# Biomarker correlates of response in patients with advanced Myxoid/Round Cell Liposarcoma (MRCLS) treated with NY-ESO-1 TCR T cells (Letetresgene autoleucel)

**Poster No. 391**


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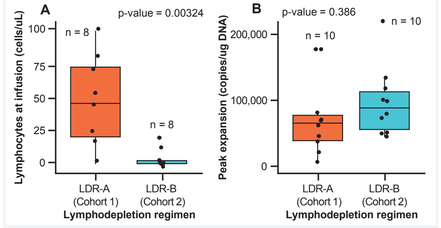
## Introduction

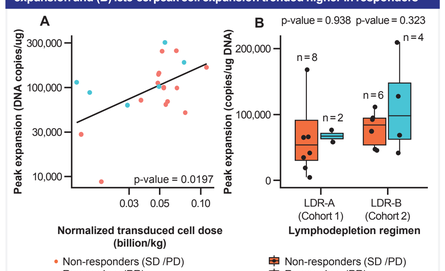
- This is an open-label pilot study (NCT02992743) of letetresgene autoleucel (lete-cel; GSK3377794), an NY-ESO-1-specific autologous CD4+ and CD8+ T cells expressing a high affinity T-cell receptor which recognizes the NY-ESO-1 antigen epitope in complex with specific human leukocyte antigen (HLA)-alleles A*02.
- Lete-cel exhibited anti-tumor activity and manageable safety profiles in patients with advanced MRCLS based on interim analysis (IA) data [1].
- Lymphodepletion has been shown to enhance the expansion, persistence, and homing of therapeutically infused T-cells, thereby potentiating therapeutic efficacy against malignant diseases [2].
- Lymphodepletion regimens (LDR) have also been shown to increase cytokines important for T-cell proliferation. Higher LDRs can induce a greater increase in cytokine levels [3].
- Initial T-cell kinetics data from this pilot study demonstrated that LDR-B (**Table 1**) robustly depleted lymphocytes at infusion (**Figure 1A**) and was trended towards higher peak cell expansion ($C_{max}$) versus LDR-A (**Table 1**, **Figure 1B**) [1].
- The peak expansion was significantly associated with weight-normalized transduced cell dose and trended with response (**Figure 2A and B**) [1].

**Figure 1. (A) Absolute endogenous lymphocyte counts at the time of infusion stratified by cohorts and (B) trend of high lete-cel peak expansion in LDR-B (Cohort 2) vs. LDR-A (Cohort 1)**




*Lymphocyte count data at infusion was missing for 4 patients across both trials;
LDR, lymphodepletion regimen.

**Figure 2. (A) Body weight-normalized lete-cel dose correlates with peak cell expansion and (B) lete-cel peak cell expansion trended higher in responders**




LDR, lymphodepletion regimen; PD, progressive disease; PR, partial response; SD, stable disease

## Objectives

- Biomarker analyses were performed following the IA response data
- Explore association of lymphocyte and monocyte depletion at infusion with peak expansion and response.
- Explore additional cell kinetics parameters and their association with response and tumor growth.
- Explore cytokines profiles in both the cohorts in relation to response.

## Methods

- Patients with advanced MRCLS were enrolled to 2 cohorts and received either planned A (N=10) or B (N=10) LDRs prior to lete-cel infusion (**Table 1**). Response was assessed per Response Evaluation Criteria in Solid Tumors v1.1.

