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Novartis interim results from global, pivotal CTL019 trial show durable complete responses in adults with r/r DLBCL

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- -- At interim analysis, three-month overall response rate (ORR) was 45%, with 37% complete response (CR); all patients in CR at three months remained in CR at data cutoff
- -- Best ORR was 59%, with 43% achieving CR; full results expected to be available later in 2017 and will serve as basis for US and EU regulatory submissions
- -- Global, multi-center Phase II JULIET study conducted in collaboration with University of Pennsylvania is basis for FDA Breakthrough Therapy designation in April 2017
- -- CTL019 is manufactured using cryopreserved leukapheresis which, in the JULIET trial, enabled the treatment of patients in 27 sites across four continents

EAST HANOVER, N.J., June 7, 2017 /PRNewswire/ -- Novartis announced findings from an interim analysis of its multi-center Phase II JULIET study (NCT02445248) of CTL019 (tisagenlecleucel) in adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL), which will be presented at the International Conference on Malignant Lymphoma (ICML) meeting, Lugano, Switzerland (Abstract #007; Wednesday, June 14, 3:40 PM CEST). The global, pivotal study showed a three-month overall response rate (ORR) of 45% (23 of the 51 patients evaluated), with 37% achieving a complete response (CR) and 8% achieving a partial response (PR), respectively. CR remained stable from three months through data cutoff among the patient group[1].

"The overall response rate seen in this early analysis is impressive for these heavily pre-treated patients with relapsed/refractory DLBCL, who have limited treatment options," said JULIET lead investigator, Stephen Schuster, MD, Professor of Hematology/Oncology in the Perelman School of Medicine at the University of Pennsylvania (Penn) and Penn's Abramson Cancer Center. "The goal for these patients is achieving durable response. The most promising aspect of these data is that, at the time of this interim analysis, all patients with complete response at three months have remained in complete response."

JULIET is the first multi-center global registration study for CTL019 in adult patients with r/r DLBCL and the second global CAR-T cell therapy trial, following the Novartis ELIANA study (NCT02435849) of CTL019 in pediatric and young adult patients 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. It is the largest study examining a CAR-T cell therapy exclusively in DLBCL patients.

The study met its primary objective at interim analysis. Among 51 patients with three months or more of follow-up or earlier discontinuation, best ORR was 59% (95% CI, 44.2-72.4; $p<0.0001$), with 43% achieving CR and 16% achieving PR. The full JULIET primary analysis is expected to be available later this year and will serve as the basis for US and EU regulatory submissions[1].

In the JULIET study, 57% of all treated patients (85) experienced any grade cytokine release syndrome (CRS), and 26% experienced grade 3/4 CRS (17% grade 3; 9% grade 4) using the Penn Grading Scale, a rigorous

scale for grading CRS. CRS is a known complication of the investigational 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].

There were no deaths attributed to CTL019, CRS or cerebral edema, and no incidents of cerebral edema were reported in the study. Thirteen percent of patients had grade 3/4 neurologic adverse events, which were managed with supportive care. Grade 3/4 cytopenias lasting more than 28 days and grade 3/4 febrile neutropenia occurred in 21% and 14% of patients, respectively. Three patients died from disease progression within 30 days of infusion[1].

In the JULIET trial, 43 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 the disease of the patients. Only nine of 141 (6%) 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.

"We are pleased the interim results from JULIET highlight the potential for CTL019 to elicit durable responses in patients with relapsed/refractory DLBCL, an area of high unmet need," said Vas Narasimhan, Global Head of Drug Development and Chief Medical Officer, Novartis. "Novartis is committed to progressing our portfolio of CAR-T therapies in hematological and solid tumors to advance the care of cancer patients."

In April 2017, the US Food and Drug Administration (FDA) granted Breakthrough Therapy designation to CTL019 based on data from the JULIET study.

About the JULIET Trial

JULIET (NCT02445248) is a single-arm, open-label, multi-center global Phase II trial of CTL019 in patients aged 18 years or older with r/r DLBCL. Prior to enrollment, patients were required to have received two or more lines of prior chemotherapy and had disease progression or were ineligible for autologous stem cell transplant (autoSCT). Sixty percent of the patients had three or more lines of chemotherapy and 51% had a prior autoSCT.

The primary endpoint of the study is best ORR (defined as CR plus PR) determined by a central review conducted by an independent review committee. Secondary endpoints from the study include overall survival, duration of response and progression-free survival.

About CTL019 Manufacturing

Novartis cryopreserved leukapheresis process allowed for successful manufacturing and treatment of patients from around the world. Cryopreserved leukapheresis gives physicians the flexibility to schedule apheresis at a time that is in the best interest of their patients. Novartis commercial manufacturing for CTL019 will build on its extensive experience in our Morris Plains facility, which has already manufactured CTL019 for hundreds of patients in global clinical trials. Novartis believes that hands-on experience matters in cell therapy manufacturing, and the experience at Morris Plains will be a foundation for manufacturing for commercial purposes and future CAR-T therapies. Novartis has made and continues to make significant investments in capacity and turnaround time and is committed to meeting the needs of CTL019 patients in the future.

About CAR-T and CTL019

CAR-T is different from typical small molecule or biologic therapies because it is manufactured for each individual patient using their own cells. During the treatment process, T cells are drawn from a patient's blood

and reprogrammed in the laboratory to create T cells that are genetically coded to hunt the patient's cancer cells and other B cells expressing a particular antigen.

CTL019 was first developed by the University of Pennsylvania (Penn) and uses the 4-1BB costimulatory domain to enhance cellular responses. In 2012, Novartis and Penn entered into a global collaboration to further research, develop and then commercialize CAR-T cell therapies, including CTL019, for the investigational treatment of cancers. In March 2017, Novartis announced that the FDA accepted the company's Biologics License Application filing and granted priority review for CTL019 in the treatment of r/r pediatric and young adult patients with B-cell ALL.

Because CTL019 is an investigational therapy, the safety and efficacy profile has not yet been established. Access to investigational therapies is available only through carefully controlled and monitored clinical trials. These trials are designed to better understand the potential benefits and risks of the therapy. Because of the uncertainty of clinical trials, there is no guarantee that CTL019 will ever be commercially available anywhere in the world.

About DLBCL

DLBCL is the most common form of lymphoma and accounts for approximately 30% of all non-Hodgkin lymphoma cases[2]. 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[3].

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "will," "later in 2017," "Breakthrough Therapy designation," "promising," "investigational," "may," "potential," "committed," "priority review," "yet," "expected," "believes," "continues," or similar terms, or by express or implied discussions regarding potential marketing approvals for CTL019, or regarding potential future revenues from CTL019. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management 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 CTL019 will be submitted or approved for sale in any market, or at any particular time. Nor can there be any guarantee that CTL019 will receive regulatory approval or be commercially successful in the future. In particular, management's expectations regarding CTL019 could be affected by, among other things, 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; the company's ability to obtain or maintain proprietary intellectual property protection; general economic and industry conditions; global trends toward health care cost containment, including ongoing pricing and reimbursement pressures; 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

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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 118,000 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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