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Novartis Kymriah® demonstrates consistent efficacy and safety outcomes in US patients when used in real-world setting

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- - Efficacy in DLBCL confirmed results seen in the pivotal trial despite treatment of a broader population, including older and more heavily pretreated patients1-3
- - Fewer known CAR-T cell therapy adverse events for patients with DLBCL, specifically rates of high-grade cytokine release syndrome (4%) and neurologic events (5%), were observed compared with the pivotal clinical trials1-3
- - In children and young adults with ALL, efficacy outcomes were similar and safety outcomes appear to be more favorable compared to the pivotal trial4
- - Understanding the Kymriah safety profile, and increased experience with administration in real-world practice supports use in the outpatient setting

EAST HANOVER, N.J., Dec. 9, 2019 /PRNewswire/ -- Novartis today announced results from two analyses of real-world experience with Kymriah® (tisagenlecleucel), the only CAR-T cell therapy approved in two distinct indications. These analyses are from a readout of a 15-year post-marketing study that add to and complement the rigor of the Kymriah pivotal trials with evidence of the Kymriah real-world experience in expanded groups of patients. When Kymriah was used in the real-world setting, efficacy and safety were consistent when compared to the pivotal trials, including the 24-month analysis of JULIET in adults with r/r diffuse large B cell lymphoma (DLBCL) and ELIANA in children and young adults with r/r B-cell acute lymphoblastic leukemia (ALL)[1-6]. The real-world experience data were presented at the 61st American Society of Hematology (ASH) annual meeting.

"With increased experience supplemented by real world data, physicians like myself have a better understanding of Kymriah and its safety profile," said lead author of this real-world experience analysis, Samantha Jaglowski, MD, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James). "This along with the current practice of supportive care for CAR-T therapy provides the ability to routinely use this therapy in the hospital outpatient setting, which can reduce financial burden on patients and hospitals alike[1,7]."

Real-world experience with Kymriah in adults with r/r DLBCL

Efficacy
Efficacy outcomes for patients who received Kymriah in the real-world setting were similar to those demonstrated in JULIET. In this analysis of 80 patients with r/r DLBCL for whom three or more months of post-infusion outcomes were available, the overall response rate (ORR) was 58% including 40% who achieved a complete response (CR). Median follow-up was 4.5 months[1]. In the 24-month analysis of the JULIET trial, ORR was 52% and CR was 38% (N=115) [3].

Safety
The anticipation and management of adverse events of CAR-T cell therapy have been crucial to successful administration of this innovative and relatively new type of therapy. In this analysis of real-world experience with Kymriah (safety set, N=83), the rate of grade 3 or higher cytokine release syndrome (CRS) and neurologic events were approximately 4% and 5%, respectively, as compared to 23% and 11% in the JULIET clinical trial (safety set, N=115), suggesting safety outcomes appear more favorable. The real-world analysis used the grading scales ASTCT for CRS and ICANs for neurologic events, whereas the JULIET trial used the Penn Grading Scale for CRS and MedDRA SMQ for neurologic events[1,3].

Further, for patients who had CRS, tocilizumab and corticosteroids were administered in 20% and 4% of patients, respectively, in the real-world setting, and in 27% and 19% of patients, respectively, in the JULIET trial[8]. Some patients in the real-world setting received tocilizumab earlier than in the clinical trial experience, indicating earlier use of supportive care may mitigate rates of high-grade CRS[9]. A total of 14 DLBCL patients died after treatment, all due to disease progression, however no deaths were attributed to toxicities from Kymriah[1].

Patient and product characteristics
More patients in the real-word analysis had a worse performance status, and on average, these patients were older and had received more lines of therapy than those treated in the JULIET trial[1-3].

Cell viability is one of many product release specifications for Kymriah. The commercial specification for the viability specification of Kymriah in the United States is set at greater than or equal to 80%. For all other markets where Kymriah is approved, the cell viability specification is greater than or equal to 70%. In this US real-world analysis, 29 of the 102 patients with evaluable data received product that was below 80% cell viability. Efficacy and safety for patients receiving product with cell viability below the commercial specification was the same as those receiving commercial Kymriah[1].

These data on the use of Kymriah in r/r DLBCL in the real-world setting will be presented in an oral session at the ASH annual meeting (Abstract # 766; Monday, December 9, 3:30 PM EST).

"As pioneers in bringing CAR-T cell therapy to patients, our dedication to reimagining how CAR-T cell therapy can impact patients in the future remains steadfast," said Susanne Schaffert, PhD, President, Novartis Oncology. "Our efforts include gathering and sharing real-world evidence, expanding and improving our manufacturing capacity and technology and going broader and deeper in our clinical research with Kymriah and other CAR-T cell therapies."

