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

Indu Ramachandran[1], Sarah Rothman[1], Mariano Clausi[1], Kile McFadden[1], Brenda Salantes[1], Gloria Jih[1], Thomas Brigman[1], Sam Kelly[1], Matthew S. Hall[1], Stephanie Yee[1], Iphigenia Koumenis[1], Poulomee Das[1], Jordan Briggs[2], Tori Braun[2], Ying Yuan[3], Elizabeth Devlin[1], Adrienne Farid[1], Nikolaus Trede[1], Tamara K. Moyo[5], Tahir Latif[4], Krish Patel[2]

[1]Century Therapeutics, Philadelphia, PA [2]Swedish Cancer Institute, Seattle, WA [3]MD Anderson Cancer Center, Houston, TX [4]Atrium Health Levine Cancer Institute, Charlotte, NC [5]University of Cincinnati Medical Center, Cincinnati, OH

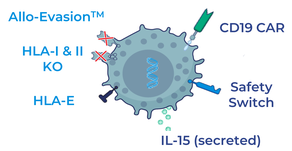
CNTY-101 aims to deliver durable responses in R/R B-cell NHL via repeat dosing facilitated by Allo-Evasion™

Aim: Extending the period of pharmacologic pressure on tumor cells

- Autologous CD19 CAR-T is curative in 40 percent of patients
- Autologous CD19 CAR-T access is limited and/or can fail in manufacturing as quality is dependent on patient-derived starting material
- Limited options and poor prognosis for patients who fail autologous CAR-T
- Off-the-shelf product offers access and consistency
- Multiple doses to increase pharmacological pressure
- Host rejection solved by Allo-Evasion™ edits

R/R: relapsed or refractory, NHL: non-Hodgkin lymphoma, CAR-T: chimeric antigen receptor T cell therapy

CNTY-101 is an iPSC-derived NK cell therapy with CD19 CAR and Allo-Evasion™ edits to avoid host rejection



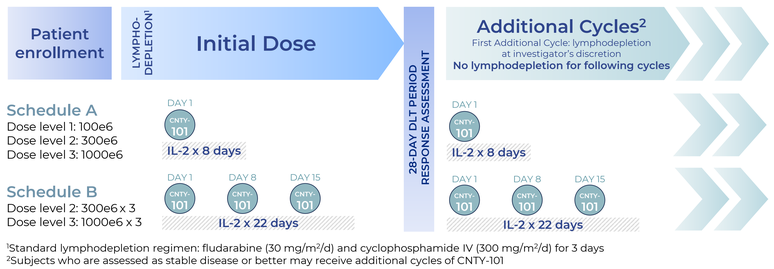
- CNTY-101 is an allogeneic anti-CD19 iPSC-derived NK cell therapy
- Century's platform for multiple step editing using CRISPR in iPSC allowed 6 edits (2 KO, 4 KI) to enable multiple functions
  - Avoid host T cell rejection: Knockout of beta-2 microglobulin (b2M) and MHC Class II Transactivator (CIITA) to eliminate HLA-I & HLA-II
  - Avoid host NK cell rejection: Knock-in of HLA-E
  - Tumor elimination: CD19 CAR with FMC63 binder
  - Safety switch: truncated Epidermal Growth Factor Receptor (EGFR) containing Cetuximab binding epitope
  - Secreted IL-15: to enhance cell persistence and modulate the tumor microenvironment

iPSC: induced pluripotent stem cell, NK: natural killer, FMC63: CD19 binding portion of CAR, HLA: human leukocyte antigens, KO: knockout, KI: knock-in

CNTY-101: ELiPSE-1 (NCT05336409) Phase 1 BOIN Design

Patients with CD19+ aggressive and high-risk indolent R/R B-NHL
- DLBCL, HGBL, MCL, PMBCL, FL3B, FL, MZL
- ≥ 2 prior lines of therapy
- Prior CD19-targeted cell therapy allowed

Part 1 - Schedule A: single dose escalation
Schedule B: 1 dose per week x 3 weeks
Part 2 - Dose expansion



