the fiscal year that the application is being considered. A discussion of the 15 applications is presented below.

a. KYMRIAH™ (Tisagenlecleucel) and YESCARTA™ (Axicabtagene Ciloleucel)

Two manufacturers, Novartis Pharmaceuticals Corporation and Kite Pharma, Inc. submitted separate applications for new technology add-on payments for FY 2019 for KYMRIAH™ (tisagenlecleucel) and YESCARTA™ (axicabtagene ciloleucel), respectively. Both of these technologies are CD–19-directed T-cell immunotherapies used for the purposes of treating patients with aggressive variants of non-Hodgkin lymphoma (NHL). We note that KYMRIAH™ was approved by the FDA on August 30, 2017, for use in the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse, which is a different indication and patient population than the new indication and targeted patient population for which the applicant submitted a request for approval of new technology add-on payments for FY 2019. Specifically, and as summarized in the following table, the new indication for which Novartis Pharmaceuticals Corporation is requesting approval for new technology add-on payments for KYMRIAH™ is as an autologous T-cell immune therapy indicated for use in the treatment of patients with relapsed/refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL) not eligible for autologous stem cell transplant (ASCT). As of the time of the development of this proposed rule, Novartis Pharmaceuticals Corporation has been granted a Breakthrough Therapy designation by the FDA, and is awaiting FDA approval for the use of KYMRIAH™ under this new indication. We also note that Kite Pharma, Inc. previously submitted an application for approval for new technology add-on payments for FY 2018 for KTE–C19 for use as an autologous T-cell immune therapy in the treatment of adult patients with R/R aggressive B-cell NHL who are ineligible for ASCT. However, Kite Pharma, Inc. withdrew its application for KTE–C19 prior to publication of the FY 2018 IPPS/LTCH PPS final rule. Kite Pharma, Inc. has resubmitted an application for approval for new technology add-on payments for FY 2019 for KTE–C19 under a new name, YESCARTA™, for the same indication. Kite Pharma, Inc. received FDA approval for this original indication and treatment use of YESCARTA™ on October 18, 2017. (We refer readers to the following table for a comparison of the indications and FDA approvals for KYMRIAH™ and YESCARTA™.)

COMPARISON OF INDICATION AND FDA APPROVAL FOR KYMRIAH™ AND YESCARTA™

FY 2019 applicant technology name	Description of indication for which new technology add-on payments are being requested	FDA approval status
KYMRIAH™ (Novartis Pharmaceuticals Corporation).	KYMRIAH™: Autologous T-cell immune therapy indicated for use in the treatment of patients with relapsed/refractory (R/R) Diffuse Large B Cell Lymphoma (DLBCL) not eligible for autologous stem cell transplant (ASCT).	Breakthrough Therapy designation granted by FDA; FDA approval pending.
YESCARTA™ (Kite Pharma, Inc.).	YESCARTA™: Autologous T-cell immune therapy indicated for use in the treatment of adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.	FDA approval received 10/18/2017.

Technology approved for other indications	Description of other indication	FDA approval of other indication
KYMRIAH™ (Novartis Pharmaceuticals Corporation).	KYMRIAH™: CD–19-directed T-cell immunotherapy indicated for the use in the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.	FDA approval received 8/30/2017.
YESCARTA™ (Kite Pharma, Inc.).	None	N/A.

We note that procedures involving the KYMRIAH™ and YESCARTA™ therapies are both reported using the following ICD–10–PCS procedure codes: XW033C3 (Introduction of engineered autologous chimeric antigen receptor t-cell immunotherapy into peripheral vein, percutaneous approach, new technology group 3); and XW043C3 (Introduction of engineered autologous chimeric antigen receptor t-cell immunotherapy into central vein, percutaneous approach, new technology group 3). We further note that, in section II.F.2.d. of the preamble of this proposed rule, we are proposing to assign cases reporting these ICD–10–PCS procedure codes to Pre-MDC MS–DRG 016 (Autologous Bone Marrow Transplant with CC/MCC) for FY 2019. We refer readers to section II.F.2.d. of this proposed rule for a complete discussion of the proposed assignment of cases reporting these procedure codes to Pre-MDC MS–DRG 016, which also includes a proposal to revise the title of MS–DRG 016 to reflect the proposed assignments.

According to the applicants, patients with NHL represent a heterogeneous group of B-cell malignancies with varying patterns of behavior and response to treatment. B-cell NHL can be classified as either an aggressive, or indolent disease, with aggressive variants including DLBCL; primary mediastinal large B-cell lymphoma (PMBCL); and transformed follicular lymphoma (TFL). Within diagnoses of NHL, DLBCL is the most common subtype of NHL, accounting for approximately 30 percent of patients who have been diagnosed with NHL, and survival without treatment is measured in months.[4] Despite improved therapies, only 50 to 70 percent of newly diagnosed patients are cured by standard first-line therapy alone. Furthermore, R/R disease continues to carry a poor prognosis because only 50 percent of patients are eligible for autologous stem cell transplantation (ASCT) due to advanced age, poor functional status, comorbidities, inadequate social support for recovery after ASCT, and provider or patient choice.[5] [6] [7] [8] Of the roughly 50 percent of patients that are eligible for ASCT, nearly 50 percent fail to respond to prerequisite salvage chemotherapy and cannot undergo ASCT.[9] [10] [11] [12] Second-line chemotherapy regimens studied to date include rituximab, ifosfamide, carboplatin and etoposide (R–ICE), and rituximab, dexamethasone, cytarabine, and cisplatin (R–DHAP), followed by consolidative high-dose therapy (HDT)/ASCT. Both regimens offer similar overall response rates (ORR) of 51 percent with 1 in 4 patients achieving long-term complete response (CR) at the expense of increased toxicity.[13] Second-line treatment with dexamethasone, high-dose cytarabine, and cisplatin (DHAP) is considered a standard chemotherapy regimen, but is associated with substantial treatment-related toxicity.[14] For patients who experience disease progression during or after primary treatment, the combination of HDT/ASCT remains the only curative option.[15] According to the applicants,

[4] Chaganti, S., et al., ''Guidelines for the management of diffuse large B-cell lymphoma,'' BJH Guideline, 2016. Available at: *www.bit.do/bsh-guidelines.*

[5] Matasar, M., et al., ''Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma,'' *Blood,* 25 July 2013, vol. 122, No 4.

[6] Hitz, F., et al., ''Outcome of patients with chemotherapy refractory and early progressive diffuse large B cell lymphoma after R–CHOP treatment,'' *Blood* (American Society of Hematology (ASH) annual meeting abstracts, poster session), 2010, pp. 116 (abstract #1751).

[7] Telio, D., et al., ''Salvage chemotherapy and autologous stem cell transplant in primary refractory diffuse large B-cell lymphoma: outcomes and prognostic factors,'' *Leukemia & Lymphoma,* 2012, vol. 53(5), pp. 836–41.

[8] Moskowitz, C.H., et al., ''Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma,'' *Journal of Clinical Oncology,* 1999, vol. 17(12), pp. 3776–85.

[9] Crump, M., et al., ''Outcomes in patients with refractory aggressive diffuse large B-cell lymphoma (DLBCL): results from the international scholar-1 study,'' Abstract and poster presented at Pan Pacific Lymphoma Conference (PPLC), July 2016.

[10] Gisselbrecht, C., et al., ''Results from SCHOLAR–1: outcomes in patients with refractory aggressive diffuse large B-cell lymphoma (DLBCL),'' Oral presentation at European Hematology Association conference, July 2016.

[11] Iams, W., Reddy, N., ''Consolidative autologous hematopoietic stem-cell transplantation in first remission for non-Hodgkin lymphoma: current indications and future perspective,'' *Ther Adv Hematol,* 2014, vol. 5(5), pp. 153–67.

[12] Kantoff, P.W., et al., ''Sipuleucel-T immunotherapy for castration-resistant prostate cancer,'' *N Engl J Med,* 2010, vol. 363, pp. 411–422.

[13] Rovira, J., Valera, A., Colomo, L., et al., ''Prognosis of patients with diffuse large B cell lymphoma not reaching complete response or relapsing after frontline chemotherapy or immunochemotherapy,'' *Ann Hematol,* 2015, vol. 94(5), pp. 803–812.

[14] Swerdlow, S.H., Campo, E., Pileri, S.A., et al., ''The 2016 revision of the World Health Organization classification of lymphoid neoplasms,'' *Blood,* 2016, vol. 127(20), pp. 2375–2390.

