Novartis announces first CAR-T cell therapy BLA for pediatric and young adult patients with r/r B-cell ALL granted FDA Priority Review

Mar 29, 2017

- Priority review for investigational CTL019 (tisagenlecleucel-T), a novel therapy that is manufactured for each individual patient using their own T cells
- Novartis made an early commitment to the emerging field of CAR-T investigational therapies through collaboration with the University of Pennsylvania including CTL019
- Novartis plans to submit an application for market authorization with the European Medicines Agency (EMA) later this year

EAST HANOVER, N.J., March 29, 2017 /PRNewswire/ -- Novartis announced today that the US Food and Drug Administration (FDA) has accepted the company's Biologics License Application (BLA) filing and granted priority review for CTL019 (tisagenlecleucel-T), an investigational chimeric antigen receptor T cell (CAR-T) therapy, in relapsed and refractory (r/r) pediatric and young adult patients with B-cell acute lymphoblastic leukemia (ALL). This is the first BLA submission by Novartis for a CAR-T. The priority review designation is expected to shorten the anticipated review time by the FDA.

CAR-T is different from typical small molecule or biologic therapies currently on the market because it is manufactured for each individual patient. 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.

"With CTL019, Novartis is at the forefront of the science and development of immunocellular therapy as a potential new innovative approach to treating certain cancers where there are limited options," said Vas Narasimhan, Global Head of Drug Development and Chief Medical Officer, Novartis. "The priority review and file acceptance of CTL019 by the FDA brings us one step closer to delivering this novel treatment option to children and young adults with r/r B-cell ALL in the United States."

CTL019 was first developed by the University of Pennsylvania. In 2012, Novartis and the University of Pennsylvania entered into a global collaboration to further research, develop and then commercialize CAR-T cell therapies for the investigational treatment of cancers, including CTL019. Through the collaboration, Novartis holds the worldwide rights to CARs developed through the collaboration with the University of Pennsylvania for all cancer indications.

"The past five years have seen tremendous progress in the development and application of cellular engineering in an effort to personalize the treatment of cancer," said the Penn team's leader, Carl June, MD, director of the Center for Cellular Immunotherapies in the Perelman School of Medicine at the University of Pennsylvania. "We now know that it is possible to treat patients in clinical trials across the world using this approach, and the results we have observed mark a potential new paradigm in the treatment of blood cancers that have not responded to standard therapies."

The priority review designation and BLA submission for CTL019 is based on the results from the Novartis-

sponsored ELIANA study (NCT02435849), the first global CAR-T cell trial with study enrollment having occurred across 25 centers in the US, EU, Canada, Australia and Japan. In the Phase II study, 82% (41 of 50) of patients infused with CAR-T cells achieved complete remission or complete remission with incomplete blood count recovery at three months post CTL019 infusion. The data were presented at the American Society of Hematology meeting in December 2016 (Abstract #221).[1]

Forty-eight percent of patients in the ELIANA trial experienced grade 3 or 4 cytokine release syndrome (CRS), a known complication of an investigational therapy that may occur when the engineered cells become activated in the patient's body. CRS was managed per protocol on a global scale using prior site education with implementation of the CRS treatment algorithm. There were no deaths due to CRS. Fifteen percent of patients experienced grade 3 neurological and psychiatric events including confusion, delirium, encephalopathy, agitation and seizure. No cerebral edema was reported and no grade 4 neurological and psychiatric events were observed.[1]

The submission is also supported by findings from a US multicenter trial and an earlier single site trial led by the Children's Hospital of Philadelphia (CHOP) examining the safety and efficacy of CTL019 among pediatric and young adult patients with r/r B-cell ALL. Stephan Grupp, MD, PhD, from CHOP was the lead investigator of the trials.

"Even if a patient has difficult-to-treat relapsed/refractory leukemia, we have seen treatment with CTL019 in clinical trials put cancer into remission," said Grupp, Director of the Cancer Immunotherapy Frontier Program and Director of Translational Research for the Center for Childhood Cancer Research at CHOP. "This could be a first-of-its-kind treatment with exciting potential to help pediatric and young adult r/r B-cell ALL patients."

Acute lymphoblastic leukemia makes up approximately 25% of cancer diagnoses among children under 15 years old and is the most common childhood cancer in the US.[2] Patients with relapsed and refractory ALL have limited treatment options, and the chance of survival for children with the disease who relapse or fail to attain remission is between 16% to 30%.[3]

According to the FDA guidelines, Priority Review status may potentially shorten the window for the agency to take action on an application to within six months of the filing acceptance compared to a standard review. The designation aims to prioritize the evaluation of products that have the potential to provide significant improvements in the treatment, diagnosis or prevention of serious conditions when compared to standard applications. CTL019 previously received Breakthrough Therapy designation from the FDA for the treatment of patients with r/r ALL.

Novartis plans additional filings for CTL019 in the US and EU markets later this year, including a BLA with the FDA for treatment of adults with r/r DLBCL and applications for marketing authorization with the European Medicines Agency in r/r B-cell ALL and r/r DLBCL.

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.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "priority review," "commitment," "investigational," "plans," "expected," "potential," "possible," "may," "could," "potentially," "aims to," "designed to," "will," or similar terms, or by express or implied discussions regarding

potential additional filings or 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 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 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.

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

Eric Althoff	Heather Bochner
Novartis Global Media Relations	Novartis Oncology
1-212-830-2408 (office)	+1 862-778-5092 (direct)
1-646-438-4335 (mobile)	+1 862-432-8472 (mobile)
eric.althoff@novartis.com	heather.bochner@novartis.com

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List of links present in page

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