NOVARTIS

Primary analysis results from Novartis pivotal JULIET trial show Kymriah™ (tisagenlecleucel) sustained complete responses at six months in adults with r/r DLBCL, a difficult-to-treat cancer

Dec 10, 2017

- - At six months, 30% of patients treated with Kymriah were in complete response, with a 74% relapse-free rate after onset of response; median duration of response was not reached
- - Grade 3/4 neurologic events occurred in 12% of patients; Grade 3/4 CRS occurred in 23% of treated patients using the Penn Grading Scale and was managed by protocol-specific algorithm
- - More than a quarter of patients received Kymriah in outpatient setting during JULIET trial
- - Cost-effectiveness and societal value of Kymriah in pediatric and young adult patients with r/r B-cell ALL to be presented at ASH

EAST HANOVER, N.J., Dec. 10, 2017 /PRNewswire/ -- Novartis today announced updated results from the JULIET clinical trial demonstrating sustained responses with Kymriah™ (tisagenlecleucel) suspension for intravenous infusion, formerly CTL019, in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL). The data from this pivotal trial, led by researchers from the University of Pennsylvania (Penn), show an overall response rate (ORR) of 53% (95% confidence interval [CI], 42% - 64%; p<0.0001), with 40% achieving a complete response (CR) and 14% achieving a partial response (PR) among 81 infused patients with three or more months of follow-up or earlier discontinuation. At six months from infusion, the ORR was 37% with a CR rate of 30%. The median duration of response was not reached. Results from this study of Kymriah, the first-ever FDA-approved chimeric antigen receptor T cell (CAR-T) therapy, were included in the US and EU regulatory filings for Kymriah in r/r DLBCL and will be presented in an oral presentation at the 59th American Society of Hematology (ASH) annual meeting (Abstract #577; Monday, December 11, 7:00 AM EST)[1].

Experience the interactive Multichannel News Release here: https://www.multivu.com/players/English/8234951-novartis-kymriah-juliet-ash-data/

"At the time of trial enrollment, these patients with DLBCL had been through multiple rounds of chemotherapy and many had unsuccessful stem cell transplants, leaving them with few options and a poor prognosis," said the study's principal investigator Stephen J. Schuster, MD, the Robert and Margarita Louis-Dreyfus Professor in Chronic Lymphocytic Leukemia and Lymphoma Clinical Care and Research in the University of Pennsylvania's (Penn) Perelman School of Medicine and director of the Lymphoma Program at the Abramson Cancer Center. "With tisagenlecleucel, we have been able to significantly increase their chance of achieving and maintaining a sustained response without stem cell transplant, demonstrating the therapy's benefit in the treatment of this lethal blood cancer."

At month three, the CR rate was 32% and the PR rate was 6%, which remained consistent to month six (30% CR, 7% PR). Response rates were also consistent among prognostic subgroups, including patients who received prior autologous stem cell transplant (ASCT) and those with a subtype of DLBCL known as double-hit lymphoma, who historically have poor outcomes. No patients in response following treatment with Kymriah proceeded to stem cell transplant[1].

In the JULIET study, the relapse-free probability at six months after first response was 74% (95% CI, 52%-87%), and median duration of response was not reached. Median overall survival was also not reached (95% CI: 6.5 months to NE [not estimable]), and the median time from infusion to data cutoff was 5.6 months[1].

"While immediate response to treatment is a marker for efficacy, patients and physicians need treatment options that provide sustained responses over time with a consistent safety profile," said Samit Hirawat, MD, Head, Novartis Oncology Global Drug Development. "We look forward to continuing to work with health authorities to bring Kymriah to patients with relapsed or refractory DLBCL."

In the JULIET study, cytokine release syndrome (CRS) occurred in 58% of all treated patients, with 23% of patients experiencing grade 3/4 CRS (15% grade 3; 8% grade 4) using the Penn Grading Scale, a rigorous scale for grading 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[1].

Twenty one percent of patients experienced any grade neurologic events, and 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 27%, 20% and 13% of patients, respectively. Three patients died from disease progression within 30 days of infusion. There were no deaths attributed to Kymriah, CRS or neurological events. No cerebral edema events were reported[1].