[15] Koristka, S., Cartellieri, M., Arndt, C., et al., ''Tregs activated by bispecific antibodies: killers or

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given the modest response to second-line therapy and/or HDT/ASCT, the population of patients with the highest unmet need is those with chemorefractory disease, which include DLBCL, PMBCL, and TFL. These patients are defined as either progressive disease (PD) as best response to chemotherapy, stable disease as best response following greater than or equal to 4 cycles of first-line or 2 cycles of later-line therapy, or relapse within less than or equal to 12 months of ASCT.[16] Based on these definitions and available data from a multi-center retrospective study (SCHOLAR–1), chemorefractory disease treated with current and historical standards of care has consistently poor outcomes with an ORR of 26 percent and median overall survival (OS) of 6.3 months.[17]

According to Novartis Pharmaceuticals Corporation, upon FDA approval of the additional indication, KYMRIAH™ will also be used for the treatment of patients with R/R DLBCL who are not eligible for ASCT. Novartis Pharmaceuticals Corporation describes KYMRIAH™ as a CD-19-directed genetically modified autologous T-cell immunotherapy which utilizes peripheral blood T-cells, which have been reprogrammed with a transgene encoding, a chimeric antigen receptor (CAR), to identify and eliminate CD–19-expressing malignant and normal cells. Upon binding to CD–19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of KYMRIAH™ cells. The transduced T-cells expand in vivo to engage and eliminate CD–19-expressing cells and may exhibit immunological endurance to help support long-lasting remission.[18] [19] [20] [21] According to the applicant, no other agent currently used in the treatment of patients with R/R DLBCL employs gene modified autologous cells to target and eliminate malignant cells.

According to Kite Pharma, Inc., YESCARTA™ is indicated for the use in the treatment of adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma. The applicant for YESCARTA™ described the technology as a CD–19-directed genetically modified autologous T-cell immunotherapy that binds to CD–19-expressing cancer cells and normal B-cells. These normal B-cells are considered to be non-essential tissue, as they are not required for patient survival. According to the applicant, studies demonstrated that following anti-CD–19 CAR T-cell engagement with CD–19-expressing target cells, the CD–28 and CD–3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to the elimination of CD–19-expressing tumor cells.

Both applicants expressed that their technology is the first treatment of its kind for the targeted adult population. In addition, both applicants asserted that their technology is new and does not use a substantially similar mechanism of action or involve the same treatment indication as any other currently FDA-approved technology. We note that, at the time each applicant submitted its new technology add-on payment application, neither technology had received FDA approval for the indication for which the applicant requested approval for the new technology add-on payment; KYMRIAH™ has been granted Breakthrough Therapy designation for the use in the treatment of patients for the additional indication that is the subject of its new technology add-on application and, as of the time of the development of this proposed rule, is awaiting FDA approval. However, as stated earlier, YESCARTA™ received FDA approval for use in the treatment of patients and the indication stated in its application on October 18, 2017, after each applicant submitted its new technology add-on payment application.

As noted, according to both applicants, KYMRIAH™ and YESCARTA™ are the first CAR T immunotherapies of their kind. Because potential cases representing patients who may be eligible for treatment using KYMRIAH™ and YESCARTA™ would group to the same MS–DRGs (because the same ICD–10–CM diagnosis codes and ICD–10–PCS procedures codes are used to report treatment using either KYMRIAH™ or YESCARTA™), and we believe that these technologies are intended to treat the same or similar disease in the same or similar patient population, and are purposed to achieve the same therapeutic outcome using the same or similar mechanism of action, we disagree with the applicants and believe these two technologies are substantially similar to each other and that it is appropriate to evaluate both technologies as one application for new technology add-on payments under the IPPS. For these reasons, and as discussed further below, we would intend to make one determination regarding approval for new technology add-on payments that would apply to both applications, and in accordance with our policy, would use the earliest market availability date submitted as the beginning of the newness period for both KYMRIAH™ and YESCARTA™. We are inviting public comments on whether KYMRIAH™ and YESCARTA™ are substantially similar.

With respect to the newness criterion, as previously stated, YESCARTA™ received FDA approval on October 18, 2017. According to the applicant, prior to FDA approval, YESCARTA™ had been available in the U.S. only on an investigational basis under an investigational new drug (IND) application. For the same IND patient population, and until commercial availability, YESCARTA™ was available under an Expanded Access Program (EAP) which started on May 17, 2017. The applicant stated that it did not recover any costs associated with the EAP. According to the applicant, the first commercial shipment of YESCARTA™ was received by a certified treatment center on November 22, 2017. As previously indicated, KYMRIAH™ is not currently approved by the FDA for use in the treatment of patients with R/R DLBCL that are not eligible for ASCT; the technology has been granted Breakthrough Therapy designation by the FDA. The applicant anticipates receipt of FDA approval to occur in the second quarter of 2018. We believe that, in accordance with our policy, if these technologies are substantially similar to each other, it is appropriate to use the earliest market availability date submitted as the beginning of the newness period for both technologies. Therefore, based on

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suppressors?,'' *OncoImmunology,* 2015, vol. (3):e994441, DOI: 10.4161/2162402X.2014.994441.

[16] Crump, M., Neelapu, S.S., Farooq, U., et al., ''Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR–1 study,'' *Blood,* Published online: August 3, 2017, doi: 10.1182/blood-2017-03-69620.

[17] Ibid.

[18] KYMRIAH™ [prescribing information], East Hanover, NJ: Novartis Pharmaceuticals Corp, 2017.

[19] Kalos, M., Levine, B.L., Porter, D.L., et al., ''T-cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia,'' *Sci Transl Med*, 2011, vol. 3(95), pp, 95ra73.

[20] FDA Briefing Document. Available at: *https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf.*

[21] Wang, X., Riviere, I., ''Clinical manufacturing of CART cells: foundation of a promising therapy,'' *Mol Ther Oncolytics,* 2016, vol. 3, pp. 16015.

our policy, with regard to both technologies, if the technologies are approved for new technology add-on payments, we believe that the beginning of the newness period would be November 22, 2017.

We previously stated that, because we believe these two technologies are substantially similar to each other, we believe it is appropriate to evaluate both technologies as one application for new technology add-on payments under the IPPS. The applicants submitted separate cost and clinical data, and we reviewed and discuss each set of data separately. However, we would intend to make one determination regarding new technology add-on payments that would apply to both applications. We believe that this is consistent with our policy statements in the past regarding substantial similarity. Specifically, we have noted that approval of new technology add-on payments would extend to all technologies that are substantially similar (66 FR 46915), and we believe that continuing our current practice of extending new technology add-on payments without a further application from the manufacturer of the competing product, or a specific finding on cost and clinical improvement if we make a finding of substantial similarity among two products is the better policy because we avoid—

- Creating manufacturer-specific codes for substantially similar products;
- Requiring different manufacturers of substantially similar products to submit separate new technology add-on payment applications;
- Having to compare the merits of competing technologies on the basis of substantial clinical improvement; and
- Bestowing an advantage to the first applicant representing a particular new technology to receive approval (70 FR 47351).

If substantially similar technologies are submitted for review in different (and subsequent) years, rather than the same year, we would evaluate and make a determination on the first application and apply that same determination to the second application. However, because the technologies have been submitted for review in the same year, and because we believe they are substantially similar to each other, we believe that it is appropriate to consider both sets of cost data and clinical data in making a determination, and we do not believe that it is possible to choose one set of data over another set of data in an objective manner. We are inviting public comments on our proposal to evaluate KYMRIAH™ and YESCARTA™ as one application for new technology add-on payments under the IPPS.

As stated earlier, we believe that KYMRIAH™ and YESCARTA™ are substantially similar to each other for purposes of analyzing these two applications as one application. We also need to determine whether KYMRIAH™ and YESCARTA™ are substantially similar to existing technologies prior to their approval by the FDA and their release onto the U.S. market. As discussed earlier, if a technology meets all three of the substantial similarity criteria, it would be considered substantially similar to an existing technology and would not be considered ''new'' for purposes of new technology add-on payments.

With respect to the first criterion, whether a product uses the same or a similar mechanism of action to achieve a therapeutic outcome, the applicant for KYMRIAH™ asserted that its unique design, which utilizes features that were not previously included in traditional cytotoxic chemotherapeutic or immunotherapeutic agents, constitutes a new mechanism of action. The deployment mechanism allows for identification and elimination of CD–19-expressing malignant and non-malignant cells, as well as possible immunological endurance to help support long-lasting remission.[22] [23] [24] [25] The applicant provided context regarding how KYMRIAH™'s unique design contributes to a new mechanism of action by explaining that peripheral blood T-cells, which have been reprogrammed with a transgene encoding, a CAR, identify and eliminate CD-19-expressing malignant and nonmalignant cells. As explained by the applicant, upon binding to CD–19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of KYMRIAH™ cells.[26] [27] [28] According to the applicant, transduced T-cells expand in vivo to engage and eliminate CD–19-expressing cells and may exhibit immunological endurance to help support long-lasting remission.[29] [30] [31]

The applicant for YESCARTA™ stated that YESCARTA™ is the first engineered autologous cellular immunotherapy comprised of CAR T-cells that recognizes CD–19 express cancer cells and normal B-cells with efficacy in patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma as demonstrated in a multi-centered clinical trial. Therefore, the applicant believed that YESCARTA™'s mechanism of action is distinct and unique from any other cancer drug or biologic that is currently approved for use in the treatment of patients who have been diagnosed with aggressive B-cell NHL, namely single-agent or combination chemotherapy regimens. The applicant also pointed out that YESCARTA™ is the only available therapy that has been granted FDA approval for the treatment of adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, PMBCL, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

With respect to the second and third criteria, whether a product is assigned to the same or a different MS–DRG and whether the new use of the technology involves the treatment of the same or similar type of disease and the same or similar patient population, the applicant for KYMRIAH™ indicated that the technology is used in the treatment of the same patient population, and potential cases representing patients that may be eligible for treatment using KYMRIAH™ would be assigned to the same MS–DRGs as cases involving

[22] KYMRIAH [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.

