BEAM-201 for the Treatment of Relapsed and/or Refractory (R/R) T-Cell Acute Lymphoblastic Leukemia (T-ALL) or T-Cell Lymphoblastic Lymphoma (T-LL): Initial Data from the Phase (Ph) 1/2 Dose-Exploration, Dose-Expansion, Safety, and Efficacy Study of Multiplex Base-Edited Allogeneic Anti-CD7 CAR-T-Cells

Caroline Diorio,[1] Paul Shaughnessy,[2] Nosha Farhadfar,[2] Anjali Advani,[3] Wen-Kai Weng,[4] Hagop Youssoufian,[5] Guo Chen,[5] Felicia Nguyen Brown,[5] Bahru Habtemariam,[5] Lalit Kumar,[5] Jigar Patel,[5] Gary Liu,[5] Sunita Goyal,[5] Amy Simon,[5] Alex Minella,[5] David Teachey[1]

[1]Division of Oncology, Children's Hospital of Philadelphia, PA, USA; [2]Sarah Cannon Transplant and Cellular Therapy Program, Methodist Hospital, San Antonio, TX, USA; [3]Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, OH, USA; [4]Division of Blood and Marrow Transplantation & Cellular Therapy, Stanford University, Palo Alto, CA, USA; [5]Beam Therapeutics Inc., Cambridge, MA, USA

Contact info: clinicalinfo@beamtx.com

Introduction

- Patients with R/R T-ALL/T-LL have poor outcomes, rapid progression, limited therapeutic options and often have treatment-resistant disease[1–3]
- CAR-T-cell strategies have shown potential to induce remission of R/R T-ALL/T-LL; however, development of these therapies faces limitations due to shared antigen expression between healthy effector cells and malignant T-cells, risk of graft-versus-host disease (GvHD), fratricide, and inability to collect T-cells for autologous therapies from patients with R/R T-ALL/T-LL[1,4,5]
- BEAM-201 is an investigational allogeneic, multiplex base-edited anti-CD7 CAR-T-cell therapy. It is the first quadruple-edited Ph 1 product, simultaneously introducing four distinct single base mutations into *TRAC*, *CD7*, *CD52*, and *PDCD1* to abolish the production of functional proteins. This enables universal compatibility and reduces risk of depletion by alemtuzumab (Alz), GvHD, fratricide, and tumor-expressed PDL-1-mediated immunosuppression[6,7]
- This study aimed to present initial dose exploration and safety, pharmacokinetic (PK), and tolerability data from the ongoing Ph 1/2 BEAM-201 study (NCT05885464) for four patients with either T-ALL or T-LL and follow up data of between 34 and 156 days at the time of data cutoff (October 17, 2024)

Method

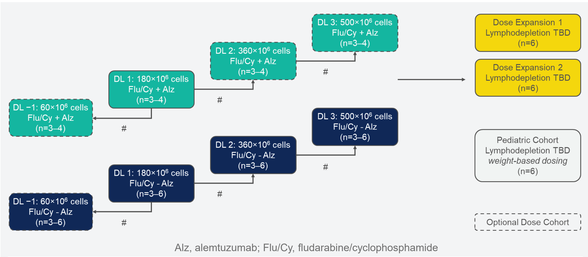
Study design and patient population

- Primary objectives of Ph 1 were to determine the safety, tolerability, and recommended Ph 2 dose of BEAM-201 in patients with R/R T-ALL or T-LL
- Secondary objectives included determining overall response rate for Ph 1 dose cohorts and survival following BEAM-201 infusion. For patients with clinical responses, objectives also included determining depth of response (MRD), proportion of patients deemed appropriate for HSCT (investigator assessment), and duration of response
- Eligible patients were aged 18–≤50 years with T-ALL/T-LL (CD7-positive with ≥2 relapses, first relapse post-transplant, or chemotherapy-refractory), considered candidates for an allo transplant, and had not undergone HSCT within 90 days prior to screening
- Post-treatment response assessments (Day 28) performed:
  - Appropriateness for HSCT (investigator determined)
  - MRD and morphology (bone marrow [BM] aspirate required)
  - Disease response and cellular kinetics (BM aspirate and biopsy at screening and Day 28, unless disease persistence or progression was documented sooner)
  - Imaging (PET/CT preferred)

Dosing exploration and manufacturing

- Starting dose was 180×10^6 cells. Subsequent dose escalation and de-escalation were guided by available safety, efficacy, and PK/pharmacodynamic (PD) data, using Bayesian optimal interval design
- The first three patients in each dose-exploration cohort were staggered for a minimum 28-day gap between treatment initiation dates
- Following lymphodepletion, patients received a single dose of BEAM-201

