Novartis announces T-Charge™, next-generation CAR-T platform with first-in-human data at ASH 2021

Dec 13, 2021

- *T-Charge, a next-generation platform that aims to revolutionize CAR-T cell therapy, will serve as foundation for various investigational CAR-T therapies*
- *Early data from first-in-human dose-escalation trials with YTB323 and PHE885 show promising results that support ongoing research and development with the hope of improving upon existing CAR-T therapies(1,2)*
- *Initial efficacy results include 73% complete response rate at month three with dose level two in the YTB323 study in DLBCL and 100% best overall response in the PHE885 study in multiple myeloma(1,2)*
- *Novartis continues to accelerate development of the T-Charge platform, which preserves T cell stemness, an important characteristic closely tied to its therapeutic potential, and implements important process efficiencies(3,4)*
- *With the implementation of important process efficiencies, the T-Charge platform will be rapid, compared with traditional CAR-T, and reliable, through simplified processes and streamlined quality control(1-4)*

EAST HANOVER, N.J., Dec. 13, 2021 - Novartis today announced the introduction of T-Charge™, the company's next-generation CAR-T platform that will serve as the foundation for various new investigational CAR-T cell therapies in the Novartis pipeline. At the 63rd American Society of Hematology Annual Meeting & Exposition (ASH) 2021, Novartis will present early clinical data from ongoing Phase I clinical trials with YTB323 (anti-CD19) and PHE885 (anti-BCMA), the first Novartis CAR-T cell therapies developed using this platform. Notably, initial efficacy data show a complete response rate of 73% (95% CI: 44.9, 92.2) at month three for the 15 patients with diffuse large B-cell lymphoma (DLBCL) who received dose level two of YTB323[1]. For the 11 patients with multiple myeloma who received the two highest doses of PHE885, the best overall response was 100%[2].

The T-Charge platform preserves T cell stemness, the ability to self-renew and mature, which results in a product containing greater proliferative potential and fewer exhausted T cells[3,4]. With T-Charge, CAR-T cell expansion occurs primarily within a patient's body (in-vivo), eliminating the need for an extended culture time outside of the body (ex-vivo)[3,4]. These unique characteristics of the T-Charge platform may lead to better and more durable responses, improved long-term outcomes and a reduced risk of severe adverse events[1-4].

"With T-Charge, we aim to build on the vast knowledge gleaned from early investment in CAR-T research and trials. Our ambition now is to go beyond incremental advances, to further reimagine CAR-T cell therapy and give patients a higher likelihood of durable responses with the ultimate potential for a cure," said Jay Bradner, President of the Novartis Institutes for BioMedical Research. "We are encouraged by these promising early clinical data from the first CAR-T cell therapies produced using the T-Charge platform as we look to accelerate their development and delivery to patients."

Phase I YTB323 clinical study[1]

YTB323, an investigational, autologous CD19-directed CAR-T cell therapy developed using the T-Charge platform, showed promising results in the diffuse large B-cell lymphoma arm of a first-in-human, multicenter, Phase I dose-escalation study. Patients received a single treatment of YTB323 at two dose levels (DL). The median administered doses were 2.5×10^6 CAR+ cells (DL1; n=4) and 12.5×10^6 CAR+ cells (DL2; n=16). Of the 15 patients who received YTB323 treatment at DL2 at least three months prior to the data cut-off, the complete response (CR) rate was 73% (95% CI: 44.9, 92.2), including two patients who were in CR prior to treatment with YTB323.

For the 20 patients evaluable for safety, there were no new safety signals beyond those previously known to be related to CD19-directed CAR-T cell therapy. All AEs were reported regardless of the study drug relationship. Six patients experienced CRS including five of grade 1/2 and one of grade 4. Five patients had neurological adverse reactions (AR), of which two events were considered serious (both at DL2; one experienced grade 3 immune effector cell-associated neurotoxicity syndrome (ICANS) and the other experienced grade 2 seizure that resulted in a grade 3 ICANS). Recruitment for this trial is ongoing. These data will be presented in an oral session at the ASH annual meeting (Abstract #740; Monday, December 13, 3:00 PM EST).

"The introduction of CAR-T cell therapy led to unprecedented efficacy results for patients facing limited treatment options and a poor prognosis. Unfortunately, some patients with late-stage B-cell malignancies relapse or do not respond after initial response when treated with traditional CAR-T cell therapies," said principal investigator Ian W. Flinn, MD, PhD, Director of the Lymphoma Research Program at Sarah Cannon Research Institute in Nashville. "As part of a community of researchers, physicians and patient advocates, I am hopeful about the promise of novel and next-generation CAR-T cell therapies."