[23] Kalos, M., Levine, B.L., Porter, D.L., et al., ''T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia,'' *Sci Transl Med,* 2011, vol. 3(95), pp. 95ra73.

[24] FDA Briefing Document. Available at: *https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf.*

[25] Maude, S.L., Frey, N., Shaw, P.A., et al., ''Chimeric antigen receptor T cells for sustained remissions in leukemia,'' *N Engl J Med,* 2014, vol. 371(16), pp. 1507–1517.

[26] KYMRIAH™ [prescribing information], East Hanover, NJ: Novartis Pharmaceuticals Corp, 2017.

[27] Kalos, M., Levine, B.L., Porter, D.L., et al., ''T-cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia,'' *Sci Transl Med,* 2011, 3(95), pp, 95ra73.

[28] FDA Briefing Document. Available at: *https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf.*

[29] Kalos, M., Levine, B.L., Porter, D.L., et al., ''T cells with chimeric antigen receptors have potent antitumor effects and can establish memory in patients with advanced leukemia,'' *Sci Transl Med,* 2011, vol. 3(95), pp. 95rs73.

[30] FDA Briefing Document. Available at: *https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf.*

[31] Maude, S.L., Frey, N., Shaw, P.A., et al., ''Chimeric antigen receptor T-cells for sustained remissions in leukemia,'' *N Engl J Med,* 2014, vol. 371(16), pp. 1507–1517.

patients with a DLBCL diagnosis. Potential cases representing patients that may be eligible for treatment using KYMRIAH™ map to 437 separate MS–DRGs, with the top 20 MS–DRGs covering approximately 68 percent of all patients who have been diagnosed with DLBCL. For patients with DLBCL and who have received chemotherapy during their hospital stay, the target population mapped to 8 separate MS–DRGs, with the top 2 MS–DRGs covering over 95 percent of this population: MS–DRGs 847 (Chemotherapy without Acute Leukemia as Secondary Diagnosis with CC), and 846 (Chemotherapy without Acute Leukemia as Secondary Diagnosis with MCC). The applicant for YESCARTA™ submitted findings that potential cases representing patients that may be eligible for treatment using YESCARTA™ span 15 unique MS–DRGs, 8 of which contain more than 10 cases. The most common MS–DRGs were: MS–DRGs 840 (Lymphoma and Non-Acute Leukemia with MCC), 841 (Lymphoma and Non-Acute Leukemia with CC), and 823 (Lymphoma and Non-Acute Leukemia with other O.R. Procedures with MCC). These 3 MS–DRGs accounted for 628 (76 percent) of the 827 cases. While the applicants for KYMRIAH™ and YESCARTA™ submitted different findings regarding the most common MS–DRGs to which potential cases representing patients who may be eligible for treatment involving their technology would map, we believe that, under the current MS–DRGs (FY 2018), potential cases representing patients who may be eligible for treatment involving either KYMRIAH™ or YESCARTA™ would map to the same MS–DRGs because the same ICD–10–CM diagnosis codes and ICD–10–PCS procedures codes would be used to report cases for patients who may be eligible for treatment involving KYMRIAH™ and YESCARTA™. Furthermore, as noted above, we are proposing that cases reporting these ICD–10–PCS procedure codes would be assigned to MS–DRG 016 for FY 2019. Therefore, under this proposal, for FY 2019, cases involving the utilization of KYMRIAH™ and YESCARTA™ would continue to map to the same MS–DRGs.

The applicant for YESCARTA™ also addressed the concern expressed by CMS in the FY 2018 IPPS/LTCH PPS proposed rule regarding Kite Pharma Inc.'s FY 2018 new technology add-on payment application for the KTE–C19 technology (82 FR 19888). At the time, CMS expressed concern that KTE–C19 may use the same or similar mechanism of action as the Bi-Specific T-Cell engagers (BiTE) technology. The applicant for YESCARTA™ explained that YESCARTA™ has a unique and distinct mechanism of action that is substantially different from BiTE's or any other drug or biologic currently assigned to any MS–DRG in the FY 2016 MedPAR Hospital Limited Data Set. In providing more detail regarding how YESCARTA™ is different from the BiTE technology, the applicant explained that the BiTE technology is not an engineered autologous T-cell immunotherapy derived from a patient's own T-cells. Instead, it is a bi-specific T-cell engager that recognizes CD–19 and CD–3 cancer cells. Unlike engineered T-cell therapy, BiTE does not have the ability to enhance the proliferative and cytolytic capacity of T-cells through ex-vivo engineering. Further, BiTE is approved for the treatment of patients who have been diagnosed with Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and is not approved for patients with relapsed or refractory large B-cell lymphoma, whereas YESCARTA™ is indicated for use in the treatment of adult patients with R/R aggressive B-cell NHL who are ineligible for ASCT.

The applicant for YESCARTA™ also indicated that its mechanism of action is not the same or similar to the mechanism of action used by KYMRIAH™'s currently available FDA-approved CD–19-directed genetically modified autologous T-cell immunotherapy indicated for use in the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.[32] The applicant for YESCARTA™ stated that the mechanism of action is different from KYMRIAH™'s FDA-approved therapy because the spacer, transmembrane and co-stimulatory domains of YESCARTA™ are different from those of KYMRIAH™. The applicant explained that YESCARTA™ is comprised of a CD–28 co-stimulatory domain and KYMRIAH™ has 4–1BB co-stimulatory domain. Further, the applicant stated the manufacturing processes of the two immunotherapies are also different, which may result in cell composition differences leading to possible efficacy and safety differences.

While the applicant for YESCARTA™ stated how its technology is different from KYMRIAH™, because both technologies are CD–19-directed T-cell immunotherapies used for the purpose of treating patients with aggressive variants of NHL, we believe that YESCARTA™ and KYMRIAH™ are substantially similar treatment options. Furthermore, we also are concerned that there may be an age overlap (18 to 25) between the two different patient populations for the currently approved KYMRIAH™ technology and YESCARTA™ technology. The currently approved KYMRIAH™ technology is indicated for use in the treatment of patients who are up to 25 years of age and YESCARTA™ technology is indicated for use in the treatment of adult patients.

As noted earlier, the applicant has asserted that YESCARTA™ is not substantially similar to KYMRIAH™. Under this scenario, if both YESCARTA™ and KYMRIAH™ meet all of the new technology add-on payment criteria and are approved for new technology add-on payments for FY 2019, for purposes of making the new technology add-on payment, because procedures utilizing either YESCARTA™ or KYMRIAH™ CAR T-cell therapy drugs are reported using the same ICD–10–PCS procedure codes, in order to accurately pay the new technology add-on payment to hospitals that perform procedures utilizing either technology, it may be necessary to use alternative coding mechanisms to make the new technology add-on payments. CMS is inviting comments on alternative coding mechanisms to make the new technology add-on payments, if necessary.

We are inviting public comments on whether KYMRIAH™ and YESCARTA™ are substantially similar to existing technologies and whether the technologies meet the newness criterion.

As we stated above, each applicant submitted separate analysis regarding the cost criterion for each of their products, and both applicants maintained that their product meets the cost criterion. We summarize each analysis below.

With regard to the cost criterion, the applicant for KYMRIAH™ searched the FY 2016 MedPAR claims data file to identify potential cases representing patients who may be eligible for treatment using KYMRIAH™. The applicant identified claims that reported an ICD–10–CM diagnosis code of: C83.30 (DLBCL, unspecified site); C83.31 (DLBCL, lymph nodes of head, face and neck); C83.32 (DLBCL, intrathoracic lymph nodes); C83.33 (DLBCL, intra-abdominal lymph nodes); C83.34 (DLBCL, lymph nodes of axilla and upper limb); C83.35 (DLBCL, lymph nodes of inquinal region and lower

[32] Food and Drug Administration. Available at: *www.accessdata.fda.gov/scripts/opdlisting/oopd/.*

limb); C83.36 (DLBCL, intrapelvic lymph nodes); C83.37 (DLBCL, spleen); C83.38 (DLBCL, lymph nodes of multiple sites); or C83.39 (DLBCL, extranodal and solid organ sites). The applicant also identified potential cases where patients received chemotherapy using two encounter codes, Z51.11 (Antineoplastic chemotherapy) and Z51.12 (Antineoplastic immunotherapy), in conjunction with DLBCL diagnosis codes.

Applying the parameters above, the applicant for KYMRIAH™ identified a total of 22,589 DLBCL potential cases that mapped to 437 MS–DRGs. The applicant chose the top 20 MS–DRGs which made up a total of 15,451 potential cases at 68 percent of total cases. Of the 22,589 total DLBCL potential cases, the applicant also provided a breakdown of DLBCL potential cases where chemotherapy was used, and DLBCL potential cases where chemotherapy was not used. Of the 6,501 DLBCL potential cases where chemotherapy was used, MS–DRGs 846 and 847 accounted for 6,181 (95 percent) of the 6,501 cases. Of the 16,088 DLBCL potential cases where chemotherapy was not used, the applicant chose the top 20 MS–DRGs which made up a total of 9,333 potential cases at 58 percent of total cases. The applicant believed the distribution of patients that may be eligible for treatment using KYMRIAH™ will include a wide variety of MS–DRGs. As such, the applicant conducted an analysis of three scenarios: Potential DLBCL cases, potential DLBCL cases with chemotherapy, and potential DLBCL cases without chemotherapy.

