A Phase 1 trial of desmoglein 3 chimeric autoantibody receptor T cells (DSG3-CAART) for targeted B cell depletion in patients with mucosal-dominant pemphigus vulgaris: The DesCAARTes™ Trial

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Introduction

CART Therapy

CAART Therapy

Chimeric AutoAntibody Receptor T cell

- Type of immunotherapy of genetically engineered autologous T cells to target and eliminate specific cells
- CD19 T cell anti-CD19 antibody fragment targeting domain against CD19+ cells including healthy B cells
- 1st CART approved 2017 for relapsed or refractory B cell leukemia or lymphomas
- Potential remission for at least 5 years
- 5 CART therapies approved for oncology indications in the US

Background

DSG3-CAART Cells

- DSG3-CAART cells express all the relevant DSG3 domains
- Since all pathogenic autoantibodies in mPv are directed against EC1, EC2, EC3, or EC4 of the DSG3 protein, the same manufacturing approach can be used for all patients.

Study Design

Major Inclusion Criteria

- Age ≥18
- History of relapsed or refractory pemphigus vulgaris
- Able to give informed consent
- Adequate bone marrow reserve

Major Exclusion Criteria

- Severe co-morbidities
- Severe autoantibody-driven disease
- Recent active infection

The DesCAARTes™ Trial

- A phase 1 open-label 36-month clinical trial in mPv patients
- The objective is to determine the maximum tolerated dose of DSG3-CAART cells

Results*

- No DLTs or clinically relevant adverse events in the 1st 8 patients
- 6 patients have been treated in the 1st 2 cohorts and monitored for at least 28 days
- Baseline characteristics of patients included a broad range of ages, disease duration, autoantibody levels, and number of prior PV therapies
- No DLTs or any clinically relevant toxicities have been observed in any patients in the setting of no pretreatment lymphodepletion, but in presence of anti-DSG3 antibodies
- DSG3-CAART cell persistence via qPCR was observed in all patients during the 28 days post infusion

Manufacturing

- Strong operating partnership with Penn manufacturing organization
- Use of validated process from CART experience at Penn
- 100% success rate for DesCAARTes™ trial manufacturing

Biologic Activity Indicators

- Ongoing and planned evaluations:
  - Persistence of DSG3-CAART detected via qPCR
  - Change in level of anti DSG3 antibodies (targeting persistent reduction)
  - Reduced mPv therapy and absence of new systemic rescue therapy
  - Change in disease activity based on clinically validated scales (e.g. PDAI)

Conclusions

- Administration of 2x10⁶ and 1x10⁶ DSG3-CAART cells in the 1st two cohorts of mPv subjects has been well-tolerated through Day 28 in the Phase 1 DesCAARTes™ trial
- Manufactured DSG3-CAART cells from the 1st subject have exhibited selective in vitro cytotoxicity
- Based on the safety data, the next cohort of subjects will be administered a dose of 5x10⁶ DSG3-CAART cells
- Ongoing and planned evaluations will assess for biologic activity indicators of DSG3-CAART

References:

- Payne: Potential remission has been observed in any patients in the setting of no pretreatment lymphodepletion, but in presence of anti-DSG3 antibodies
- DSG3-CAART cell persistence via qPCR was observed in all patients during the 28 days post infusion

Samples run in triplicate

1 x 10⁶ target cells per well

Manufactured DSG3-CAART cells have exhibited target elimination in vivo

- An image-based in vitro cytotoxicity assay incubated manufactured DSG3-CAART cells from the 1st subject with anti-DSG3 expressing target cells labeled with GFP at various DSG3-CAART effector to target cell ratios
- The manufactured DSG3-CAART cells exhibited elimination of target cells in a dose dependent manner.

Disclosures:

- Payne: Co-founder with equity, consulting, grant funding, Cabaletta Bio; inventor on patents licensed by Novartis, Cabaletta Bio