Phase I PHE885 clinical study[2]

PHE885, an investigational, autologous BCMA-directed CAR-T cell therapy developed using the T-Charge platform, demonstrated promising results in patients with relapsed or refractory multiple myeloma in a first-in-human Phase I, multicenter, dose-escalation study. Fifteen patients were evaluated for efficacy and safety and the fixed doses received were 2.5×10^6 (n=4), 5×10^6 (n=10) and 14.3×10^6 CAR-T cells (n=1). Although the follow-up period was brief, PHE885 shows encouraging initial clinical activity with a best overall response of 100% for patients receiving the 5×10^6 or 14.3×10^6 CAR-T cell dose, with responses deepening over time. With a median follow-up of 3.5 months, eight of 15 patients had ongoing responses at the time of data cutoff. Of the evaluable patients at three months post administration, 34% (2/6) were MRD-negative by next-generation sequencing (NGS) at 10^{-6}; 43% (3/7) were MRD-negative at 10^{-5}.

All patients experienced CRS with two patients experiencing grade ≥3 CRS. No patients experienced grade 4 or 5 CRS. All neurotoxicity events (n=4) were nonserious, grade 1-2, reversible, and temporally associated with CRS. Recruitment for this trial is ongoing. These data will be presented in a poster presentation session at the ASH annual meeting (Abstract #3864; Monday, December 13, 6:00 PM EST).

Results from pre-clinical studies of YTB323 and PHE885 that served as the scientific rationale to initiate these Phase I clinical trials will also be presented at the meeting (Abstracts #2848 and #2770).

About T-Charge™[1-4]

T-Charge is a next-generation CAR-T platform, innovated at the Novartis Institutes for BioMedical Research (NIBR), that will serve as the foundation for various new investigational CAR-T cell therapies in the Novartis pipeline. By implementing the T-Charge platform, we aim to revolutionize CAR-T cell therapy with new products that have the potential to offer patients a higher likelihood of better and more durable responses,

improved long-term outcomes and a reduced risk of severe adverse events. The T-Charge platform preserves T cell stemness (T cell ability to self-renew and mature), an important T cell characteristic closely tied to its therapeutic potential, which results in a product containing greater proliferative potential and fewer exhausted T cells. With T-Charge, CAR-T cell expansion occurs primarily within the patient's body (in-vivo), eliminating the need for an extended culture time outside of the body (ex-vivo). The T-Charge platform, which implements important process efficiencies, will be rapid, compared with traditional CAR-T, and reliable, through simplified processes and streamlined quality control. Multiple CAR-T therapies, including YTB323 and PHE885, are being developed using the Novartis T-Charge platform.

About Novartis commitment to Oncology Cell Therapy

Novartis has a mission to reimagine medicine by bringing curative cell therapies to patients worldwide. Novartis has a deep CAR-T pipeline and ongoing investment in manufacturing and supply chain process improvements. With active research underway to broaden the impact of cell and gene therapy in oncology, Novartis is going deeper in hematological malignancies, reaching patients with other cancer types and evaluating next-generation CAR-T cell therapies that focus on new targets and utilize new platforms.

Novartis was the first pharmaceutical company to significantly invest in pioneering CAR-T research and initiate global CAR-T trials.

About Novartis

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of Novartis – is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis employs nearly 15,000 people in the United States. For more information, please visit https://www.novartis.us.

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1. Flinn, I. et al. A First-in-Human Study of YTB323, a Novel, Autologous CD19-Directed CAR-T Cell Therapy Manufactured Using the Novel T-Charge platform, for the Treatment of Patients (Pts) with Relapsed/Refractory (r/r) Diffuse Large B-Cell Lymphoma (DLBCL). Oral Presentation #740. 2021 American Society of Hematology (ASH) Annual Meeting, Dec 11-14, Atlanta, GA and Virtual.
2. Sperling, A. et al. Phase I Study of PHE885, a Fully Human BCMA-Directed CAR-T Cell Therapy for Relapsed/Refractory Multiple Myeloma Manufactured in<2 days Using the T-Charge. Poster #3864. 2021 American Society of Hematology (ASH) Annual Meeting, Dec 11-14, Atlanta, GA and Virtual.
3. Engels, B. et al. Preservation of T-Cell Stemness with a Novel Expansionless CAR-T Manufacturing Process, Which Reduces Manufacturing Time to Less Than Two Days, Drives Enhanced CAR-T Cell Efficacy. Abstract #2848. 2021 American Society of Hematology (ASH) Annual Meeting, Dec 11-14, Atlanta, GA and Virtual.
4. Bu, D. et al. Identification and Development of PHE885: A Novel and Highly Potent Fully Human Anti-BCMA CAR-T Manufactured with a Novel T-Charge Platform for the Treatment of Multiple Myeloma. Abstract #2770. 2021 American Society of Hematology (ASH) Annual Meeting, Dec 11-14, Atlanta, GA and Virtual.

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political, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity 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.

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