The applicant removed reported historic charges that would be avoided through the use of KYMRIAH™. Next, the applicant removed 50 percent of the chemotherapy pharmacy charges that would not be required for patients that may be eligible to receive treatment using KYMRIAH™. The applicant standardized the charges and then applied an inflation factor of 1.09357, which is the 2-year inflation factor in the FY 2018 IPPS/LTCH PPS final rule (82 FR 38527), to update the charges from FY 2016 to FY 2018. The applicant did not add charges for KYMRIAH™ to its analysis. However, the applicant provided a cost analysis related to the three categories of claims data it previously researched (that is, potential DLBCL cases, potential DLBCL cases with chemotherapy, and potential DLBCL cases without chemotherapy). The applicant's analysis showed the inflated average case-weighted standardized charge per case for potential DLBCL cases, potential DLBCL cases with chemotherapy, and potential DLBCL cases without chemotherapy was $63,271, $39,723, and $72,781, respectively. The average case-weighted threshold amount for potential DLBCL cases, potential DLBCL cases with chemotherapy, and potential DLBCL cases without chemotherapy was $58,278, $48,190, and $62,355 respectively. While the inflated average case-weighted standardized charge per case ($39,723) is lower than the average case-weighted threshold amount ($48,190) for potential DLBCL cases with chemotherapy, the applicant expects the cost of KYMRIAH™ to be higher than the new technology add-on payment threshold amount for all three cohorts. Therefore, the applicant maintained that it meets the cost criterion.

We note that, as discussed earlier, in section II.F.2.d. of the preamble of this proposed rule, we are proposing to assign the ICD–10–PCS procedure codes that describe procedures involving the utilization of these CAR T-cell therapy drugs and cases representing patients receiving treatment involving CAR T-cell therapy procedures to Pre-MDC MS–DRG 016 for FY 2019. Therefore, in addition to the analysis above, we compared the inflated average case-weighted standardized charge per case from all three cohorts above to the average case-weighted threshold amount for MS–DRG 016. The average case-weighted threshold amount for MS–DRG 016 from Table 10 in the FY 2018 IPPS/LTCH PPS final rule is $161,058. Although the inflated average case-weighted standardized charge per case for all three cohorts ($63,271, $39,723, and $72,781) is lower than the average case-weighted threshold amount for MS–DRG 016, similar to above, the applicant expects the cost of KYMRIAH™ to be higher than the new technology add-on payment threshold amount for MS–DRG 016. Therefore, it appears that KYMRIAH™ would meet the cost criterion under this scenario as well.

We appreciate the applicant's analysis. However, we note that the applicant did not provide information regarding which specific historic charges were removed in conducting its cost analysis. Nonetheless, we believe that even if historic charges were identified and removed, the applicant would meet the cost criterion because, as indicated, the applicant expects the cost of KYMRIAH™ to be higher than the new technology add-on payment threshold amounts listed earlier.

We are inviting public comments on whether KYMRIAH™ meets the cost criterion.

With regard to the cost criterion in reference to YESCARTA™, the applicant conducted the following analysis. The applicant examined FY 2016 MedPAR claims data restricted to patients discharged in FY 2016. The applicant included potential cases reporting an ICD–10 diagnosis code of C83.38. Noting that only MS–DRGs 820 (Lymphoma and Leukemia with Major O.R. Procedure with MCC), 821 (Lymphoma and Leukemia with Major O.R. Procedure with CC), 823 and 824 (Lymphoma and Non-Acute Leukemia with Other O.R. Procedure with MCC, with CC, respectively), 825 (Lymphoma and Non Acute Leukemia with Other O.R Procedure without CC/MCC), and 840, 841 and 842 (Lymphoma and Non-Acute Leukemia with MCC, with CC and without CC/MCC, respectively) consisted of 10 or more cases, the applicant limited its analysis to these 8 MS–DRGs. The applicant identified 827 potential cases across these MS–DRGs. The average case-weighted unstandardized charge per case was $126,978. The applicant standardized charges using FY 2016 standardization factors and applied an inflation factor of 1.09357 from the FY 2018 IPPS/LTCH PPS final rule (82 FR 38527). The applicant for YESCARTA™ did not include the cost of its technology in its analysis.

Included in the average case-weighted standardized charge per case were charges for the current treatment components. Therefore, the applicant for YESCARTA™ removed 20 percent of radiology charges to account for chemotherapy, and calculated the adjusted average case-weighted standardized charge per case by subtracting these charges from the standardized charge per case. Based on the distribution of potential cases within the eight MS–DRGs, the applicant case-weighted the final inflated average case-weighted standardized charge per case. This resulted in an inflated average case-weighted standardized charge per case of $118,575. Using the FY 2018 IPPS Table 10 thresholds, the average case-weighted threshold amount was $72,858. Even without considering the cost of its technology, the applicant maintained that because the inflated average case-weighted standardized charge per case exceeds the average case-weighted threshold amount, the technology meets the cost criterion.

We note that, as discussed earlier, in section II.F.2.d. of the preamble of this proposed rule, we are proposing to assign the ICD–10–PCS procedure codes that describe procedures involving the utilization of these CAR T-cell therapy

drugs and cases representing patients receiving treatment involving CAR T-cell therapy procedures to Pre-MDC MS–DRG 016 for FY 2019. Therefore, in addition to the analysis above, we compared the inflated average case-weighted standardized charge per case ($118,575) to the average case-weighted threshold amount for MS–DRG 016. The average case-weighted threshold amount for MS–DRG 016 from Table 10 in the FY 2018 IPPS/LTCH PPS final rule is $161,058. Although the inflated average case-weighted standardized charge per case is lower than the average case-weighted threshold amount for MS–DRG 016, the applicant expects the cost of YESCARTA™ to be higher than the new technology add-on payment threshold amount for MS–DRG 016. Therefore, it appears that YESCARTA™ would meet the cost criterion under this scenario as well.

We are inviting public comments on whether YESCARTA™ technology meets the cost criterion.

With regard to substantial clinical improvement for KYMRIAH™, the applicant asserted that several aspects of the treatment represent a substantial clinical improvement over existing technologies. The applicant believed that KYMRIAH™ allows access for a treatment option for those patients who are unable to receive standard of care treatment. The applicant stated in its application that there are no currently FDA-approved treatment options for patients with R/R DLBCL who are ineligible for or who have failed ASCT. Additionally, the applicant maintained that KYMRIAH™ significantly improves clinical outcomes, including ORR, CR, OS, and durability of response, and allows for a manageable safety profile. The applicant asserted that, when compared to the historical control data (SCHOLAR–1) and the currently available treatment options, it is clear that KYMRIAH™ significantly improves clinical outcomes for patients with R/R DLBCL who are not eligible for ASCT. The applicant conveyed that, given that the patient population has no other available treatment options and an expected very short lifespan without therapy, there are no randomized controlled trials of the use of KYMRIAH™ in patients with R/R DLBCL and, therefore, efficacy assessments must be made in comparison to historical control data. The SCHOLAR–1 study is the most comprehensive evaluation of the outcome of patients with refractory DLBCL. SCHOLAR–1 includes patients from two large randomized controlled trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and two clinical databases (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence).[33]

The applicant for KYMRIAH™ conveyed that the PARMA study established high-dose chemotherapy and ASCT as the standard treatment for patients with R/R DLBCL.[34] However, according to the applicant, many patients with R/R DLBCL are ineligible for ASCT because of medical frailty. Patients who are ineligible for ASCT because of medical frailty would also be adversely affected by high-dose chemotherapy regimens.[35] Lowering the toxicity of chemotherapy regimens becomes the only treatment option, leaving patients with little potential for therapeutic outcomes. According to the applicant, the lack of efficacy of these aforementioned salvage regimens was demonstrated in nine studies evaluating combined chemotherapeutic regimens in patients who were either refractory to first-line or first salvage. Chemotherapy response rates ranged from 0 percent to 23 percent with OS less than 10 months in all studies.[36] For patients who do not respond to combined therapy regimens, the National Comprehensive Cancer Network (NCCN) offers only clinical trials or palliative care as therapeutic options.[37]

According to the applicant for KYMRIAH™, the immunomodulatory agent Lenalidomide was only able to show an ORR of 30 percent, a CR rate of 8 percent, and a 4.6-month median duration of response.[38] M-tor inhibitors such as Everolimus and Temserolimus have been studied as single agents, or in combination with Rituximab, as have newer monoclonal antibodies Dacetuzumab, Ofatumomab and Obinutuzumab. However, none induced a CR rate higher than 20 percent or showed a median duration of response longer than 1 year.[39]

According to the applicant, although controversial, allogeneic stem cell transplantation (allo-SCT) has been proposed for patients who have been diagnosed with R/R disease. It is hypothesized that the malignant cell will be less able to escape the immune targeting of allogenic T-cells—known as the graft-vs-lymphoma effect.[40] [41] The use of allo-SCT is limited in patients who are not eligible for ASCT because of the high rate of morbidity and mortality. This medically frail population is generally excluded from participation. The population most impacted by this is the elderly, who are often excluded based on age alone. In seven studies evaluating allo-SCT in patients with R/R DLBCL, the median age at transplant was 43 years old to 52 years old, considerably lower than the median age of patients with DLBCL of 64 years old. Only two studies included any patients over 66 years old. In these studies, allo-SCT provided OS rates ranging from 18 percent to 52 percent at 3 to 5 years, but was accompanied by treatment-related mortality rates ranging from 23 percent to 56 percent.[42] According to the applicant, this toxicity and efficacy profile of allo-SCT substantially limits its use, especially in patients 65 years old and older. Given the high unmet medical need, the applicant maintained that KYMRIAH™ represents a substantial clinical improvement by offering a treatment option for a patient population unresponsive to, or ineligible for, currently available treatments.

