Safety and efficacy of letetresgene autoleucel (lete-cel; GSK3377794) in advanced myxoid/round cell liposarcoma (MRCLS) following high lymphodepletion (Cohort 2): interim analysis

Poster No. 11521

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Background

- There is a need for novel immunotherapies, such as cell therapies, in solid tumors, including myxoid/round cell liposarcoma (MRCLS).
- MRCLS accounts for one-third to half of all liposarcomas,[1] which are one of the most common histological types of soft tissue sarcomas (STS).[2]
  - Approximately 33% of MRCLS cases are metastatic.[3]
    - Survival rates for metastatic disease are 78% and 8.2% at 1 year and 5 years, respectively.[3]
  - While MRCLS is relatively sensitive to radiation therapy and front-line chemotherapy compared to other STS subtypes, outcomes with metastatic disease are poor as they all eventually progress, and systemic treatment options are limited for this subtype.[3,4]
- New York esophageal squamous cell carcinoma-1 (NY-ESO-1) is a cancer testis antigen that is highly immunogenic and expressed in multiple solid tumor types, including 80%–90% of MRCLS.[5,6]
- Letetresgene autoleucel (lete-cel; GSK3377794) is a novel T-cell receptor (TCR) therapy, which consists of autologous CD4+ and CD8+ T cells that are genetically modified to express a TCR recognizing the NY-ESO-1 peptide presented by human leukocyte antigen (HLA)-A*02:01, A*02:05, or A*02:06.
  - Lete-cel has shown encouraging clinical activity in patients with synovial sarcoma (SS).[7,8]
- In this study, a planned interim analysis of lete-cel efficacy and safety in patients with advanced MRCLS following low-dose lymphodepletion (Cohort 1; n=10) showed that lete-cel is well tolerated and was linked with 2 confirmed partial responses (PR; overall response rate [ORR], 20%) and stable disease (SD) in 8 patients.
  - More-intense lymphodepletion regimens have been associated with increased T-cell expansion and efficacy in patients receiving cell therapy.[9]
    - In patients with advanced SS exhibiting high NY-ESO-1 tumor expression, lete-cel infusion following high-dose lymphodepletion chemotherapy resulted in a 50% ORR (including 1 complete response [CR] which lasted 34 weeks) with median OS of 24.3 (95% confidence interval [CI], 8.5–48.8) months.[7]
- In accordance with the protocol for this study, the decision was made to enroll a further 10 patients with advanced MRCLS who would receive a high-dose lymphodepletion regimen (Cohort 2) prior to lete-cel treatment.

Aim

To present the results of the Cohort 2 interim analysis for the efficacy, safety, and T-cell kinetics of lete-cel in patients with NY-ESO-1–expressing advanced MRCLS after high-dose lymphodepletion, with reference to lete-cel kinetics in Cohort 1 (low-dose lymphodepletion).

Methods

- This is an open label, pilot study (GSK 208469; NCT02992743) evaluating lete-cel efficacy and safety in advanced MRCLS following low-dose (Cohort 1) or high-dose (Cohort 2) lymphodepletion regimens.
- This interim analysis was conducted on data as of December 4, 2020.