Real-world experience with Kymriah in children and young adults with r/r ALL
Efficacy outcomes were similar and safety outcomes appear to be more favorable in the real world setting compared to the ELIANA pivotal trial[4-6]. Among 146 children and young adult patients with r/r ALL treated in the real world setting for whom three or more months of post-infusion outcomes were available, CR was 85% as compared to 82% in the ELIANA trial (n=79). Median follow-up in the real-world analysis was 6 months. In this analysis (safety set, N=154), the rate of grade 3 or higher CRS and neurologic events were 14% and 8%, respectively, as compared to 48% and 13% in the ELIANA clinical trial. The real-world analysis used the grading scales ASTCT for CRS and ICANs for neurologic events, whereas the ELIANA trial used the Penn Grading Scale for CRS and MedDRA SMQ for neurologic events[4-6].

"It is exciting to see how oncologists are using Kymriah and how patients are responding to it in routine clinical practice," said Stephan A. Grupp, MD, PhD, Director of the Cancer Immunotherapy Program and Section Chief of Cell Therapy and Transplant at Children's Hospital of Philadelphia, and a Professor of Pediatrics in the Perelman School of Medicine at the University of Pennsylvania. "We are seeing broader efficacy data that replicate what we saw in the pivotal trial, and the collection of these data is ensuring that we are getting a clear view of adverse events when administering Kymriah."

These data on the use of Kymriah in r/r pediatric ALL in the real-world setting will be presented in a poster presentation at the ASH annual meeting (Abstract #2619; Sunday, December 8, 6:00 – 8:00 PM EST).

The collection of this real-world experience data was made possible by a collaboration between the CIBMTR® (Center for International Blood and Marrow Transplant Research – the research collaboration between the National Marrow Donor Program®/Be The Match® and the Medical College of Wisconsin) and Novartis, developed to capture long-term

follow-up of recipients of Kymriah who agree to participate in the registry. For patients whose cell viability was below 80%, product is provided through an established EAP program and long-term follow-up is captured through the CIBMTR. Globally, 90% patients who have been prescribed Kymriah have received the final manufactured product, either commercially, or when out of commercial specification.

Kymriah® (tisagenlecleucel, formerly CTL019) US Important Safety information
Kymriah may cause side effects that are severe or life-threatening, such as Cytokine Release Syndrome (CRS) or Neurological Toxicities. Patients with CRS may experience symptoms including difficulty breathing, fever (100.4°F/38°C or higher), chills/shaking chills, severe nausea, vomiting and diarrhea, severe muscle or joint pain, very low blood pressure, or dizziness/lightheadedness. Patients may be admitted to the hospital for CRS and treated with other medications.

Patients with neurological toxicities may experience symptoms such as altered or decreased consciousness, headaches, delirium, confusion, agitation, anxiety, seizures, difficulty speaking and understanding, or loss of balance. Patients should be advised to call their healthcare provider or get emergency help right away if they experience any of these signs and symptoms of CRS or neurological toxicities.

Because of the risk of CRS and neurological toxicities, Kymriah is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Kymriah REMS.

Serious allergic reactions, including anaphylaxis, may occur after Kymriah infusion. Kymriah can increase the risk of life-threatening infections that may lead to death. Patients should be advised to tell their healthcare provider right away if they develop fever, chills, or any signs or symptoms of an infection.

Patients may experience prolonged low blood cell counts (cytopenia), where one or more types of blood cells (red blood cells, white blood cells, or platelets) are decreased. The patient's healthcare provider will do blood tests to check all of their blood cell counts after treatment with Kymriah. Patients should be advised to tell their healthcare provider right away if they get a fever, are feeling tired, or have bruising or bleeding.

Patients may experience hypogammaglobulinemia, a condition in which the level of immunoglobulins (antibodies) in the blood is low and the risk of infection is increased. It is expected that patients may develop hypogammaglobulinemia with Kymriah, and may need to receive immunoglobulin replacement for an indefinite amount of time following treatment with Kymriah. Patients should tell their healthcare provider about their treatment with Kymriah before receiving a live virus vaccine.

After treatment with Kymriah, patients will be monitored lifelong by their healthcare provider, as they may develop secondary cancers or recurrence of their cancer.

Patients should not drive, operate heavy machinery, or do other dangerous activities for eight weeks after receiving Kymriah because the treatment can cause temporary memory and coordination problems, including sleepiness, confusion, weakness, dizziness, and seizures.

Some of the most common side effects of Kymriah are difficulty breathing, fever (100.4°F/38°C or higher), chills/shaking chills, confusion, severe nausea, vomiting and diarrhea, severe muscle or joint pain, very low blood pressure, dizziness/lightheadedness, and headache. However, these are not all of the possible side effects of Kymriah. Patients should talk to their healthcare provider for medical advice about side effects.

Prior to a female patient starting treatment with Kymriah, their healthcare provider may do a pregnancy test. There is no information available for Kymriah use in pregnant or breast-feeding women. Therefore, Kymriah is not recommended for women who are pregnant or breast feeding. Patients should talk to their healthcare provider about birth control and pregnancy.

Patients should tell their healthcare provider about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

After receiving Kymriah, patients should be advised that some commercial HIV tests may cause a false-positive test result. Patients should also be advised not to donate blood, organs, or tissues and cells for transplantation after receiving Kymriah.

Please see the full Prescribing Information for Kymriah, including Boxed WARNING, and Medication Guide at www.Kymriah.com

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9. Novartis Data on file.

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