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Novartis JULIET trial of Kymriah demonstrates more than one-year durability of responses in adults with relapsed or refractory DLBCL

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- Overall response rate was 52% and median duration of response was not reached at a median follow-up of 14 months, signifying responses were durable (1)
- Patients had a 65% chance of being relapse-free one year after onset of response (1)
- With eight months of additional follow-up, response rates remained consistent with previous reports and the safety profile was maintained with no emergence of new safety signals

EAST HANOVER, N.J., June 16, 2018 /PRNewswire/ -- Novartis today announced 14-month results from the pivotal JULIET clinical trial showing ongoing durable responses are achievable with Kymriah® (tisagenlecleucel) when administered to adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL). The overall response rate (ORR) was 52% (95% confidence interval [CI], 41% - 62%), among 93 evaluable patients who were followed for at least 3 months or discontinued earlier[1]. A complete response (CR) was achieved in 40% of patients and 12% achieved a partial response (PR). Of the patients in CR at month 3, 83% remained in CR at month 12, and the median duration of response was not reached, indicating sustainability of response. These data will be presented in an oral presentation at the 23rd Annual Congress of the European Hematology Association (EHA) (Abstract # S799; Saturday, June 16, 11:30AM CEST)[1].

"Advanced aggressive lymphoma patients who once faced a poor prognosis now have the possibility of sustained remission after a single course of therapy – a previously unimaginable and revolutionary breakthrough," said the lead author of the updated JULIET analysis Peter Borchmann, MD, Department of Internal Medicine, University Hospital of Cologne, Germany. "With 14 months of data from JULIET, we are seeing that Kymriah may continue to redefine outcomes for patients with relapsed or refractory DLBCL."

In the JULIET study, the relapse-free probability at 12 months after a patient's first response (n=48) was 65% (95% CI, 49%-78%). In fact, 54% (13/24) of patients who had achieved a PR converted to CR, including two patients between months 9 and 12. Median overall survival (OS) was not reached for patients in CR (95% CI, 17.9-NE). The OS rate at 12 months was 49% and median OS was 11.7 months among all infused patients (n=111) (95% CI, 6.6-NE). The median time from infusion to data cutoff was 14 months with a maximum time from infusion of 23 months. At the time of data cutoff, no patients in response following treatment with Kymriah proceeded to stem cell transplant[1].

"These results from JULIET continue to show Kymriah delivers strong efficacy with durable responses, and a predictable and consistent safety profile more than a year after infused in patients with advanced DLBCL," said Samit Hirawat, MD, Head, Novartis Oncology Global Drug Development. "Novartis is committed to bringing this important and innovative treatment option to more patients around the world."

Within eight weeks of infusion with Kymriah, Grade 3/4 cytokine release syndrome (CRS), as defined by the Penn Grading Scale – a rigorous scale for grading CRS –, was reported in 22% of patients (14% grade 3; 8% grade 4). Fifteen percent of patients received tocilizumab for treatment of CRS, including only 3% of patients with Grade 2 CRS and 50% of patients with Grade 3 CRS. CRS is a known complication of CAR-T therapy that may occur when the engineered cells become activated in the patient's body. CRS was managed globally using prior site education on implementation of the CRS treatment algorithm. No deaths due to cerebral edema were reported[1].

In this analysis, 12% of patients had grade 3/4 neurologic adverse events, which were managed with supportive care. Grade 3/4 cytopenias lasting more than 28 days, grade 3/4 infections and grade 3/4 febrile neutropenia occurred in 32%, 20% and 15% of patients, respectively[1].

"When we continued follow-up with DLBCL patients in the global JULIET study, we were extremely pleased that response rates were maintained a year or more after infusion with Kymriah, which was consistent with the durable responses seen in the pilot studies conducted at Penn," said Stephen J. Schuster, MD, the Robert and Margarita Louis-Dreyfus Professor in Chronic Lymphocytic Leukemia and Lymphoma Clinical Care and Research in Penn's Perelman School of Medicine and director of the Lymphoma Program at the Abramson Cancer Center. "We look forward to continuing to follow these patients who we hope will remain in remission from their disease."