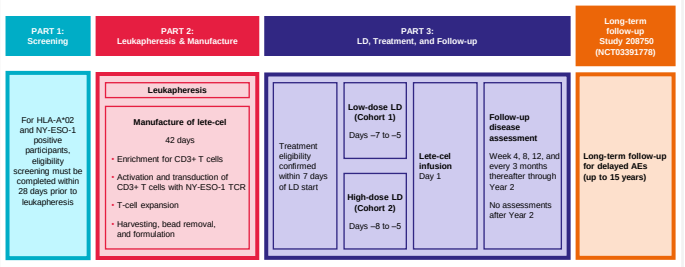
Study design

- Patients identified through screening as HLA-A*02:01, A*02:05, or A*02:06 positive and NY-ESO-1 antigen positive were further screened for enrollment using defined eligibility criteria.
  - Key eligibility criteria: patients aged ≥18 years with histologically confirmed advanced (metastatic or inoperable), high-grade MRCLS with chromosomal translocation t(12;16)(q13;p11) or t(12;22)(q13;q12) and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, who had received or were intolerant to anthracycline-based therapy.
  - Key exclusion criteria: receiving specified anti-cancer therapy prior to leukapheresis or lymphodepletion; history of chronic/recurrent severe autoimmune/immune disease requiring immunosuppressive treatment; prior malignancy not in complete remission; active brain or leptomeningeal metastases.
- Patients underwent leukapheresis for lete-cel manufacture followed by lymphodepletion with a low-dose regimen (Cohort 1 [n=10]: 30 mg/m^2 fludarabine x 3 days + 600 mg/m^2 cyclophosphamide x 3 days) or a high-dose regimen (Cohort 2 [n=10]: 30 mg/m^2 fludarabine x 4 days + 900 mg/m^2 cyclophosphamide x 3 days) (**Figure 1**).
- Patients received lete-cel infusion on Day 1, and disease assessments were performed throughout defined on-study follow-up.
- Patients were subsequently transferred to a long-term follow-up study for up to 15 years.

Study assessments and endpoints

- Tumor response assessments were performed at Weeks 4, 8, 12, and 24, following lete-cel infusion, then every 3 months to disease progression, death, withdrawal from the study, or 2 years after lete-cel infusion.
- Planned interim analysis for Cohort 2 was performed once all 10 treated patients had ≥3 post-baseline disease assessments or had progressed, died, or withdrawn from the study.
- The primary efficacy outcome was investigator-assessed ORR (CR or PR) per RECIST v1.1.
- Secondary efficacy outcomes included time-to-response (TTR), duration of response (DoR), and progression-free survival (PFS).
- Safety was assessed as a secondary outcome throughout the study, with the reporting of adverse events (AEs), serious adverse events (SAEs), and AEs of special interest evaluated using Common Terminology Criteria for Adverse Events v4.0 (CTCAE v4.0).
- Exploratory outcomes included the peak expansion of transduced T cells and its association with lymphodepletion regimen and cell dose.

Figure 1. Study design



AE, adverse event; HLA, human leukocyte antigen; LD, lymphodepletion; NY-ESO-1, New York esophageal squamous cell carcinoma-1; TCR, T-cell receptor.
Low-dose LD consists of 30 mg/m^2 fludarabine x 3 days + 600 mg/m^2 cyclophosphamide x 3 days.
High-dose LD consists of 30 mg/m^2 fludarabine x 4 days + 900 mg/m^2 cyclophosphamide x 3 days.

Results

- Patients with high-dose lymphodepletion (Cohort 2) were mostly male (70%), with a median (range) age of 41.0 (33–72) years. All patients had received prior chemotherapy (100%), and the majority of patients had received ≤2 systemic therapy regimens (90%) (**Table 1**).

Efficacy

- High-dose lymphodepletion (Cohort 2) investigator-assessed ORR was 40% (95% CI: 12.2%–73.8%) (4/10 PR; **Figure 2**); PFS data were not mature.
  - Median (range) TTR was 1.9 (1.9–2.8) months.
  - DoR ranges from 1.0 (ongoing) to 7.8 months with two of the responders still ongoing (**Figure 3**).
  - SD was observed in 5 (50%) of patients and was ongoing in 3 patients, with duration ranging from 2.7 (ongoing) to 10.6 months (**Figure 3**).
  - Tumor shrinkage was observed in 9/10 patients (**Figures 2 & 3**).