[1]Standard lymphodepletion regimen: fludarabine (30 mg/m²/d) and cyclophosphamide IV (300 mg/m²/d) for 3 days
[2]Subjects who are assessed as stable disease or better may receive additional cycles of CNTY-101

BOIN: Bayesian Optimal Interval, DLT: dose limiting toxicity, IL-2: Interleukin-2 (dose: 3e6 IU; subcutaneous)

Patient case presentation and treatment

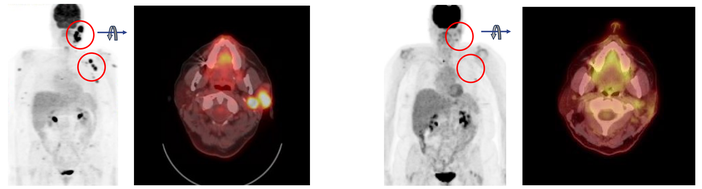
Sex/Age	**Female/63**
Tumor subtype	**Follicular Lymphoma**
Dose/Schedule	**100e6 cells x 1 per cycle (Dose Level 1; Schedule A)**

- 4 prior lines of therapy including anti-CD20, bispecific, and investigational therapy
- High-risk R/R - Relapsed within 12 months of starting R-CHOP

IL-2: subcutaneous 3e6 IU for 8 days, except for initial cycle

Clinical data cut-off: September 14, 2023

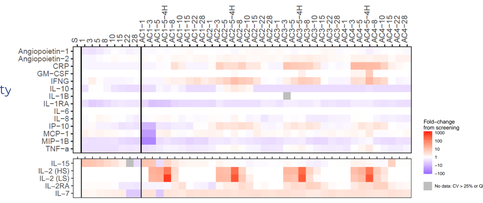
Complete response ongoing through 6 months



Baseline | Post-initial dose (Day 28)

Clinical assessments and cytokine profiles support favorable CNTY-101 safety profile

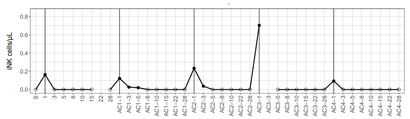
- No DLTs, no CRS, no ICANS
- No AEs related to CNTY-101
- Factors associated with CRS and neurotoxicity were not significantly elevated
- Elevation in peripheral IL-2 is observed, coinciding with IL-2 administration



DLT: Dose-limiting toxicity, CRS: cytokine release syndrome, ICANS: immune effector cell–associated neurotoxicity syndrome, AE: adverse event, AC: Additional Cycle

CNTY-101 persists outside of circulation; detectable by cfDNA

Peripheral blood pharmacokinetics



Detection of CNTY-101 cell-free DNA

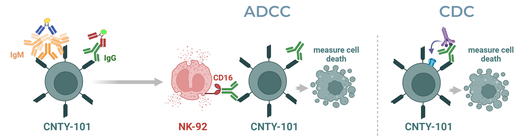
	Initial Dose	Additional Cycle			
		1	2	3	4
LDC?	Yes	Yes	No	No	No
DAY 3		+	+	+	+
DAY 10		+	+	+	-
DAY 15		-		-	-
DAY 28	+	-	+	-	-

Timepoints with no samples collected are shaded in dark grey

- CNTY-101 has limited duration in circulation; maximum concentration is observed at 1 hr post-infusion by ddPCR (left). Cell density is derived from CNTY-101 percentage (ddPCR) and PBMC cell counts (flow cytometry).
- CNTY-101 cell-free DNA in plasma is detected at multiple timepoints using ddPCR (right). Detectable signal (+) was determined to be significantly above negative controls.

cfDNA: cell-free DNA, LDC: lymphodepleting chemotherapy, PBMCs: Peripheral blood mononuclear cells