Figure 1: BEAM-201 Dose-Exploration into Dose-Expansion Schema*



Alz, alemtuzumab; Flu/Cy, fludarabine/cyclophosphamide

*The lymphodepletion (LD) regimen was optimized for both CAR-T expansion and safety. #Dose exploration will begin at DL 1 in two parallel cohorts using a Flu/Cy or Flu/Cy + Alz (LD) regimen.
Alz is a CD52-targeting monoclonal antibody used with allogeneic CAR-T-cells to facilitate their robust expansion and persistence by depleting host lymphocytes while sparing modified cells. Both inter- and intra-cohort staggering rules were implemented. The SRC will review all safety, any available efficacy, and any available PK/PD data and make decisions regarding dose escalation, expansion at the current DL or de-escalation, guided by Bayesian design-based recommendation

Results

- Patient disposition as of October 17, 2024: 4 patients were dosed; 1 withdrew owing to distance from treatment site, and 1 patient died. Two patients are currently in follow up

Table 1: Baseline demographics and characteristics

Summary of baseline demographics, N=4	
Age in years, median (range)	27.5 (18–47)
Sex, n	
Male	3
Female	1
Disease status, n	
Relapsed T-ALL	2
R/R T-LL	2
Summary of patient characteristics, N=4	
Prior treatments, n	
Anti-cancer chemotherapy	4
Anti-cancer radiotherapy	1
HSCT	2
Extramedullary disease	2
Summary of treatment regimens	**Number of patients (n)**
BEAM-201 180×10^6 cells (DL1)	
Flu/Cy (120/1500 mg/m^2)	2
Flu/Cy (120/1500 mg/m^2) + Alz (20 mg)	1
BEAM-201 60×10^6 cells (DL-1)	
Flu/Cy (120/1500 mg/m^2) + Alz (20 mg)	1

- P1 presented with T-LL, a large mediastinal mass, and malignant pericardial and bilateral pleural effusions and had five prior lines of chemotherapy treatment
- P2 presented with T-ALL paresthesia, constipation, anemia and decreased platelet count, and had two prior chemotherapy treatment lines
- P3 presented with primary refractory T-LL and extramedullary disease, with one previous line of chemotherapy treatment
- P4 presented with T-ALL, had four prior chemotherapy lines and one prior radiotherapy treatment, and had previously had prior HSCT and relapsed

Safety

- CRS, neurotoxicity/ICANS, and infections occurred in 4 (maximum grade: G4, 1 patient; G2, 1 patient; G1, 2 patients), 1 (G1, aphasia), and 4 patients, respectively. There were no cases of GvHD
- One death (P1) occurred 40 days post-infusion due to disease progression and was deemed unrelated to study treatment or procedure
- ≥G3 TEAEs related to BEAM-201 included platelet count decreased, febrile neutropenia, pneumonia, anemia, CRS, cytopenia, decreased appetite, hypoalbuminemia, hypocalcemia, hypokalemia, lymphocyte count decreased, nausea, vascular access complication, and white blood cell count decreased

Table 2: Summary of treatment-emergent adverse events*

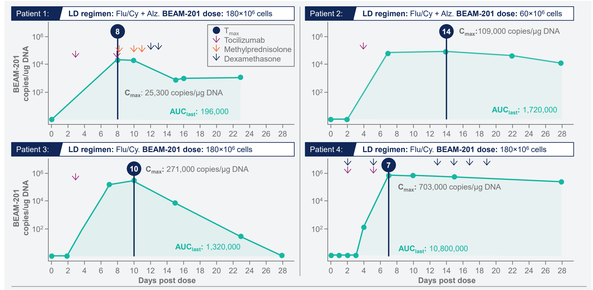
Safety	N=4	Events
All TEAEs	4	89
Related to BEAM-201	4	47
TEAEs ≥G3	3	29
Related to BEAM-201	3	18
Serious TEAEs	2	6
Related to BEAM-201	2	4
AEs leading to discontinuation	0	0
Most common TEAEs†		
Cytokine release syndrome	4	8
Related to BEAM-201	4	8
Nausea	3	3
Related to BEAM-201	1	1

*Treatment-emergent AEs (TEAEs) are defined as any new AEs or pre-existing conditions that worsen in severity grade after the first dose of BEAM-201 and up to the start of pre-HSCT conditioning and HSCT (for patients with HSCT) or 6 months after the last dose of BEAM-201, or any BEAM-201 related AEs. †**Defined as TEAEs occurring in at least 3 patients**

PK assessments

- The extent of BEAM-201 expansion and persistence varied between patients
- All patients showed detectable expansion, with 3 / 4 patients showing very robust expansion. In addition, 3 of the patients showed good persistence with detectable CAR-T up to 28 days

