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

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Disclosures

DB, XZ, BG, CPG, LMT and JLB report employment, hold stocks and patents in Novartis. MPO and KM report employment and hold stocks in Novartis, XL reports employment in Novartis. PB and NB have current affiliation Bristol Myers Squibb and former employment in the last 24 months with Novartis. LB has current affiliation AstraZeneca and former employment in the last 24 months with Novartis. PV reports employment with Takeda and former employment in the last 24 months with Novartis.
Background

• BCMA is a clinically validated target in MM, with therapies targeting BCMA currently approved or in clinical development\textsuperscript{1,2}

• Anti-BCMA CAR-T cells have shown greatest results in early-phase clinical trials to date
  – However, duration of response is limited, and patients with rapidly progressing disease require a fast and reliable CAR-T cell manufacturing process

• To improve on existing BCMA CAR-Ts, two critical attributes of the CAR-T product were investigated:
  – The potency of the BCMA CAR construct, and
  – A rapid manufacturing process that would both preserve the stemness of T cells to ensure longer duration of response and provide timely access for patients with rapidly progressing, aggressive disease.

• Through extensive panning and discriminating CART functional assays to assess performance, we have identified a superior anti-BCMA CAR construct that when combined with a innovative T-Charge™ manufacturing platform produces a highly potent product

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cells; MM, multiple myeloma.
T-Charge™ Platform, an Innovative Manufacturing Platform Preserves Naive/T_{scm} Cells in the Final Product

- Naive (Tn) and stem-like memory T cells (T_{scm}) can expand into a more multifunctional pool of antigen-specific T cells in the patient
- Extended T-cell culture periods in vitro deplete the CAR-T final product of Tn and T_{scm} populations that are associated with improved antitumor efficacy
- Novartis’s novel T-Charge™ platform is an expansionless CAR-T manufacturing process that takes <2 days to generate functional CAR-Ts retains Tn and T_{scm} cells


CAR, chimeric antigen receptor; CCR, C-C motif chemokine receptor; CD, cluster of differentiation; Tn, Naive T cells; T_{scm}, stem-like memory T cells; Tcm, central memory T cells; Tem, effector T cells; Teff, effector memory T cells.

Discovery Path of a Superior Anti-BCMA CAR Construct

• We have developed a novel anti-BCMA CAR-T product for the treatment of MM.

• Selection of our development candidate was based on a screening of eighteen anti-BCMA CARs carried by lentiviral vectors, each comprising a distinct scFv derived from phage display libraries and hybridoma with a wide range of affinities and epitopes.

• One candidate clone from the fully human B cell library was identified after rigorous assessment of transduction efficiency, CAR expression, antigen specificity/selectivity and CAR-T cell function against a MM cell line, both in vitro and in vivo.

PHE885 scFv clone selection process

Jurkat cell expression and reporter assay
CAR expression and in vitro function in Primary T cell
In vivo Efficacy in MM xenograft models
Target binding specificity evaluation
Lead scFv nomination and characterization

Clone #s

18 11 7 4 3 1

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cells; CD, cluster of differentiation; MM, multiple myeloma; scFv, single-chain variable fragment.
PHE885 Is a Novel Autologous BCMA-Directed CAR-T Cell Therapy

PHE885 CAR contains

- An extracellular region composed of a fully human scFv domain, the lead clone identified via a serial screening process as described above
- A CD8α-hinge and transmembrane region
- An intracellular region composed of a 4-1BB (CD137) costimulatory domain
- An intracellular CD3-zeta chain domain
- The lead scFv carried by PHE885 demonstrates high specificity to human BCMA, by Retrogenix platform, using a commercial human plasma membrane protein array assay.
- PHE885 is manufactured using the novel T-Charge™ platform

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T-Charge™ Retains Less Differentiated PHE885 Cells

Flow cytometry analysis shows that T-Charge™ processed PHE885 retains naïve/Tstem T cells (CD45RO-/CCR7+) while the traditionally manufactured cell product (TM_PHE885) mainly contains central-memory T cells (Tcm) (CD45RO+/CCR7+).

CCR, C-C motif chemokine receptor; CD, cluster of differentiation; Tstem, stem-like memory T cells; Tcm, central memory T cells.
PHE885 Exhibits Potent Anti-tumor Activity and Robust Cellular Expansion in a Preclinical MM Model

A. Tumor kinetics is measured in NOD-scid IL2R gamma null (NSG) mice, injected with MM cell line KMS11, expressing the luciferase reporter gene. The tumor burden is expressed as total body luminescence (p/s), depicted as mean tumor burden +SEM. On day 8 post tumor inoculation, mice were treated with CAR-T cells at the respective doses (approximate number of viable CAR+ T cells). PBS and non-transduced T cells (UTD) served as negative controls. N=5 mice for all groups. B) Peripheral blood cellular kinetics in KMS11 tumor-bearing mice treated with CAR-T cells at different doses. Blood were taken post CAR-T injection and were analyzed by flow cytometry at designed time points. MCM998 is a TM product used in a clinical trial (NCT02546167).

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BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cells; CD, cluster of differentiation; IL, interleukin; MM, multiple myeloma; NOD, non-obese diabetic; NSG, NOD-scid IL2R gamma; PBS, phosphatebuffer saline; PK, pharmacokinetics; scFv, single-chain variable fragment; SEM, standard error of mean; TM, traditionally manufactured.
Conclusions

• PHE885 was discovered and designed to enhance potency and drive persistence of CAR-T through the combination of:
  
  – a novel CAR construct carrying a fully human anti-BCMA scFv fused to 4-1BB/CD3ζ signaling domains
  
  
• The novel T-Charge™ platform takes <2 days to manufacture the final product, allows PHE885 to preserve a significantly high proportion of naïve/ T\textsubscript{scm} cells, and enables PHE885 to effectively engraft, expand and reject tumors at a dose 5 fold lower than traditionally manufactured (TM) CAR-T cells

• Based on these results, a Phase 1, open-label trial assessing PHE885 in patients with r/r MM (NCT04318327) was initiated. Initial data from the dose escalation portion of the Phase 1 study is presented separately (refer to Sperling A, et al. ASH 2021. Poster 3864)\textsuperscript{3}

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cells; CD, cluster of differentiation; MM, multiple myeloma; r/r, relapsed/ refractory; scFv, single-chain variable fragment; TM, traditionally manufactured; T\textsubscript{scm}, stem-like memory T cells.

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