To express how KYMRIAH™ has improved clinical outcomes, including ORR, CR rate, OS, and durability of response, the applicant referenced clinical trials in which KYMRIAH™ was tested. Study 1 was a single-arm, open-label, multi-site, global Phase II study to determine the safety and efficacy of tisagenlecleucel in patients

[33] Crump, M., Neelapu, S.S., Farooq, U., et al., ''Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR–1 study,'' *Blood,* Published online: August 3, 2017, doi: 10.1182/blood-2017-03-769620.

[34] Philip, T., Guglielmi, C., Hagenbeek, A., et al., ''Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma,'' *N Engl J Med,* 1995, vol. 333(23), pp. 1540–1545.

[35] Friedberg, J.W., ''Relapsed/refractory diffuse large B-cell lymphoma,'' *Hematology AM Soc Hematol Educ Program,* 2011, vol. (1), pp. 498–505.

[36] Crump, M., Neelapu, S.S., Farooq, U., et al., ''Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR–1 study,'' *Blood,* Published online: August 3, 2017, doi: 10.1182/blood-2017-03-769620.

[37] National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN GuidelinesR), ''B-cell lymphomas: Diffuse large b-cell lymphoma and follicular lymphoma (Version 3.2017),'' May 25, 2017. Available at: *https://www.nccn.org/professionals/physician_gls/pdf/b-cell_blocks.pdf.*

[38] Klyuchnikov, E., Bacher, U., Kroll, T., et al., ''Allogeneic hematopoietic cell transplantation for diffuse large B cell lymphoma: who, when and how?,'' *Bone Marrow Transplant,* 2014, vol. 49(1), pp. 1–7.

[39] Ibid.

[40] Ibid.

[41] Maude, S.L., Teachey, D.T., Porter, D.L., Grupp, S.A., ''CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia,'' *Blood,* 2015, vol. 125(26), pp. 4017–4023.

[42] Klyuchnikov, E., Bacher, U., Kroll, T., et al., ''Allogeneic hematopoietic cell transplantation for diffuse large B cell lymphoma: who, when and how?,'' *Bone Marrow Transplant,* 2014, vol. 49(1), pp. 1–7.

with R/R DLBCL (CCTL019C2201/CT02445248/'JULIET' study).[43] [44] [45] Key inclusion criteria included patients who were 18 years old and older, patients with refractory to at least two lines of chemotherapy and either relapsed post ASCT or who were ineligible for ASCT, measurable disease at the time of infusion, and adequate organ and bone marrow function. The study was conducted in three phases. In the screening phase patient eligibility was assessed and patient cells collected for product manufacture. Patients were also able to receive bridging, cytotoxic chemotherapy during this time. In the pre-treatment phase patients underwent a restaging of disease followed by lymphodepleting chemotherapy with fludarabine 25mg/m2 x3 and cyclophosphamide 250mg/m2/d x3 or bendamustine 90mg/m2/d x2 days. The treatment and follow-up phase began 2 to 14 days after lymphodepleting chemotherapy, when the patient received a single infusion of tisagenlecleucel with a target dose of $5x10^8$ CTL019 transduced viable cells. The primary objective was to assess the efficacy of tisagenlecleucel, as measured by the best overall response (BOR), which was defined as CR or partial response (PR). It was assessed on the Chesson 2007 response criteria amended by Novartis Pharmaceutical Corporation as confirmed by an Independent Review Committee (IRC). One hundred forty-seven patients were enrolled, and 99 of them were infused with tisagenlecleucel. Forty-three patients discontinued prior to infusion (9 due to inability to manufacture and 34 due to patient-related issues).[46] The median age of treated patients was 56 years old with a range of 24 to 75; 20 percent were older than 65 years old. Patients had received 2 to 7 prior lines of therapy, with 60 percent receiving 3 or more therapies, and 51 percent having previously undergone ASCT. A primary analysis was performed on 81 patients infused and followed for more than or at least 3 months. In this primary analysis, the BOR was 53 percent; the study met its primary objective based on statistical analysis (that is, testing whether BOR was greater than 20 percent, a clinically relevant threshold chosen based on the response to chemotherapy in a patient with R/R DLBCL). Forty-three percent (43 percent) of evaluated patients reached a CR, and 14 percent reached a PR. ORR evaluated at 3 months was 38 percent with a distribution of 32 percent CR and 6 percent PR. All patients in CR at 3 months continued to be in CR. ORR was similar across subgroups including 64.7 percent response in patients who were older than 65 years old, 61.1 percent response in patients with Grade III/IV disease at the time of enrollment, 58.3 percent response in patients with Activated B-cell, 52.4 percent response in patients with Germinal Center B-cell subtype, and 60 percent response in patients with double and triple hit lymphoma. Durability of response was assessed based on relapse free survival (RFS), which was estimated at 74 percent at 6 months.

The applicant for KYMRIAH™ reported that Study 2 was a supportive Phase IIa single institution study of adults who were diagnosed with advanced CD19+ NHL conducted at the University of Pennsylvania.[47] [48] Tisagenlecleucel cells were produced at the University of Pennsylvania using the same genetic construct and a similar manufacturing technique as employed in Study 1. Key inclusion criteria included patients who were at least 18 years old, patients with CD19+ lymphoma with no available curative options, and measurable disease at the time of enrollment. Tisagenlecleucel was delivered in a single infusion 1 to 4 days after restaging and lymphodepleting chemotherapy. The median tisagenlecleucel cell dose was 5.0×108 transduced cells. The study enrolled 38 patients; of these, 21 were diagnosed with DLBCL and 13 received treatment involving KYMRIAH™. Patients ranged in age from 25 to 77 years old, and had a median of 4 prior therapies. Thirty-seven percent had undergone ASCT and 63 percent were diagnosed with Grade III/IV disease. ORR at 3 months was 54 percent. Progression free survival was 43 percent at a median follow-up of 11.7 months. Safety and efficacy results are similar to those of the multi-center study.

The applicant for KYMRIAH™ reported that Study 3 was a supportive, patient-level meta-analysis of historical outcomes in patients who were diagnosed with refractory DLBCL (SCHOLAR–1).[49] This study included a pooled data analysis of two Phase III clinical trials (Lymphoma Academic Research Organization-CORAL and Canadian Cancer Trials Group LY.12) and two observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). Refractory disease was defined as progressive disease or stable disease as best response to chemotherapy (received more than or at least 4 cycles of first-line therapy or 2 cycles of later-line therapy, respectively) or relapse in less than or at 12 months post-ASCT. Of 861 abstracted records, 636 were included based on these criteria. All patients from each data source who met criteria for diagnosis of refractory DLBCL, including TFL and PMBCL, who went on to receive subsequent therapy were considered for analysis. Patients who were diagnosed with TFL and PMBCL were included because they are histologically similar and clinically treated as large cell lymphoma. Response rates were similar across the 4 datasets, ranging from 20 percent to 31 percent, with a pooled response rate of 26 percent. CR rates ranged from 2 percent to 15 percent, with a pooled CR rate of 7 percent. Subgroup analyses including patients with primary refractory, refractory to second or later-line therapy, and relapse in less than 12 months post-ASCT revealed response rates similar to the pooled analysis, with worst outcomes in the primary refractory group (20 percent). OS from the commencement of therapy was 6.3 months and was similar across subgroup analyses. Achieving a CR after last salvage chemotherapy predicted a longer OS of 14.9 months compared to 4.6 months in nonresponders. Patients who had not undergone ASCT had an OS of 5.1

[43] Data on file, Oncology clinical trial protocol CCTL019C2201: ''A Phase II, single-arm, multi-center trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large Bcell lymphoma (DLBCL),'' Novartis Pharmaceutical Corp, 2015.

[44] Schuster, S.J., Bishop, M.R., Tam, C., et al., ''Global trial of the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma: an interim analysis,'' Presented at: 22nd Congress of the European Hematology Association, June 22–25, 2017, Madrid, Spain.

[45] *ClinicalTrials.gov*, ''Study of efficacy and safety of CTL019 in adult DLBCL patients (JULIET).'' Available at: *https://clinicaltrials.gov/ct2/show/NCT02445248.*

[46] Schuster, S.J., Bishop, M.R., Tam, C., et al., ''Global trial of the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma: an interim analysis,'' Presented at: 22nd Congress of the European Hematology Association, June 22–25, 2017, Madrid, Spain.