Analyses to better characterize and predict severe CRS and neurologic events, including relationships with baseline clinical and laboratory parameters, dose and cellular kinetics will also be presented.

Fifty patients discontinued before infusion and the majority did so due to rapid progression of their disease or deterioration in their clinical status reflecting the acute and progressive nature of r/r DLBCL. Twelve out of 165 (7.3%) enrolled patients could not be infused due to inability to manufacture an adequate dose of CAR-T cells.

In May 2018, the US Food and Drug Administration (FDA) approved Kymriah for the treatment of adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma based on data from the JULIET study. Kymriah is not approved for the treatment of patients with primary central nervous system lymphoma. The European Medicines Agency (EMA) is evaluating the Marketing Authorization Application (MAA) for Kymriah for the treatment of children and young adults with r/r B-cell acute lymphoblastic leukemia (ALL) and for adult patients with r/r DLBCL.

About the JULIET Trial

JULIET is the first multi-center global registration study for Kymriah in adult patients with r/r DLBCL. JULIET, led by researchers at the University of Pennsylvania, is the largest and only globally conducted study examining a CAR-T cell therapy in DLBCL, enrolling patients from 27 sites in 10 countries across the US, Canada, Australia, Japan and Europe, including Austria, France, Germany, Italy, Norway and the Netherlands. In 2012, Novartis and Penn entered into a global collaboration to further research, develop and commercialize CAR-T cell therapies, including Kymriah, for the investigational treatment of cancers.

About DLBCL

DLBCL is the most common form of non-Hodgkin lymphoma, a cancer of the lymphatic system, accounting for up to 40% of all NHL cases globally[2]. An estimated 27,650 new cases of DLBCL were diagnosed in the US in 2016[3]. The crude incidence of DLBCL in Europe per year is 3.8 cases per 100,000 people, and incidence increases with age and varies considerably across Europe[4]. Roughly one-third of patients with DLBCL relapse after receiving first-line treatment[4]. Out of those patients diagnosed with DLBCL, about 10% have refractory disease and about 75% of patients who relapse or are refractory to treatment are ineligible for ASCT[2,5]. For patients who relapse or don't respond to initial therapy, there are limited treatment options that provide durable responses and median life expectancy is approximately six months[6].

About Kymriah Manufacturing

Kymriah is manufactured for each individual patient using their own cells at the Novartis Morris Plains, New Jersey facility. The reliable and integrated manufacturing and supply chain platform for Kymriah allows for an individualized treatment approach on a global scale. The process includes cryopreservation of a patient's harvested (or leukapheresed) cells, giving treating physicians and centers the flexibility to initiate therapy with Kymriah based on the individual patient's condition. Novartis has significant CAR-T manufacturing experience and has demonstrated a reproducible product. Novartis has manufactured CAR-T cells for more than 300 patients from 11 countries. Novartis continues to advance its CAR-T manufacturing expertise in Morris Plains.

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

Disclaimer

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "potential," "can," "will," "plan," "expect," "anticipate," "look forward," "believe," "committed," "investigational," "pipeline," "launch," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Kymriah, regarding our ability to scale and sustain commercial manufacturing for Kymriah, or regarding potential future revenues from Kymriah. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Kymriah will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Neither can there be any guarantee that Novartis will successfully scale and sustain commercial manufacturing for Kymriah, or successfully sustain a network of treatment centers to offer Kymriah. Nor can there be any guarantee that Kymriah will be commercially successful in the future. In particular, our expectations regarding Kymriah could be affected by, among other things, our ability to successfully scale and sustain commercial manufacturing and sustain a network of treatment centers; the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic and biosimilar pharmaceuticals and eye care. Novartis has leading positions globally in each of these areas. In 2017, the Group achieved net sales of USD 49.1 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 124,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

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List of links present in page

1. https://qa1.novartis.us/us-en/us-en/news/media-releases/novartis-juliet-trial-kymriah-demonstrates-more-one-year-durability-responses-adults-relapsed-or-refractory-dlbcl
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