Safety

- All patients in Cohort 2 experienced Grade ≥3 treatment-emergent cytopenias.
- All patients experienced T-cell related cytokine release syndrome (CRS), of which 3 (30%) were reported as Grade 3 AE (**Table 2**) and 5 (50%) were reported as serious (**Table 3**).
  - The median (range) onset for CRS was 2.0 (1–5) days, and median duration was 7.5 (3–25) days.
  - All instances of CRS were resolved; 4/10 patients required tocilizumab as a single dose to resolve CRS, of whom 3 experienced CRS as a SAE.
- No Grade 5 AEs occurred in Cohort 2; Grade 4 treatment-emergent AEs occurred in 9 patients (1 serious) and Grade 4 T-cell infusion-related AEs in 4 patients (1 serious).
- There were no reports of graft-*vs*-host disease (GvHD), immune effector cell–associated neurotoxicity syndrome (ICANS), pancytopenia, severe aplastic anemia, or Guillain-Barre syndrome.

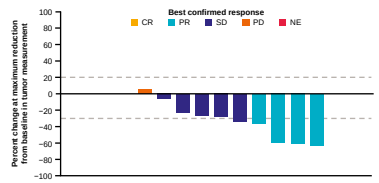
Transduced T-cell kinetics

- All patients showed T-cell peak expansion within 2 weeks post-infusion (**Figure 4**).
  - Sustained T-cell persistence was more commonly observed for responders compared to non-responders during 1-year post-infusion.
  - Non-responders in Cohort 2 compared to Cohort 1 showed shorter duration of T-cell persistence.
  - One patient from Cohort 2 with prolonged SD (>10 months) also demonstrated prolonged T-cell persistence in the periphery (**Figure 4B**).
  - Compared to Cohort 1, Cohort 2 resulted in lower levels of endogenous (residual) lymphocytes and a trend towards higher peak expansion (**Figure 5**).
  - A higher body weight–normalized cell dose was found to be significantly associated with peak expansion (P=0.0197) (**Figure 6**).

Table 1. Baseline patient characteristics

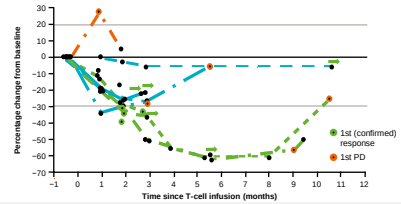
Parameter	High-dose lymphodepletion (Cohort 2 [N=10])
Sex, n (%)	
Male	7 (70)
Female	3 (30)
Median age (range), years	41.0 (33–72)
Prior anti-cancer therapies, n (%)	
Any	10 (100)
Chemotherapy	10 (100)
Surgery	6 (60)
Radiotherapy	2 (20)
Vaccine	1 (10)
Immunotherapy	0 (0)
Number of prior systemic therapy regimens, n (%)	
0	0 (0)
1	6 (60)
2	3 (30)
3	0 (0)
>3	1 (10)
Number of prior radiotherapy regimens, n (%)	
0	8 (80)
1	0 (0)
>1	2 (20)
Bridging therapy, n (%)	2 (20)

Figure 2. Maximum percentage reduction from baseline in sum of target lesion diameters by RECIST v1.1



CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NE, not evaluable; RECIST v1.1, Response Evaluation Criteria in Solid Tumors v1.1.

Figure 3. Percentage change from baseline in sum of target lesion diameters by RECIST v1.1 over time



PD, progressive disease; RECIST v1.1, Response Evaluation Criteria in Solid Tumors v1.1. Arrows indicate patients who have not progressed or initiated new anti-cancer therapy and whose interventional phase follow-up was ongoing as of the data cut-off date. Orange line indicates progressive disease, blue lines indicate stable disease, and green lines indicate partial response.