[47] *ClinicalTrials.gov*, ''Phase IIa study of redirected autologous T-cells engineered to contain anti-CD19 attached to TCRz and 4-signaling domains in patients with chemotherapy relapsed or refractory CD19+ lymphomas,'' Available at: *https://clinicaltrials.gov/ct2/show/NCT02030834.*

[48] Schuster, S.J., Svoboda, J., Nasta, S.D., et al., ''Sustained remissions following chimeric antigen receptor modified T-cells directed against CD–19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas,'' Presented at: 57th Annual Meeting of the American Society of Hematology, December 6, 2015, Orlando, FL.

[49] Crump, M., Neelapu, S.S., Farooq, U., et al., ''Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR–1 study,'' *Blood,* Published online: August 3, 2017, doi: 10.1182/blood-2017-03-769620.

months with a 2 year OS rate of 11 percent.

The applicant asserted that KYMRIAH™ provides a manageable safety profile when treatment is performed by trained medical personnel and, as opposed to ASCT, KYMRIAH™ mitigates the need for high-dose chemotherapy to induce response prior to infusion. Adverse events were most common in the 8 weeks following infusion and were manageable by a trained staff. Cytokine Relapse Syndrome (CRS) occurred in 58 percent of patients with 23 percent having Grade III or IV events as graded on the University of Pennsylvania grading system.[50] [51] Median time to onset of CRS was 3 days and median duration was 7 days with a range of 2 to 30 days. Twenty-four percent of the patients required ICU admission. CRS was managed with supportive care in most patients. However, 16 percent required anti-cytokine therapy including tocilizumab (15 percent) and corticosteroids (11 percent). Other adverse events of special interest include infection in 34 percent (20 percent Grade III or IV) of patients, cytopenias not resolved by day 28 in 36 percent (27 percent Grade III or IV) of patients, neurologic events in 21 percent (12 percent Grade III or IV) of patients, febrile neutropenia in 13 percent (13 percent Grade III or IV) of patients, and tumor lysis syndrome 1 percent (1 percent Grade III). No deaths were attributed to tisagenlecleucel including no fatal cases of CRS or neurologic events. No cerebral edema was observed.[52] Study 2 safety results were consistent to those of Study 1.[53]

After reviewing the studies provided by the applicant, we are concerned that the applicant included patients who were diagnosed with TFL and PMBCL in the SCHOLAR–1 data results for their comparison analysis, possibly skewing results. Furthermore, the discontinue rate of the JULIET trial was high. Of 147 patients enrolled for infusion involving KYMRIAH™, 43 discontinued prior to infusion (9 discontinued due to inability to manufacture, and 34 discontinued due to patient-related issues). Finally, the rate of patients who experienced a diagnosis of CRS was high, 58 percent.[54]

The applicant for YESCARTA™ stated that YESCARTA™ represents a substantial clinical improvement over existing technologies when used in the treatment of patients with aggressive B-cell NHL. The applicant asserted that YESCARTA™ can benefit the patient population with the highest unmet need, patients with R/R disease after failure of first-line or second-line therapy, and patients who have failed or who are ineligible for ASCT. These patients, otherwise, have adverse outcomes as demonstrated by historical control data.

Regarding clinical data for YESCARTA™, the applicant stated that historical control data was the only ethical and feasible comparison information for these patients with chemorefractory, aggressive NHL who have no other available treatment options and who are expected to have a very short lifespan without therapy. According to the applicant, based on meta-analysis of outcomes in patients with chemorefractory DLBCL, there are no curative options for patients with aggressive B-cell NHL, regardless of refractory subgroup, line of therapy, and disease stage with their median OS being 6.6 months.[55]

In the applicant's FY 2018 new technology add-on payment application for the KTE–C19 technology, which was discussed in the FY 2018 IPPS/LTCH PPS proposed rule (82 FR 19889), the applicant cited ongoing clinical trials. The applicant provided updated data related to these ongoing clinical trials as part of its FY 2019 application for YESCARTA™.[56] [57] [58] The updated analysis of the pivotal Study 1 (ZUMA–1, KTE–C19–101), Phase I and II occurred when patients had been followed for 12 months after infusion of YESCARTA™. Study 1 is a Phase I–II multi-center, open-label study evaluating the safety and efficacy of the use of YESCARTA™ in patients with aggressive refractory NHL. The trial consists of two distinct phases designed as Phase I (n=7) and Phase II (n=101). Phase II is a multi-cohort open-label study evaluating the efficacy of YESCARTA™.[59] The applicant noted that, as of the analysis cutoff date for the interim analysis, the results of Study 1 demonstrated rapid and substantial improvement in objective, or ORR. After 6 and 12 months, the ORR was 82 and 83 percent, respectively. Consistent response rates were observed in both Study 1, Cohort 1 (DLBCL; n=77) and Cohort 2 (PMBCL or TFL; n=24) and across covariates including disease stage, age, IPI scores, CD–19 status, and refractory disease subset. In the updated analysis, results were consistent across age groups. In this analysis, 39 percent of patients younger than 65 years old were in ongoing response, and 50 percent of patients at least 65 years old or older were in ongoing response. Similarly, the survival rate at 12 months was 57 percent among patients younger than 65 years old and 71 percent among patients at least 65 years old or older versus historical control of 26 percent. The applicant further stated that evidence of substantial clinical improvement regarding the efficacy of YESCARTA™ for the treatment of patients with chemorefractory, aggressive B-cell NHL is supported by the CR of YESCARTA™ in Study 1, Phase II (54 percent) versus the historical control (7 percent).[60] [61] [62] [63]

[50] *ClinicalTrials.gov,* ''Phase IIa study of redirected autologous T-cells engineered to contain anti-CD19 attached to TCRz and 4-signaling domains in patients with chemotherapy relapsed or refractory CD19+ lymphomas.'' Available at: *https://clinicaltrials.gov/ct2/show/NCT02030834.*

[51] Schuster, S.J., Svoboda, J., Nasta, S.D., et al., ''Sustained remissions following chimeric antigen receptor modified T-cells directed against CD–19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas,'' Presented at: 57th Annual Meeting of the American Society of Hematology, December 6, 2015, Orlando, FL.

[52] Schuster, S.J., Bishop, M.R., Tam, C., et al., ''Global trial of the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma: an interim analysis,'' Presented at: 22nd Congress of the European Hematology Association, June 22–25, 2017, Madrid, Spain.

[53] Ibid.

[54] Schuster, S.J., Bishop, M.R., Tam, C., et al., ''Global trial of the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma: an interim analysis,'' Presented at: 22nd Congress of the European Hematology Association, June 22–25, 2017, Madrid, Spain.

[55] Seshardi, T., et al., ''Salvage therapy for relapsed/refractory diffuse large B-cell lymphoma,'' *Biol Blood Marrow Transplant,* 2008 Mar, vol. 14(3), pp. 259–67.

[56] Locke, F.L., et al., ''Ongoing complete remissions in Phase 1 of ZUMA–1: A phase I–II multicenter study evaluating the safety and efficacy of KTE–C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B-cell non-Hodgkin lymphoma (NHL),'' Oral presentation (abstract 10480) presented at European Society for Medical Oncology (ESMO), October 2016.

[57] Locke, F.L., et al., ''Primary results from ZUMA–1: A pivotal trial of axicabtagene ciloretroleucel (axi-cel; KTE–C19) in patients with refractory aggressive non-Hodgkins lymphoma (NHL),'' Oral presentation, American Association of Cancer Research (AACR).

[58] Locke, F.L., et al., ''Phase I results of ZUMA–1: A multicenter study of KTE–C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma,'' *Mol Ther,* vol. 25, No 1, January 2017.

[59] Neelapu, S.S., Locke, F.L., et al., 2016, ''KTE–C19 (anti-CD19 CAR T cells) induces complete remissions in patients with refractory diffuse large B-cell lymphoma (DLBCL): Results from the pivotal Phase II ZUMA–1,'' Abstract presented at American Society of Hematology (ASH) 58th Annual Meeting, December 2016.

[60] Locke, F.L., et al., ''Ongoing complete remissions in Phase I of ZUMA–1: a phase I–II multicenter study evaluating the safety and efficacy of KTE–C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B-cell non-Hodgkin lymphoma (NHL),'' Oral presentation (abstract 10480) presented at European Society for Medical Oncology (ESMO), October 2016.

[61] Locke, F.L., et al., ''Primary results from ZUMA–1: a pivotal trial of axicabtagene ciloretroleucel (axi-cel; KTE–C19) in patients with

The applicant noted that CR rates were observed in both Study 1, Cohort 1. The applicant reported that, in the updated analysis, results were in ongoing response (46 percent of patients at least 65 years old or older were in ongoing response). Similarly, the survival rate at 12 months was 57 percent among patients younger than 65 years old and 71 percent among patients at least 65 years old or older.[64] [65] [66] [67] The applicant also provided the following tables to depict data to support substantial clinical improvement (we refer readers to the two tables below).

OVERALL RESPONSE RATES ACROSS ALL YESCARTA™ STUDIES VS. SCHOLAR–1

%	Study 1, Phase I n=7	Study 1, Phase II n=101	Scholar-1 n=529
Overall Response Rate (%)	71	83	26
Month 6 (%)	43	41	.....
Ongoing with >15 Months of follow-up (%)	43	42	.....
Ongoing with >18 Months of follow-up (%)	43	Follow-up ongoing	.....

