ZENYTH-ESO: Master protocol to assess the safety and recommended phase II dose of next generation NY-ESO-1-specific TCR T-cells in HLA-A*02 patients with synovial sarcoma and myxoid/round cell liposarcoma [Substudy 3, GSK4427296, Epi-R]

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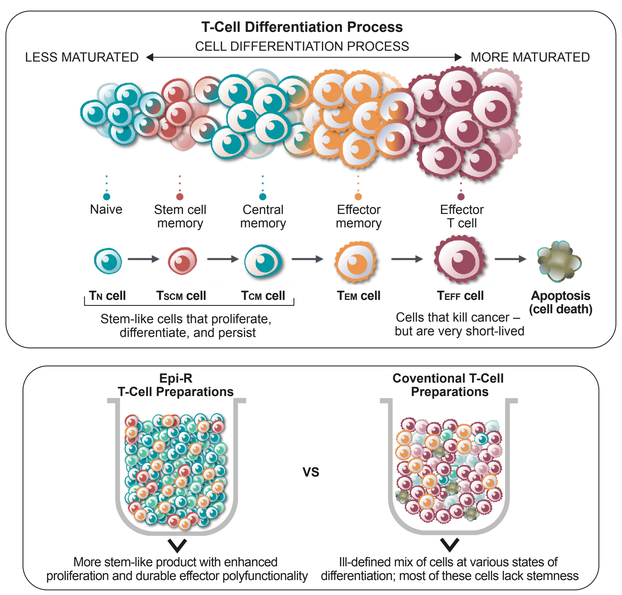
Background

- NY-ESO-1 is a member of the cancer-testis family of tumor antigens, expressed in multiple solid tumor types, including synovial sarcoma (SS) and myxoid/round cell liposarcoma (MRCLS). Cancer-testis antigens are a family of immunogenic proteins that are aberrantly overexpressed in neoplastic cells, with normal expression exclusively in the immune privileged testicular tissue, making them attractive targets for cancer immunotherapy
- Letetresgene autoleucel (lete-cel; GSK3377794) is an autologous T-cell therapy that expresses an affinity-enhanced TCR designed to recognize NY-ESO-1 and/or LAGE-1a tumor antigens
  - Initial response rate and durability in NY-ESO-1–positive solid tumors have been encouraging, although not all patients experience a clinical benefit and some of those who achieved a response eventually relapsed[1]
  - Next-generation technologies aim to improve response rates and durability of response, with the ultimate goal of achieving no evidence of disease
- All next-generation T-cell therapies to be investigated in this master protocol (NCT04526509) encode the same NY-ESO-1–specific TCR
  - Each enhancement technology is investigated in a separate substudy within the master protocol, with potential combinations in the future once initial safety and efficacy have been individually assessed
  - Two substudies are already ongoing: one investigating co-expression of a CD8α receptor (GSK3901961, Substudy 1), and one investigating co-expression of a dominant-negative TGFβ receptor (GSK3845097, Substudy 2)
- Substudy 3 investigates GSK4427296, a next-generation T-cell therapy based on lete-cel that incorporates a proprietary epigenetic reprogramming technology, Epi-R™ (Lyell Immunopharma) (**Figure 1**)
  - Epi-R is an optimized manufacturing process designed to intentionally and reproducibly generate populations of T cells with properties of durable stemness, metabolic fitness, and functional persistence of the manufactured product
  - Such cells can proliferate, persist, and are able to provide prolonged anti-tumor functionality, and are therefore anticipated to enhance efficacy over lete-cel

Figure 1. Composition of conventional T-cell preparations vs Epi-R T-cell preparations



Study objective

- To assess the safety, tolerability, and determine RP2D of GSK4427296 in HLA-A*02:01-, HLA-A*02:05-, and/or HLA-A*02:06-positive participants with NY-ESO-1- and/or LAGE-1a-positive, previously treated, advanced (metastatic or unresectable) SS and MRCLS

Study design

- This is a first-in-human, single-cohort, non-randomized, open-label substudy to investigate GSK4427296 in previously treated participants with advanced (metastatic or unresectable) SS and MRCLS (**Figure 2**)
- This substudy will consist of two phases: dose confirmation and dose expansion (**Figure 3**)
- The initial dose selected for the dose confirmation phase is based on the dose investigated for lete-cel