Table 2. Grade ≥3 AEs

	Treatment-emergent AEs (N=10)	T-cell infusion-related AEs (N=10)
Any event, n (%)	10 (100)	8 (80)
Leukopenia	8 (80)	4 (40)
Anemia	7 (70)	1 (10)
Thrombocytopenia	6 (60)	1 (10)
Neutropenia	5 (50)	3 (30)
Febrile neutropenia	4 (40)	3 (30)
Lymphopenia	4 (40)	1 (10)
Cytokine release syndrome	3 (30)	3 (30)
Rash	3 (30)	2 (20)
Arthralgia	1 (10)	–
Bone pain	1 (10)	1 (10)
Headache	1 (10)	1 (10)
Hyperglycemia	1 (10)	–
Hypokalemia	1 (10)	–
Hypophosphatasemia	1 (10)	–
Pyrexia	1 (10)	1 (10)
Urticaria	1 (10)	1 (10)

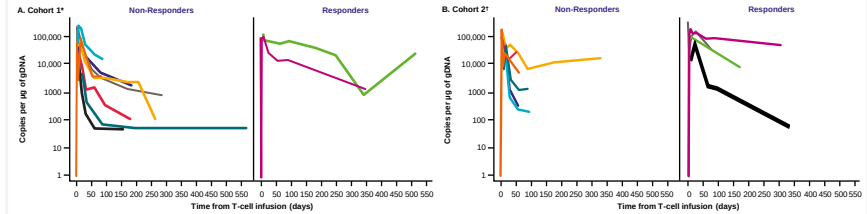
AE, adverse event. Treatment-emergent is defined as onset on or after lymphodepletion chemotherapy start date. T-cell infusion-related is as identified by the investigator.

Table 3. Grade ≥3 SAEs

	Treatment-emergent SAEs (N=10)	T-cell infusion-related SAEs (N=10)
Any event, n (%)	5 (50)	4 (40)
Cytokine release syndrome	3 (30)	3 (30)
Rash	3 (30)	2 (20)
Neutropenia	1 (10)	1 (10)
Thrombocytopenia	1 (10)	1 (10)

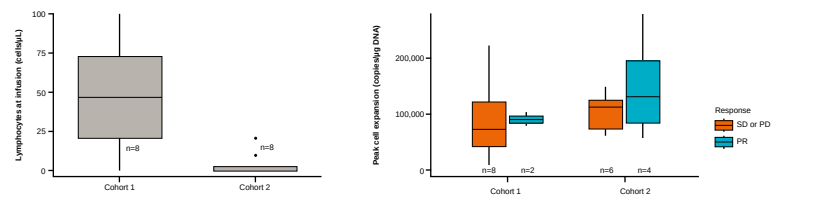
SAE, serious adverse event. Treatment-emergent is defined as onset on or after lymphodepletion and infusion chemotherapy start date. T-cell infusion-related is as identified by the investigator.

Figure 4. Persistence profiles for low-dose (Cohort 1) and high-dose (Cohort 2) lymphodepletion



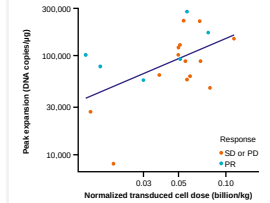
*Complete data for Cohort 1; †Data collection ongoing.

Figure 5. Lymphocyte count and peak expansion for low-dose (Cohort 1) and high-dose (Cohort 2) lymphodepletion



PD, progressive disease; PR, partial response; SD, stable disease.

Figure 6. Transduced dose (normalized to body weight) correlated to peak expansion in Cohorts 1 and 2



PD, progressive disease; PR, partial response; SD, stable disease.