RESULTS FOR YESCARTA™ STUDY 1, PHASE II: COMPLETE RESPONSE

	Study 1, Phase II n=101
Complete Response (%) (95 Percent Confidence Interval)	54 (44,64).
Duration of Response, median (range in months)	not reached.
Ongoing Responses, CR (%); Median 8.7 months follow-up; median overall survival has not been reached	39.
Ongoing Responses, CR (%); Median 15.3 months follow-up; median overall survival has not been reached	40.

According to the applicant, the 6-month and 12-month survival rates (95 percent CI) for patients enrolled in the SCHOLAR–1 study were 53 percent (49 percent, 57 percent) and 28 percent (25 percent, 32 percent).[68] In contrast, the 6-month and 12–month survival rates (95 percent CI) in the Study 1 updated analysis were 79 percent (70 percent, 86 percent) and 60 percent (50 percent, 69 percent).[69] [70] [71]

The applicant also cited safety results from the pivotal Study 1, Phase II. According to the applicant, the clinical trial protocol stipulated that patients were infused with YESCARTA™ in the hospital inpatient setting and were monitored in the inpatient setting for at least 7 days for early identification and treatment involving YESCARTA™-related toxicities, which primarily included CRS diagnoses and neurotoxicities. The applicant noted that the interim analysis showed the length of stay following infusion of YESCARTA™ was a median of 15 days. Ninety-three percent of patients experienced CRS diagnoses, 13 percent of whom experienced Grade III or higher (severe, life threatening or fatal) CRS diagnoses. The median time to onset of CRS diagnosis was 2 days (range 1 to 12 days) and the median time to resolution was 8 days. Ninety-eight percent of patients recovered from CRS diagnosis. Neurologic events occurred in 64 percent of patients, 28 percent of whom experienced Grade III or higher (severe or life threatening) events. The median time to onset of neurologic events was 5 days (range 1 to 17 days). The median time to resolution was 17 days. Nearly all patients recovered from neurologic events. The medications most often used to treat these complications included growth factors, blood products, anti-infectives, steroids, tocilizumab, and vasopressors. Two patients died from YESCARTA™-related adverse events (hemophagocytic lymphohistiocytosis and cardiac arrest in the hospital setting as a result of CRS diagnoses). According to the applicant, there were no clinically important differences in adverse event rates across age groups (younger than 65 years old; 65 years old or older), including CRS diagnoses and neurotoxicity.[72] [73]

The applicant for YESCARTA™ provided information regarding a safety expansion cohort, Study 1 Phase II Safety Expansion Cohort 3 that was created and carried out in 2017.

refractory aggressive non-Hodgkins lymphoma (NHL),'' Oral presentation, American Association of Cancer Research (AACR).

[62] Locke, F.L., et al., ''Phase I results of ZUMA–1: A multicenter study of KTE–C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma,'' *Mol Ther,* vol. 25, No 1, January 2017.

[63] Crump, et al., 2017, ''Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR–1 study,'' *Blood,* vol. 0, 2017, pp. blood-2017-03-769620v1.

[64] Locke, F.L., et al., ''Ongoing complete remissions in Phase I of ZUMA–1: A phase I–II multicenter study evaluating the safety and efficacy of KTE–C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B-cell non-Hodgkin lymphoma (NHL),'' Oral presentation (abstract 10480) presented at European Society for Medical Oncology (ESMO), October 2016.

[65] Locke, F.L., et al., ''Primary results from ZUMA–1: A pivotal trial of axicabtagene ciloretroleucel (axi-cel; KTE–C19) in patients with refractory aggressive non-Hodgkins lymphoma (NHL),'' Oral presentation, American Association of Cancer Research (AACR).

[66] Locke, F.L., et al., ''Phase I results of ZUMA–1: A multicenter study of KTE–C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma,'' *Mol Ther,* vol. 25, No 1, January 2017.

[67] Crump, et al., ''Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR–1 study,'' *Blood,* vol. 0, 2017, pp. blood-2017-03-769620v1.

[68] Crump, et al., ''Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR–1 study,'' *Blood,* vol. 0, 2017, pp. blood-2017-03-769620v1.

[69] Locke, F.L., et al., ''Ongoing complete remissions in Phase I of ZUMA–1: a phase I–II multicenter study evaluating the safety and efficacy of KTE–C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B-cell non-Hodgkin lymphoma (NHL),'' Oral presentation (abstract 10480) presented at European Society for Medical Oncology (ESMO), October 2016.

[70] Locke, F.L., et al., ''Primary results from ZUMA–1: a pivotal trial of axicabtagene ciloretroleucel (axi-cel; KTE–C19) in patients with refractory aggressive non-Hodgkins lymphoma (NHL),'' Oral presentation, American Association of Cancer Research (AACR).

[71] Locke, F.L., et al., ''Phase I results of ZUMA–1: a multicenter study of KTE–C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma,'' *Mol Ther,* vol. 25, No 1, January 2017.

[72] Locke, F.L., et al., ''Ongoing complete remissions in Phase I of ZUMA–1: a phase I–II multicenter study evaluating the safety and efficacy of KTE–C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B-cell non-Hodgkin lymphoma (NHL),'' Oral presentation (abstract 10480) presented at European Society for Medical Oncology (ESMO), October 2016.

[73] Locke, F.L., et al., ''Primary results from ZUMA–1: a pivotal trial of axicabtagene ciloretroleucel (axi-cel; KTE–C19) in patients with refractory aggressive non-Hodgkins lymphoma (NHL),'' Oral presentation, American Association of Cancer Research (AACR).

According to the applicant, this Safety Expansion Cohort investigated measures to mitigate the incidence and/or severity of anti-CD–19 CAR T therapy and evaluated an adverse event mitigation strategy by prophylactically using levetiracetam (Keppra), an anticonvulsant, and tocilizumab, an IL–6 receptor inhibitor. Of the 30 patients treated, 2 patients experienced Grade III CRS diagnoses; 1 of the 2 patients recovered. In late April 2017, the other patient also experienced multi-organ failure and a neurologic event that subsequently progressed to a fatal Grade V cerebral edema that was deemed related to YESCARTA™ treatment. This case of cerebral edema was observed in a 21 year-old male with refractory, rapidly progressive, symptomatic, stage IVB PMBCL. Analysis of the baseline serum and cerebrospinal fluid (CSF) obtained prior to any study treatment demonstrated high cytokine and chemokine levels. According to the applicant, this suggests a significant preexisting underlying inflammatory process, both systemically and within the central nervous system. Rapidly progressing disease, recent mediastinal XRT (external beam radiation therapy) and/or CMV (cytomegalovirus) reactivation may have contributed to the pre-existing state. There were no prior cases of cerebral edema in the 200 patients who have been treated with YESCARTA™ in the ZUMA clinical development program. The single patient event from the Study 1 Phase II Safety Expansion Cohort 3 was the first Grade V cerebral edema event.[74] [75]

After reviewing the information submitted by the applicant as part of its FY 2019 new technology add-on payment application for YESCARTA™, we are concerned that it does not appear to include patient mortality data that was included as part of the applicant's FY2018 new technology add-on payment application for the KTE–C19 technology. In that application, as discussed in the FY 2018 IPPS/LTCH PPS proposed rule (82 FR 19890), the applicant provided that by an earlier cutoff date for the interim analysis of Study 1, among all KTE–C19 treated patients, 12 patients in Study 1, Phase II, including 10 from Cohort 1, and 2 from Cohort 2, died. Eight of these deaths were due to disease progression. One patient had disease progression after receiving KTE–C19 treatment and subsequently had ASCT. After ASCT, the patient died due to sepsis. Two patients (3 percent) died due to KTE–C19-related adverse events (Grade V hemophagocytic lymphohistiocytosis event and Grade V anoxic brain injury), and one died due to an adverse event deemed unrelated to treatment involving KTE–C19 (Grade V pulmonary embolism), without disease progression. We believe it would be relevant to include this information because it is related to the same treatment that is the subject of the applicant's FY 2019 new technology add-on payment application.

We also are concerned that there are few published results showing any survival benefits from the use of this treatment. In addition, we are concerned with the limited number of patients (n=108) that were studied after infusion involving YESCARTA™ T-cell immunotherapy. Finally, we are concerned about the data related to the percentage of patients who experience complications or toxicities related to YESCARTA™ treatment. According to the applicant, of the patients who participated in YESCARTA™ clinical trials, 93 percent developed CRS diagnoses and 64 percent experienced neurological adverse events.

We are inviting public comments on whether KYMRIAH™ and YESCARTA™ meet the substantial clinical improvement criterion.