Figure 2: BEAM-201 expansion and persistence



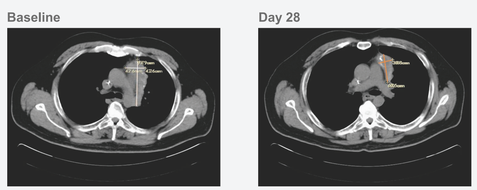
AUC_{last} units are copies × days/µg DNA. AUC_{last}, area under curve from time of dosing to time of last measurable concentration; Alz, alemtuzumab; C_{max}, peak concentration; T_{max}, time to peak concentration; Flu/Cy, fludarabine/cyclophosphamide; LD, lymphodepletion

Efficacy

Day 28 clinical response assessment

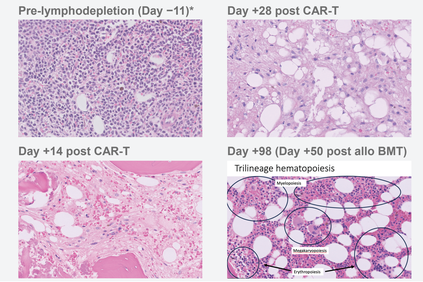
- P3 had complete response (CR) based on imaging, and proceeded to HSCT
  - There was a complete metabolic response to the extramedullary disease on Day 28 and 56 assessments with no bone marrow involvement and P3 was deemed suitable to go on to allogeneic stem cell transplant

Figure 3: Baseline and Day 28 CT scans for Patient 3



- P2 and P4 showed complete response with incomplete (CRi) hematologic recovery. P4 proceeded to HSCT in CRi; P2 was deemed appropriate for HSCT but consent was withdrawn before transplant occurred
  - P2 had low tumor burden and post-transplant relapse
  - P4 showed high tumor burden, 97% marrow blasts and has been pancytopenic for many months. This patient had a complicated course with prolonged hospitalization due primarily to cytopenias and infection; cytokine release syndrome (CRS), and hyperferritinemia but no neurologic complications

Figure 4: Bone marrow biopsy for Patient 4



*Most cells are blasts

- P1 death occurred as a result of disease progression
  - Prior to this, during Grade 4 CRS workup, a computed tomography (CT) scan showed a marked reduction (~70–80%) in mediastinal mass following BEAM-201 infusion compared with baseline and marked reduction in arm swelling by physical examination due to prior thrombosis and vascular compression from mediastinal mass
  - Increased mass and pericardial effusion within 2 weeks consistent with disease progression and death due to disease progression

Table 3: All patients achieving CR or CRi following BEAM-201 infusion were deemed suitable for HSCT

Patient	AE assessment requiring Safety Review Committee discussion	MRD negative response	Response	HSCT suitability
1	DLT;* dose de-escalation for next patient in the same LD regimen	Biopsy not taken	-	-
2	No DLT	<0.01%	CRi	Suitable for HSCT
3	No DLT	No bone marrow involvement pre-or post-treatment	CR (D28 and D56; based on screening)	Suitable for HSCT
4	No DLT	MRD not sent	CRi	Suitable for HSCT

Please note: all AE assessments were performed through Day 28; *defined as any Grade 5 TEAE, ASTCT Grade 4 CRS (any duration), or Grade 3 CRS that does not improve to ≤Grade 2 within 7 days with therapy; ASTCT Grade 3/4 neurotoxicity (any duration); ≥Grade 3 GvHD (MAGIC grading); or Grade 3/4 nonhematologic toxicity (any duration) affecting heart, CNS, or lungs

Conclusions

- Initial data suggest a BEAM-201 safety profile similar to other allogeneic products
- 3 / 4 participants achieved CR or CRi, demonstrating early evidence for the efficacy of CAR-T-cell doses of <200 million cells in a highly refractory patient population
- PK data show robust expansion of BEAM-201 following infusion in 3 / 4 patients and persistence in 3 / 4 patients. Such magnitude of CAR-T expansion at relatively low dose levels of 60×10^6 and 180×10^6 CAR-T-cells with standard LD agents compares favorably with other allogeneic CAR-T products

References

1. Raetz EA, Teachey DT. Hematology Am Soc Hematol Educ Program 2016;2016:580–588
2. Frismantas V, et al. Blood 2017;129:e26–37
3. Summers RJ, Teachey DT. Clin Lymphoma Myeloma Leuk 2022;22:718–725
4. Gill S, Brudno JN. Am Soc Clin Oncol Educ Book 2021;41:1–20
5. Dourthe ME, Baruchel A. EJC Paediatr Oncol 2024;3:100150
6. Chiesa R, et al. N Engl J Med 2023;389:899–910
7. Chen G, et al. Nature 2018;560:382–386

Acknowledgments

- Thank you to the study participants, their families, and their caregivers for their participation, and the study investigators for their contributions This study is sponsored by Beam Therapeutics
- **Medical editorial support was funded by Beam Therapeutics and provided by:** Freya Haycox-Ferguson, PhD, of Helios Medical Communications, part of Helios Global Group, and Audrey W. Hou, PharmD, of Beam Therapeutics, under the guidance of the authors and in accordance with Good Publication Practice 2022