In the JULIET trial, 26 patients (26%) were infused in the outpatient setting; of those, 20 patients (77%) remained outpatient for three or more days after infusion. Forty-three patients discontinued before infusion and the majority did so due to rapid progression of their disease or deterioration in their clinical status. This reflects the acute and progressive nature of relapsed or refractory DLBCL. Only 9 of 147 (6.1%) enrolled patients could not be infused due to inability to manufacture an adequate dose of CAR-T cells. Over the course of JULIET, with continuous process improvements, manufacturing success rate improved to 97% for the last 30 patients.

JULIET is the first multi-center global registration study for Kymriah in adult patients with r/r DLBCL and the second global CAR-T cell therapy trial, following the Novartis ELIANA study of Kymriah in children and young adults with r/r B-cell acute lymphoblastic leukemia (ALL). JULIET was conducted in collaboration with Penn and enrolled patients from 27 sites in 10 countries across the US, Canada, Europe, Australia and Japan. 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.

The results from JULIET build upon a pilot study of Kymriah in r/r DLBCL and follicular lymphoma published online today in the New England Journal of Medicine, which was led by and conducted at Penn and supported by Novartis and grants from the National Institutes of Health, as well as through philanthropic support. Among patients with r/r DLBCL, the study demonstrated an ORR and safety profile similar to results seen in JULIET. The study demonstrated sustained remissions at a follow up of 28.6 months among patients who responded at six months[2].

In April 2017, the US Food and Drug Administration (FDA) granted Breakthrough Therapy designation to Kymriah based on data from the JULIET study. In October 2017, Novartis submitted an application to the FDA for Kymriah in adult patients with r/r DLBCL who are ineligible for or relapse after ASCT, followed shortly by an application to the European Medicines Agency (EMA) in November for Kymriah for the treatment of adult patients with r/r DLBCL who are ineligible for ASCT, and for children and young adults with r/r B-cell ALL. Additional filings beyond the US and EU are anticipated in 2018.

Economic and Societal Value of Kymriah in ALL Presented at ASH
Results of a cost-effectiveness analysis of Kymriah for the treatment of r/r B-cell ALL in the US will be presented in an oral presentation at the meeting (Abstract #609; Monday, December 11, 7:30 AM EST).

The analysis showed that, based on the current US list price of $475,000, Kymriah is cost-effective compared to standard of care. The analysis compared the life years and quality-adjusted life years gained with Kymriah compared to clofarabine monotherapy, clofarabine combination therapy, blinatumomab, other salvage chemotherapies and allogeneic stem cell transplant. Quality-adjusted life years is a measure of value of health outcomes based on disease burden, including both the quality and quantity of life lived[3].

In addition, results of another analysis to determine the potential societal value of Kymriah to patients with r/r ALL in the United Kingdom were presented in a poster presentation at the meeting (Abstract #1330; Saturday, December 9, 5:30 PM EST).

To quantify the societal value of Kymriah, the analysis looked at the economic value of the incremental quality adjusted life years gained along with the patient's expected productivity using nationally representative data on employment rates and earnings. Results show that therapies such as Kymriah have the potential to provide benefit to patients and society, particularly through gains in survival, contributing to productivity[4].

About Kymriah
In August 2017, Kymriah became the first available chimeric antigen receptor T cell (CAR-T) therapy when it received FDA approval for children and young adults with B-cell acute lymphoblastic leukemia (ALL) that is refractory or has relapsed at least twice. Kymriah is a novel immunocellular therapy and a one-time treatment that uses a patient's own T cells to fight cancer. Kymriah uses the 4-1BB costimulatory domain in its chimeric antigen receptor to enhance cellular expansion and persistence.

About Kymriah Manufacturing
Kymriah will be manufactured for each individual patient using their own cells at the Novartis Morris Plains, New Jersey facility. Novartis has successfully demonstrated a 22-day turnaround time for manufacturing Kymriah in the commercial setting, and this will continue to be the target. 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. Building on the company's experience, having manufactured CAR-T cells for over 250 patients from 11 countries across various indications in clinical trials, it has demonstrated a high-quality and reproducible product. Novartis continues to advance its CAR-T manufacturing expertise and make investments to support the anticipated demand to meet the needs of patients.