Summary

- In a planned interim analysis, for high-dose lymphodepletion (Cohort 2), lete-cel demonstrated a higher ORR (40%), compared to low-dose lymphodepletion (Cohort 1 [ORR: 20%]), in patients with NY-ESO-1–positive advanced (metastatic or inoperable) MRCLS who had received, were intolerant to, or had progressed on anthracycline-based therapy.
  - A similar outcome was observed in patients with metastatic SS treated, with a greater ORR observed in patients who had received a high-dose lymphodepletion regimen.[7]
  - This level of activity is of interest given the historical response rates described in patients with second-line agents in MRCLS,[5] and notable for an immune-based therapy in a tumor type that has a low mutational burden at baseline.[10]
  - Tumor shrinkage was observed in 9/10 Cohort 2 patients.
  - All responses (4/10) were PR, occurring 8–12 weeks after treatment, and responses deepened over time; responses were durable and were ongoing in 2 patients.
  - Clinical benefit was observed in patients who achieved SD as best response.
- Lete-cel demonstrated a tolerable safety profile in Cohort 2, with toxicity mostly consistent with lymphodepleting chemotherapy; no new safety signals were detected.
  - All patients experienced CRS; 30% of cases were Grade 3 and all resolved.
  - Treatment-emergent cytopenias occurred in all patients.
  - There was no evidence of neurotoxicity, GvHD, ICANS, pancytopenia, or severe aplastic anemia.
- Analysis of T-cell kinetics demonstrated lower levels of endogenous (residual) lymphocytes and a trend towards higher peak expansion in Cohort 2 compared with Cohort 1.
- Transduced cell dose (normalized by weight) has a statistically significant association with peak cell expansion.
- 100% (or 10/10) of the enrolled patients had successful apheresis and were dosed with T-cells demonstrating feasibility of the lete-cel supply chain.
- The trial is active but no longer recruiting (NCT02992743). MRCLS is included in a separate, ongoing lete-cel study (NCT03967223).

Disclosures

SPDA reports paid consultancy for Amgen, EMD Serono, GSK, Immune Design, Immunocore, Incyte, Merck, Adaptimmune, and Nektar; travel, accommodations, and expenses from Adaptimmune, EMD Serono, and Nektar; and research support, paid to her institution, from EMD Serono, Amgen, Incyte, Nektar, BMS, Deciphera, and Merck. **MD** declares honoraria from Adaptimmune, Blueprint, Daiichi Sankyo, Deciphera, and Epizyme. **BAVT** holds board membership/committee appointment for Polaris; declares paid consultancy or advisory roles for EMD Serono, Novartis, Epizyme, Daiichi Sankyo, Pfizer, Adaptimmune, Bayer, GSK, Lilly, Cytokinetics Inc, Apexigen Inc, and Deciphera; has participated in speakers bureaus/paid presentations for Adaptimmune, GSK, Lilly, and Novartis; has received research funding from GSK, Merck, Pfizer, and Tracon; has received travel, accommodations, and expenses from Lilly, Adaptimmune, and Advenchen Laboratories; and holds patents/licensing agreements on the use of ME1 as a biomarker, ALEXT3102, and for work performed with Accuronix Therapeutics. **DL** reports paid consulting or advisory roles for Epizyme, Blueprint Medicines, and Foundation Medicine; travel, accommodations, and expenses from Epizyme, Blueprint Medicines, and Foundation Medicine; and holds patents pertaining to methods for predicting prognosis that have been licensed to MatchTx, LLC. **SS** reports travel, accommodations, and expenses received from Blueprint Medicines and has received research funding, paid to his institution, from Amgen, Karyopharm Therapeutics, Adaptimmune, Blueprint Medicines, and GSK. **ANH** is a former employee of and holds stocks/shares in GSK and receives royalties from Atara Biotherapeutics. **APH** is an employee of Veramed UK; has an immediate family member who is employed by Phastar; and reports travel, accommodations, and expenses from Veramed. **AH** is a current employee of GSK and holds stocks/shares in GSK and Pfizer. **GK** and **SZ** are current employees of and hold stock/shares in GSK. **NS** reports paid consultancy or advisory roles for Deciphera, Bayer, and Blueprint Medicines; has an immediate family member who holds stocks/shares in Pfizer and Johnson and Johnson; and has received research funding from MedImmune, GSK, Karyopharm Therapeutics, Deciphera, Ascentage Pharma, and Daiichi Sankyo/Lilly.

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