Figure 2. Substudy 3 patient treatment pathway

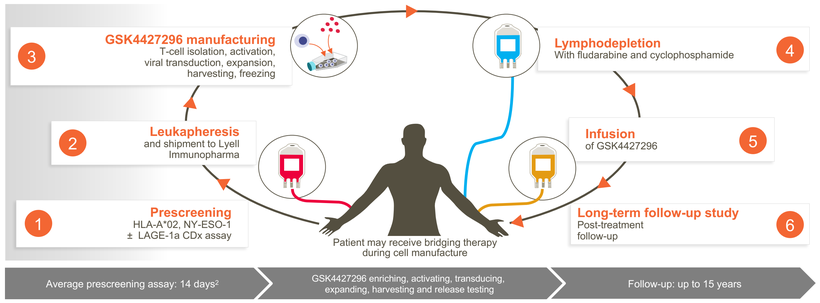
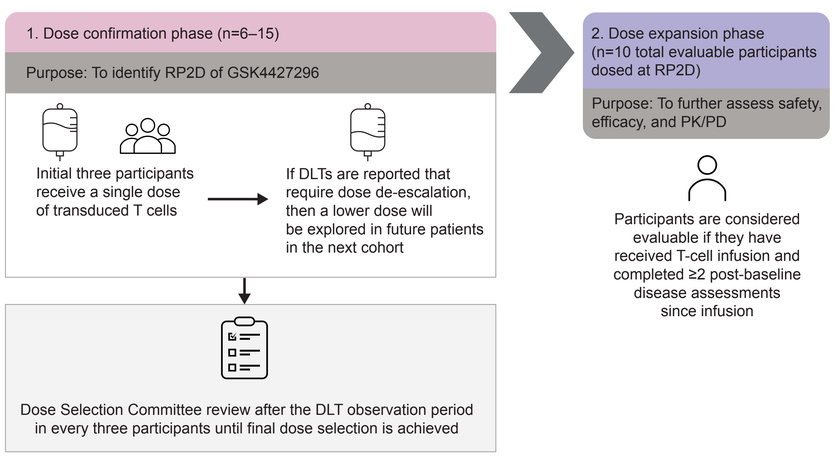


Figure 3. Dose confirmation and dose expansion phases



Study population

Key inclusion criteria	Key exclusion criteria
≥18 years of age	Prior malignancy that is not in complete remission
Measurable disease per RECIST v1.1	Clinically significant systemic illness
Positive for HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 alleles	Previous treatment with genetically engineered NY-ESO-1–specific T cells, NY-ESO-1 vaccine, or NY-ESO-1–targeting antibody
Archival specimen or fresh biopsy of tumor tests positive for NY-ESO-1/LAGE-1a	Prior gene therapy using an integrating vector
Histologically confirmed advanced (metastatic or unresectable) SS or MRCLS	Previous allogeneic hematopoietic stem cell transplant within the past 5 years or solid organ transplant
For SS, presence of a translocation involving chromosome 18 and/or chromosome X	Central nervous system metastases
For MRCLS, presence of a translocation involving *DDIT3* and/or *FUS* and/or *EWSR1* genes	
Completed at least one standard of care treatment with an anthracycline or anthracycline with ifosfamide, or intolerant to therapy	

Study endpoints

Primary endpoints	Secondary endpoints
Frequency of DLTs	Investigator-assessed overall response rate per RECIST v1.1
Frequency and severity of AEs, serious AEs and AEs of special interest (including CRS, ICANS, pancytopenia, GBS, GvHD)	Duration of response
	Maximum transgene expansion (C_{max})
	Time to C_{max} (T_{max})
	Area under the persistence time curve from zero to time t ($AUC_{[0\text{-}t]}$)

Exploratory endpoints
Change in laboratory parameters, vital signs, ECOG PS, ECG
Overall survival, progression-free survival, disease control rate, time to response
Biomarker analyses will include cell expansion (PK), cytokine, and tumor analyses to understand correlations with safety and response

Current status

- The master protocol is currently open and recruiting

Abbreviations

- AE, adverse event; AUC, area under curve; CD8, cluster of differentiation 8; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GBS, Guillain-Barre syndrome; GvHD, graft versus host disease; HLA, human leukocyte antigen; ICANS, immune effector cell-associated neurotoxicity syndrome; lete-cel, letetresgene autoleucel; MRCLS, myxoid/round cell liposarcoma; NY-ESO-1, New York esophageal squamous cell carcinoma-1; PD, pharmacodynamics; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; SS, synovial sarcoma; TCR, T-cell receptor; TGFβ, transforming growth factor β; T_{SCM}, T memory stem cell.

References

1. D'Angelo SP, et al. *Cancer Discov*. 2018;8(8):944–957.
2. D'Angelo SP, et al. Poster presented at SITC 2019 [poster P453].

Disclosures

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