Finally, we believe that in the context of these pending new technology add-on payment applications, there may also be merit in the suggestions from the public to create a new MS–DRG for the assignment of procedures involving the utilization of CAR T-cell therapy drugs and cases representing patients who receive treatment involving CAR T-cell therapy as an alternative to our proposed MS–DRG assignment to MS–DRG 016 for FY 2019, or the suggestions to allow hospitals to utilize a CCR specific to procedures involving the utilization of KYMRIAH™ and YESCARTA™ CAR T-cell therapy drugs for FY 2019 as part of the determination of the cost of a case for purposes of calculating outlier payments for individual FY 2019 cases, new technology add-on payments, if approved, for individual FY 2019 cases, and payments to IPPS-excluded cancer hospitals beginning in FY 2019. If as discussed in section II.F.2.d. of the preamble of this proposed rule a new MS–DRG were to be created, then consistent with section 1886(d)(5)(K)(ix) of the Act there may no longer be a need for a new technology add-on payment under section 1886(d)(5)(K)(ii)(III) of the Act. With respect to an alternative considered for the use of a CCR specific to procedures involving the utilization of KYMRIAH™ and YESCARTA™ CAR T-cell therapy drugs for FY 2019 as part of the determination of the cost of a case for purposes of calculating outlier payments for individual FY 2019 cases, new technology add-on payments, if approved, for individual FY 2019 cases, and payments to IPPS-excluded cancer hospitals beginning in FY 2019, we refer readers to the discussion in section II.A.4.g.2. of the Addendum to this proposed rule.

We are inviting public comments regarding the most appropriate mechanism to provide payment to hospitals for new technologies such as CAR T-cell therapy drugs, including through the use of new technology add-on payments.

We also are inviting public comments on how these payment alternatives would affect access to care, as well as how they affect incentives to encourage lower drug prices, which is a high priority for this Administration. In addition, we are considering alternative approaches and authorities to encourage value-based care and lower drug prices. We solicit comments on how the payment methodology alternatives may intersect and affect future participation in any such alternative approaches.

We did not receive any written public comments in response to the New Technology Town Hall meeting notice published in the **Federal Register** regarding the application of KYMRIAH™ for new technology add-on payments for FY 2019.

Below we summarize and respond to a written public comment we received during the open comment period regarding YESCARTA™ in response to the New Technology Town Hall meeting notice published in the **Federal Register**.

Comment: The applicant commented that the use of YESCARTA™ as a treatment option has resulted in unprecedented and consistent treatment for patients with refractory large B-cell lymphoma who previously did not have a curative option. In addition, the applicant summarized the substantial clinical improvement differences between YESCARTA™ and the results of KYMRIAH™'s SCHOLAR–1 study. The applicant noted that, for the patients enrolled in the SCHOLAR–1 study, the median overall survival was 6 months and complete remission was

[74] Locke, F.L., et al., ''Ongoing complete remissions in Phase I of ZUMA–1: a phase I–II multicenter study evaluating the safety and efficacy of KTE–C19 (anti-CD19 CAR T cells) in patients with refractory aggressive B-cell non-Hodgkin lymphoma (NHL),'' Oral presentation (abstract 10480) presented at European Society for Medical Oncology (ESMO), October 2016.

[75] Locke, F.L., et al., ''Primary results from ZUMA–1: a pivotal trial of axicabtagene ciloretroleucel (aci-cel; KTE–C19) in patients with refractory aggressive non-Hodgkins lymphoma (NHL),'' Oral presentation, American Association of Cancer Research (AACR).

7 percent. Conversely, the applicant conveyed that, for the patients enrolled in YESCARTA™'s Study 1, at median 15.4 months follow-up, responses were ongoing in 42 percent of the patients and 40 percent of the patients were in complete remission.

Response: We appreciate the applicant's input. We will take these comments into consideration when deciding whether to approve new technology add-on payments for YESCARTA™ for FY 2019.

We note that the applicant also provided comments that were unrelated to the substantial clinical improvement criterion. As stated earlier, the purpose of the new technology town hall meeting is specifically to discuss the substantial clinical improvement criterion in regard to pending new technology add-on payment applications for FY 2019. Therefore, we are not summarizing these additional comments in this proposed rule. However, the applicant may resubmit its comments in response to proposals presented in this proposed rule.

b. VYXEOS™ (Cytarabine and Daunorubicin Liposome for Injection)

Jazz Pharmaceuticals, Inc. submitted an application for new technology add-on payments for the VYXEOS™ technology for FY 2019. (We note that Celator Pharmaceuticals, Inc. submitted an application for new technology add-on payments for VYXEOS™ for FY 2018. However, Celator Pharmaceuticals did not receive FDA approval by the July 1, 2017 deadline for applications for FY 2018.) VYXEOS™ was approved by FDA on August 3, 2017, for the treatment of adults with newly diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML–MRC).

AML is a type of cancer in which the bone marrow makes abnormal myeloblasts (immature bone marrow white blood cells), red blood cells, and platelets. If left untreated, AML progresses rapidly. Normally, the bone marrow makes blood stem cells that develop into mature blood cells over time. Stem cells have the potential to develop into many different cell types in the body. Stem cells can act as an internal repair system, dividing, essentially without limit, to replenish other cells. When a stem cell divides, each new cell has the potential to either remain a stem cell or become a specialized cell, such as a muscle cell, a red blood cell, or a brain cell, among others. A blood stem cell may become a myeloid stem cell or a lymphoid stem cell. Lymphoid stem cells become white blood cells. A myeloid stem cell becomes one of three types of mature blood cells: (1) Red blood cells that carry oxygen and other substances to body tissues; (2) white blood cells that fight infection; or (3) platelets that form blood clots and help to control bleeding. In patients diagnosed with AML, the myeloid stem cells usually become a type of myeloblast. The myeloblasts in patients diagnosed with AML are abnormal and do not become healthy white blood cells. Sometimes in patients diagnosed with AML, too many stem cells become abnormal red blood cells or platelets. These abnormal cells are called leukemia cells or blasts.

AML is defined by the World Health Organization (WHO) as greater than 20 percent blasts in the bone marrow or blood. AML can also be diagnosed if the blasts are found to have a chromosome change that occurs only in a specific type of AML diagnosis, even if the blast percentage does not reach 20 percent. Leukemia cells can build up in the bone marrow and blood, resulting in less room for healthy white blood cells, red blood cells, and platelets. When this occurs, infection, anemia, or increased risk for bleeding may result. Leukemia cells can spread outside the blood to other parts of the body, including the central nervous system (CNS), skin, and gums.

Treatment of AML diagnoses usually consists of two phases; remission induction and post-remission therapy. Phase one, remission induction, is aimed at eliminating as many myeloblasts as possible. The most common used remission induction regimens for AML diagnoses are the ''7+3'' regimens using an antineoplastic and an anthracycline. Cytarabine and daunorubicin are two commonly used drugs for ''7+3'' remission induction therapy. Cytarabine is continuously administered intravenously over the course of 7 days, while daunorubicin is intermittently administered intravenously for the first 3 days. The ''7+3'' regimen typically achieves a 70 to 80 percent complete remission (CR) rate in most patients under 60 years of age.

High rates of CR are not generally seen in older patients for a number of reasons, such as different leukemia biology, much higher incidence of adverse cytogenetic abnormalities, higher rate of multidrug resistant leukemic cells, and comparatively lower patient performance status (the standard criteria for measuring how the disease impacts a patient's daily living abilities). Intensive induction therapy has worse outcomes in this patient population.[76] The applicant asserted that many older adults diagnosed with AML have a poor performance status[77] at presentation and multiple medical comorbidities that make the use of intensive induction therapy quite difficult or contraindicated altogether. Moreover, the CR rates of poor-risk patients diagnosed with AML are substantially lower in patients over 60 years of age; owing to a higher proportion of secondary AML, disease developing in the setting of a prior myeloid disorder, or prior cytotoxic chemotherapy. Therefore, less than half of older adults diagnosed with AML achieve CR with combination induction regimens.[78]

According to the applicant, the combination of cytarabine and an anthracycline, either as ''7+3'' regimens or as part of a different regimen incorporating other cytotoxic agents, may be used as so-called ''salvage'' induction therapy in the treatment of adults diagnosed with AML who experience relapse in an attempt to achieve CR. According to the applicant, while CR rates of success vary widely depending on underlying disease biology and host factors, there is a lower success rate overall in achievement of CR with ''7+3'' regimens compared to VYXEOS™ therapy. According to the applicant, ''7+3'' regimens produce a CR rate of approximately 50 percent in younger adult patients who have relapsed, but were in CR for at least 1 year.[79]

VYXEOS™ is a nano-scale liposomal formulation containing a fixed combination of cytarabine and daunorubicin in a 5:1 molar ratio. This formulation was developed by the applicant using a proprietary system known as CombiPlex. According to the applicant, CombiPlex addresses several fundamental shortcomings of conventional combination regimens, specifically the conventional ''7+3'' free drug dosing, as well as the challenges inherent in combination drug development, by identifying the most effective synergistic molar ratio of the

[76] Juliusson, G., Lazarevic, V., Horstedt, A.S., Hagberg, O., Hoglund, M., ''Acute myeloid leukemia in the real world: why population-based registries are needed'', *Blood,* 2012 Apr 26; vol. 119(17), pp. 3890–9.

[77] Stone, R.M., et al., (2004), ''Acute myeloid leukemia. Hematology'', Am Soc Hematol Educ Program, 2004, pp. 98–117.

[78] Appelbaum, F.R., Gundacker, H., Head, D.R., ''Age and acute myeloid leukemia'', *Blood* 2006, vol. 107, pp. 3481–3485.

[79] Kantarjian, H., Rayandi, F., O'Brien, S., et al., ''Intensive chemotherapy does not benefit most older patients (age 70 years and older) with acute myeloid leukemia,'' *Blood,* 2010, vol. 116(22), pp. 4422.