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POSTER ABSTRACTS

622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

Multiple Doses of Cnty-101, an iPSC-Derived Allogeneic CD19 Targeting CAR-NK Product, Are Safe and Result in Tumor Microenvironment Changes Associated with Response: A Case Study

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Introduction

Despite recent approvals of autologous cell therapy products for relapsed, refractory (R/R) non-Hodgkin lymphoma, there remains a clear unmet need for safe, efficacious, and affordable off-the-shelf products that can deliver durable responses. CNTY-101 is an allogeneic iPSC-derived chimeric antigen receptor NK (CAR-NK) cell product with a CD19-targeting CAR, secreted IL-15 to enhance persistence, EGFR safety switch, and a suite of Alloevasion ^{TM} edits (B2M and CIITA knock outs, and HLA-E knock in) intended to reduce allo-rejection in the recipient, thereby allowing for repeated dosing. Here we describe a case-study of the first subject dosed in ELiPSE-1, a first-in-human phase 1, multicenter, open-label study of CNTY-101 in subjects with R/R CD19-Positive B-cell malignancies, which is currently enrolling patients (NCT05336409).

Methods

A 63-year-old subject with R/R POD 24 (progression of disease within 2 years) follicular lymphoma, treated with 4 prior lines of therapy was enrolled at dose level 1 (DL1), 100 million cells CNTY-101. To date, the patient has received four 28-day cycles of a single infusion of CNTY-101 at DL1 with day 1 of each cycle being approximately 6 weeks apart (Table 1). Cycles 1 and 2 included three days of standard Fludarabine and Cyclophosphamide lymphodepletion (LDC), cycles 3 and 4 were given with no LDC. In cycles 2-4, low dose (3 million units) subcutaneous interleukin-2 (IL-2) was administered on days 1-8 of each cycle. Each cycle of CNTY-101 beyond cycle 1 required FDA approval. The described schedule facilitated evaluation of feasibility, safety, biomarker and efficacy evaluations after each infusion, +/- IL-2, and +/- LDC. Biomarker assessments were performed on blood and serum collected pre- and post- each infusion, and on tumor biopsies collected pre- and post-1 st infusion only. Pharmacokinetic (PK) assessments were performed using ddPCR, serum cytokines were measured using Meso Scale Discovery technology, serum anti-drug-antibodies (ADA) were measured using flow-based assays to detect direct IgG and IgM binding to the cell product or assays specifically measuring ADA targeting the CAR construct. Functional ADA were evaluated using an assay to detect complement-dependent cytotoxicity (CDC) function of bound ADA. Tumor biopsies at baseline and day 8 were interrogated for changes in the immune microenvironment using custom Vectra multiplexed immunofluorescence panels and RNA-ISH methodology.

Results

All doses of CNTY 101 with and without IL-2 or LDC demonstrated acceptable safety and clinical benefit (i.e. stable disease or better per Lugano 2014 criteria). No concerted changes in inflammatory cytokines and mediators associated with cytokine release syndrome or neurotoxicity were detected. The IL-2 dosing regimen resulted in continuous measurable bioavailability of IL-2 during the period of dosing, including trough periods. PK measurements showed that CNTY-101 cells were detected after each infusion with comparable kinetics, with a limited duration in circulation. Serum assessments after the 1 st three cycles showed that, despite administration of two cycles with and one cycle without LDC, no evidence of functional (CDC-inducing) pre-existing or induced ADA were observed. Importantly, tumor microenvironment analyses demonstrated a dramatic increase in T cells within 8 days of the 1 st CNTY-101 cell infusion. Specific increases in proliferating cytotoxic T cells, intratumoral production of TNFα and IFNγ, and key checkpoint molecules were observed, suggestive of induction of

adaptive immune responses within the tumor. These responses were associated with tumor shrinkage and ongoing CR of a duration of 5 months since the first CNTY-101 infusion.

Conclusions

The presented case study demonstrates the potential and feasibility of safely delivering up to 4 cycles of CNTY-101 +/- IL-2 and +/- LDC, at the 100 million dose level. No measurable induction of CDC-inducing functional ADA was detected after the 1 st 3 cycles. Additionally, tumor studies have provided early insight into the mechanism of action. The treatment was associated with changes in tumor microenvironment within 8 days post-infusion, augmentation of adaptive T cell responses, and tumor shrinkage. Updated data will be presented at the conference.

Disclosures Ramachandran: *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company; *Adaptimmune:* Current equity holder in publicly-traded company. **Rothman:** *Bristol Myers Squibb:* Ended employment in the past 24 months; *Century Therapeutics:* Current Employment. **Clausi:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Mcfadden:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Salantes:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Jih:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Brigman:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Kelly:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Hall:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Divested equity in a private or publicly-traded company in the past 24 months; *Astella Pharmaceutical:* Ended employment in the past 24 months. **Yee:** *Century Therapeutics:* Current Employment. **Koumenis:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Das:** *Century Therapeutics:* Current Employment. **Yuan:** *abbvie:* Consultancy; *amgen:* Consultancy; *Bexion Pharma:* Consultancy; *BeyondSpring Pharma:* Consultancy; *Boehringer Ingelheim:* Consultancy; *BMS:* Consultancy; *Century Therapeutics:* Consultancy; *Enliven:* Consultancy; *GT Medical:* Consultancy; *NeoImmuneTech:* Consultancy; *NGM Biopharma:* Consultancy; *Merck:* Consultancy; *Repare Therapeutics:* Consultancy; *Servier Pharma:* Consultancy; *Syneos Health:* Consultancy; *Xinthera:* Consultancy; *Vertex Pharma:* Consultancy. **Devlin:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company. **Farid:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company; *schrodinger Inc:* Current Employment, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company, Honoraria; *Ajax Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Structure Thearpeutics:* Membership on an entity's Board of Directors or advisory committees; *Oak Hill Bio:* Membership on an entity's Board of Directors or advisory committees. **Trede:** *Century Therapeutics:* Current Employment, Current equity holder in publicly-traded company, Current holder of *stock options* in a privately-held company. **Moyo:** *Kite Pharmaceuticals:* Consultancy. **Patel:** *Xencor:* Consultancy, Research Funding; *Trillium Therapeutics/Pfizer:* Consultancy, Research Funding; *TG Therapeutics:* Consultancy, Speakers Bureau; *Sunesis Pharmaceuticals:* Research Funding; *Pharmacyclics/Janssen:* Consultancy, Research Funding; *Nurix:* Research Funding; *Morphosys:* Consultancy; *Merck:* Consultancy, Research Funding; *MEI Pharma:* Consultancy, Research Funding; *Loxo Oncology:* Consultancy, Research Funding; *Kite:* Consultancy, Research Funding, Speakers Bureau; *Genentech/Roche:* Consultancy, Research Funding; *Fate Therapeutics:* Research Funding; *Epizyme:* Consultancy, Research Funding; *Curis, Inc:* Research Funding; *CRISPR Therapeutics:* Research Funding; *Caribou Biosciences:* Consultancy; *Bristol Myers Squibb:* Consultancy, Research Funding, Speakers Bureau; *BeiGene:* Consultancy; *AstraZeneca:* Consultancy, Research Funding, Speakers Bureau; *ADC Therapeutics:* Consultancy; *Adaptive Biotechnologies:* Research Funding; *Abbvie:* Consultancy.

Table 1: Treatment cycles received by the subject.

CNTY-101 DL1	Dose cycle #	LDC	IL-2
100M cells x 1	1	+	-
100M cells x 1	2	+	+
100M cells x 1	3	-	+
100M cells x 1	4	-	+

Figure 1

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