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Novartis highlights new CTL019 clinical data showing complete remissions in children and young adults with relapsed/refractory acute lymphoblastic leukemia

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- - Data shows 36 of 39 pediatric patients with relapsed/refractory acute lymphoblastic leukemia (r/r ALL) (92%) experienced complete remissions[1]
- - Additionally, sustained remissions were achieved up to one year or more with 6-month event-free survival of 70% and overall survival of 75%, in most cases without further therapy[1]
- - Novartis and Penn have exclusive global collaboration to research, develop and commercialize CAR T cell therapies for the investigational treatment of cancers

EAST HANOVER, N.J., Dec. 6, 2014 /PRNewswire/ -- Findings from continued clinical studies of investigational chimeric antigen receptor (CAR) therapy, CTL019, demonstrate its potential role in the treatment of certain types of lymphocytic leukemia. In one long-term study of pediatric patients with acute lymphoblastic leukemia (ALL), results showed that 36 of 39 pediatric patients with relapsed/refractory (r/r) ALL, or 92%, experienced complete remissions (CR) with CTL019[1]. These results, which will be presented in an oral session at the 56th American Society of Hematology (ASH) annual meeting in San Francisco, continue to increase scientific understanding of CTL019 (Abstract #380, December 8, 10:45 AM)[1]. Additional abstracts will be presented at ASH that evaluate the efficacy and safety of CTL019 in the treatment of B cell cancers including ALL, chronic lymphocytic leukemia (CLL) and B cell non-Hodgkin lymphoma (NHL).

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"We're seeing pediatric patients who have not responded to any other therapy achieve complete remission as a result of treatment with CTL019," said lead investigator Stephan Grupp, MD, PhD, the Yetta Deitch Novotny Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania and director of Translational Research in the Center for Childhood Cancer Research at the Children's Hospital of Philadelphia (CHOP). "However, this is only the first step. Now that these patients have been followed for a longer period of time, we're seeing that a number of them remain in remission for one year or more. This leads me to believe the persistence and durability of CAR-modified cells may help protect against relapse."

Additional highlights of the pediatric r/r ALL study include findings that patients have ongoing CR. Median follow-up was 6 months. Sustained remissions were achieved up to one year or more with 6-month event-free survival of 70% and overall survival of 75%, in most cases without further therapy[1]. The probability of six-month CTL019 persistence was 68%, which was accompanied by B cell aplasia, a pharmacodynamic marker of CTL019 persistence and function[2]. Persistence of CTL019 cells detected by flow cytometry and/or qPCR, and accompanied by B cell aplasia, continued for up to 30 months after infusion in patients with ongoing responses[1].

All responding patients developed cytokine release syndrome (CRS) at peak T cell expansion. Treatment for CRS was required for hemodynamic or respiratory instability in 33% of patients and CRS was managed with an IL-6 receptor antagonist, together with corticosteroids in five patients. These events were delayed, and few patients

experienced infusional toxicities, including infusion-associated fever[1].

"Innovation in the cellular therapy field is accelerating right now. When we see the response patients have to CTL019 when they have few options left, it's incredibly inspiring," said Usman Azam, Global Head, Cell & Gene Therapies Unit, Novartis Pharmaceuticals. "Novartis will leverage our facility in Morris Plains, the first FDA-approved Good Manufacturing Practices quality site for a cell therapy, and the multi-center study for CTL019 in collaboration with the University of Pennsylvania, to broaden the reach of this therapy to additional patients in the clinical setting."

Also included among the presentations at ASH is a study investigating CTL019 in the treatment of individuals with CD19+ B cell lymphomas (Abstract #3087; December 7, 6:00 PM – 8:00 PM) that reveals complete responses in patients with advanced, relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma[3]. In addition, data will be presented on three cases of refractory cytokine release syndrome (CRS) in adult patients with ALL (Abstract #2296, December 7, 6:00 PM – 8:00 PM)[4]. CRS is correlated with CTL019 proliferation and the severity of CRS is correlated with disease burden[1],[2],[4].

Additional CTL019 Highlights at ASH include:

- Randomized, Phase II Dose Optimization Study of Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) in Patients with Relapsed, Refractory CLL (Abstract #1982; December 6, 5:30 PM – 7:30 PM)[5]
- Cytokine Release Syndrome (CRS) after Chimeric Antigen Receptor (CAR) T Cell Therapy for Relapsed/Refractory (R/R) CLL (Abstract #1983; December 6, 5:30 PM – 7:30 PM)[6]
- Humoral Immunity and Plasma Cell Changes in Patients Responding to CD19-Specific Chimeric Antigen Receptor (CAR)-Modified T-cell Adoptive Immunotherapy (Abstract #1110; December 6, 5:30 PM – 7:30 PM)[7]

Other CAR T Highlights at ASH include:

- Novel Chimeric Antigen Receptor T cells for the Treatment of CD19-negative Relapses Occurring after CD19-targeted Immunotherapies (Abstract #966; December 6, 5:30 PM – 7:30 PM)[8]
- Novel Chimeric Antigen Receptor T Cells for the Treatment of Hodgkin Lymphoma (Abstract #806; December 9, 7:45 AM)[9]
- Signaling Domain of Chimeric Antigen Receptors Can Reprogram T Cells (Abstract #551; December 8, 3:45 PM)[10]
- Glycopeptide-Specific Chimeric Antigen Receptor Targeting of T Cell Leukemia (Abstract #4803; December 8, 6:00 PM – 8:00 PM)[11]

In July 2014, the FDA designated CTL019 as a Breakthrough Therapy for the treatment of pediatric and adult patients with r/r ALL under the Penn IND. Breakthrough Therapy designation is intended to expedite the development and review of drugs that treat serious or life-threatening conditions if the therapy has demonstrated substantial improvement over an available therapy on at least one clinically significant endpoint[12]. Novartis holds the worldwide rights to CARs developed through the collaboration with Penn for all cancer indications, including the lead program, CTL019.

About CTL019
CTL019 uses CAR technology to reprogram a patient's own T cells to "hunt" cancer cells that express specific proteins, called CD19. After they have been reprogrammed, the T cells (now called CTL019) are re-introduced into the patient's blood; they proliferate and bind to the targeted CD19+ cancer cells and potentially kill these tumor cells.

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 uncertainty of clinical trials, there is no guarantee that CTL019 will ever be commercially available anywhere in the world.

About Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children, representing approximately 25% of cancer diagnoses among children younger than 15 years, according to data published in 2013[13]. It can also occur in adults. ALL is a type of cancer in which the bone marrow makes too many abnormal white blood cells (lymphocytes). ALL usually gets worse quickly if it is not treated and can be fatal within a few months; therefore, it is critical for patients to start treatment soon after diagnosis. Patients with relapsed ALL experience ALL cells returning in the marrow and a decrease in normal blood cells following their remission. Patients with refractory ALL still have leukemia cells in their bone marrow following treatment[14].

About Cytokine Release Syndrome

After CTL019 infusion, cytokine release syndrome (CRS) occurs when the engineered cells become activated and multiply in the patient's body resulting in the release of cytokines. During CRS, patients typically experience varying degrees of flu-like symptoms with high fevers, nausea, muscle pain, and in some cases, low blood pressure and breathing difficulties. CRS severity correlates with disease burden. Additionally, CRS also can occur in other non-CAR therapy settings including some monoclonal antibodies[15].

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "potential," "will," "first step," "believe," "may," "inspiring," "Breakthrough Therapy," "intended," "potentially," "investigational," "has not yet," 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 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 unexpected clinical trial results and additional analysis of existing clinical data; unexpected 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; unexpected 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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