Humoral immune response against CNTY-101 not detected



		Initial Dose		Additional Cycle 1		Additional Cycle 2		Additional Cycle 3		Additional Cycle 4	
Timepoint	**Screen**	**DAY 15**	**DAY 28**	**DAY 15**	**DAY 28**	**DAY 15**	**DAY 28**	**DAY 15**	**DAY 28**	**DAY 15**	**DAY 28**
IgG binding fold change	1	1.08	1.10	0.99	0.91	0.86	0.82	0.87	0.87	1.07	0.96
IgM binding fold change	1	0.90	0.87	0.78	0.85	1.17	0.83	0.78	1.03	1.92	1.77
FMC63 ADA	No	No	No	No	No	No	No	No	No	No	No
CDC	No	No	No	No	No	No	No	No	No	No	No
ADCC	No	No	No	No	No	No	No	No	No	No	No

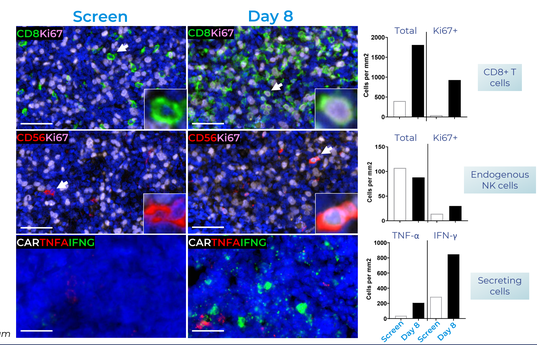
- All tested patient serums exhibited binding of IgG and IgM to CNTY-101; MFI fold change over screen sample was calculated for CNTY-101-bound IgG or IgM
- No FMC63 ADA was detected
- Negative results from functional humoral immunogenicity assays (CDC and ADCC) suggest that bound IgG/IgM are not ADA

ADA: anti-drug antibody, FMC63: CD19 binding portion of CAR, CDC: complement-dependent cytotoxicity, ADCC: antibody-dependent cellular cytotoxicity, MFI: mean fluorescent intensity

Intra-tumoral adaptive immune response observed

- Biopsy was collected on Day 8 after first infusion of CNTY-101 in the absence of IL-2
- Fluorescent IHC showed increase in total and proliferating (Ki67+) CD8+ T cells (top) as well as increase in proliferating endogenous NK cells (middle).
- RNA-ISH showed increase in TNF-α and IFN-γ-producing immune cells
- Quantification is performed on whole biopsy

IHC: immunohistochemistry,
ISH: RNA in situ hybridization



Scale bar: 50µm

Summary

- CNTY-101 is the first cell therapy product candidate engineered with six precision gene edits including a CD19-CAR, Allo-Evasion™ technology, IL-15 cytokine support, and a safety switch.
- CNTY-101 is well tolerated at 100 million cells in high-risk, heavily pre-treated R/R B-NHL patients
- The presented case study demonstrates the potential and feasibility of safely delivering up to 6 cycles of CNTY-101 +/- IL-2 and +/- lymphodepletion, at the 100 million dose level resulting in durable CR at 6 months and ongoing*.
- ddPCR analysis of CNTY-101 genomic DNA and cell-free DNA from Dose Level 1 (n=4) patient samples suggest that CNTY-101 cells traffic out of circulation shortly after infusion and likely persist in tissues.
- Overall, preliminary results indicate that CNTY-101 exposure may be maintained upon administration of additional cycles without lymphodepletion due to lack of allo-rejection.

Current study status: Enrollment is ongoing; in dose escalation phase
- Dose Level 1 Safety Summary (n=4): No DLTs, no GvHD, no ICANS, n=1 CRS (Gr 1)
- Dose Level 1 Efficacy Summary at 1 month (n=4): 3 PD, 1 CR
- Dose Level 2 opened: Two patients dosed; one patient in DLT period, one patient received an additional cycle*

*Data as of Nov 2, 2023

GvHD: graft versus host disease, CR: complete remission, PD: progressive disease

Corresponding author: Krish Patel, MD (krish.patel@swedish.org)
Swedish Cancer Institute, Seattle, WA

Scan for poster

Scan to find study on ClinicalTrials.gov

65th ASH Annual Meeting
December 9-12, 2023
San Diego, CA