About DLBCL
DLBCL is the most common form of non-Hodgkin lymphoma, a cancer of the lymphatic system, with an estimated 27,650 new cases diagnosed in 2016[5,6]. Ten to 15% of DLBCL patients fail to respond to initial therapy or relapse within three months of treatment, and an additional 20% to 25% relapse after initial response to therapy[5]. Nearly 40% of patients with DLBCL will die of relapsed or refractory disease[7].

Kymriah™ (tisagenlecleucel) Important Safety information (for pediatric and young adult patients with B-cell precursor acute lymphoblastic leukemia)

The full prescribing information, including Boxed WARNING, for Kymriah can be found at:
https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf

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 high fever, difficulty breathing, 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 health care 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) in the US 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 health care 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 health care provider will do blood tests to check all of their blood cell counts after treatment with Kymriah. Patients should be advised to tell their health care 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 health care provider about their treatment with Kymriah before receiving a live virus vaccine.

After treatment with Kymriah, patients will be monitored life-long by their health care provider, as they may develop secondary cancers or recurrence of their leukemia.

Patients should not drive, operate heavy machinery, or do other dangerous activities for 8 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, and dizziness/lightheadedness. However, these are not all of the possible side effects of Kymriah. Patients should talk to their health care provider for medical advice about side effects.

Prior to a female patient starting treatment with Kymriah, their health care 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. If either sex partner has received Kymriah, patients should talk to their health care provider about birth control and pregnancy.

Patients should tell their health care 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.

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, regarding our ability to build and sustain a network of treatment centers to offer 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 build and 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 build 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; our ability to obtain or maintain proprietary intellectual property

protection; the particular prescribing preferences of physicians and patients; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; general economic and industry conditions, including the effects of the persistently weak economic and financial environment in many countries; safety, quality or manufacturing issues, 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
Located in East Hanover, NJ Novartis Pharmaceuticals Corporation is an affiliate of Novartis which 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 2016, the Group achieved net sales of USD 48.5 billion, while R&D throughout the Group amounted to approximately USD 9.0 billion. Novartis Group companies employ approximately 121,000 full-time-equivalent associates. Novartis products are sold in approximately 155 countries around the world. For more information, please visit http://www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis and @NovartisCancer at http://twitter.com/novartiscancer
For Novartis multimedia content, please visit www.novartis.com/news/media-library
For questions about the site or required registration, please contact media.relations@novartis.com

References

1. Schuster S., et al. Primary Analysis of Juliet: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. 59th American Society of Hematology Annual Meeting and Exposition. Abstract #577.
2. Schuster S., et al. CAR-T cells (CTL019) in Refractory B-cell Lymphomas. N Engl J Med. December 10, 2017. doi: 10.1056/NEJMoa1708566. [Epub ahead of print].
3. Hao Y., et al. Cost-Effectiveness Analysis of CTL019 for the Treatment of Pediatric and Young Adult Patients with Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia in the United States. 59th American Society of Hematology Annual Meeting and Exposition. Abstract #609.
4. Snider J., et al. The Economic Value of CTL019 Therapy for Pediatric Patients with Relapsed and Refractory Acute Lymphoblastic Leukemia in the United Kingdom. 59th American Society of Hematology Annual Meeting and Exposition. Abstract #1330.
5. American Society of Clinical Oncology. Lymphoma - Non-Hodgkin: Subtypes (Dec. 2016 revision). http://www.cancer.net/cancer-types/lymphoma-non-hodgkin/subtypes. Accessed December 2017.
6. Teras LR., DeSantis CE., Cerhan JR., et al. 2016 US Lymphoid Malignancy Statistics by World Health Organization Subtypes. CA CANCER J CLIN. September 2016;66(6):443-459.
7. Vaidya R., Witzig T.E. Prognostic factors for diffuse large B-cell lymphoma in the R(X)CHOP era. Ann of Onc. March 2014; Volume 25(11):2124-33.

Novartis Media Relations
Central media line: +41 61 324 2200
E-mail: media.relations@novartis.com

Eric Althoff	Fiona Phillips
Novartis Global Media Relations	Novartis Oncology Communications
1-212-830-2408 (office)	+1 862-778-7705 (direct)
1-646-438-4335 (mobile)	+1 862-217-9396 (mobile)
eric.althoff@novartis.com	fiona.phillips@novartis.com

SOURCE Novartis