**Table 1. Patient Baseline Demographics and Clinical Characteristics at Enrollment (mTT)**

| Parameter | Cohort 1 (N=10) | Cohort 2 (N=10) |
|---|---|---|
| **NY-ESO-1 expression criteria** | IHC score 2+ or 3+ in ≥50% of tumor cells | IHC score 2+ or 3+ in ≥50% of tumor cells |
| **Lymphodepletion regimen (LDR)** | **LDR-A:** • Fludarabine: 30 mg/m² IV on Days –7 to –5 • Cyclophosphamide: 600 mg/m² IV on Days –7 to –5 | **LDR-B:** • Fludarabine: 30 mg/m² IV Days –8 to –5 • Cyclophosphamide: 900 mg/m² IV on Days –7 and –5 |
| **Confirmed Response rate (%)** | 2/10 (20) | 4/10 (40) |
| **Sex, n (%)** | | |
| Female | 4 (40) | 3 (30) |
| Male | 6 (60) | 7 (70) |
| **Median age (min, max), ye`ars** | 52.5 (37,60) | 41 (33,72) |
| **Race, n (%)** | | |
| Black or African American | 1 (10) | 0 |
| White | 9 (90) | 10 (100) |
| **HLA-A status, N (Allele 1: Allele 2)** | | |
| HLA-A*02:01 | (7, 4) | (8, 4) |
| HLA-A*02:05 | (0, 0) | (0,0) |
| HLA-A*02:06 | (0, 0) | (0, 0) |
| Others | (3, 6) | (1, 4) |
| Ambiguous | (0, 0) | (1, 2) |
| **Disease stage at enrollment, n (%)** | | |
| Stage IIIB | 1 (10) | 3 (33) |
| Stage IV | 9 (90) | 6 (67) |
| **Mean transduced cell in billions (min, max)** | 3.58 (1.01, 5.7) | 4.42 (2.8, 6.3) |
| **Mean (SD) peak persistence (vector copies/µg gDNA)** | 94,097.62 (73,670.816) | 121,956 (66,302.35) |

IHC, Immunohistochemistry; HLA, Human Leukocyte Antigen; IV, Intravenous; mITT, Modified intent-to-treat; NY-ESO-1, New York Esophageal Squamous Cell Carcinoma-1; SD, Standard deviation

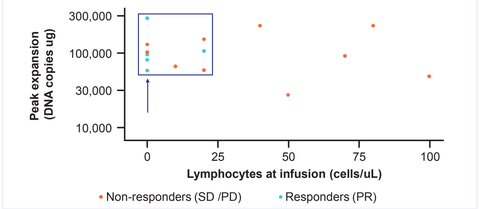
- Transduced cell kinetics were measured by quantitative polymerase chain reaction of transgene vector copies (vector copies/µg gDNA) in DNA from peripheral blood mononuclear cells.
- Serum cytokines were measured by Meso Scale Discovery immunoassay.
- Potential biomarker correlates of clinical response were tested in a post-hoc analysis using generalized linear models and linear mixed models accounting for left-censoring when applicable.

## Results

### Association of decreased lymphocyte and monocyte counts at the time of infusion with response

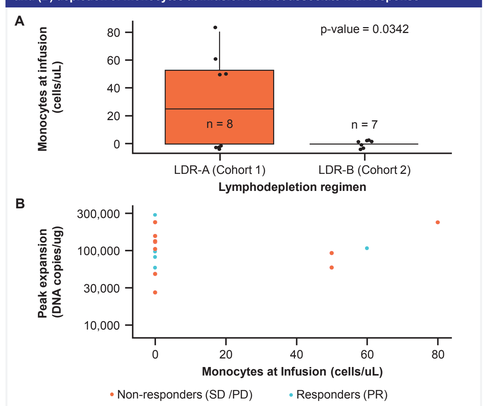
- Five out of 6 responders with available laboratory data exhibited robust lymphocyte depletion at infusion (0–25 cell/uL) and high $C_{max}$ (>50,000 vector copies/ µg gDNA) with LDR (**Figure 3**)
- Only 6/14 non-responders exhibited low lymphocyte counts at the time of infusion and high $C_{max}$ (**Figure 3**).
- LDR-B induced strong depletion of monocytes at the time of infusion (p=0.03) versus LDR-A (**Figure 4A**), however, depletion of monocytes did not show any association with response (**Figure 4B**).

**Figure 3. Responders showed robust lymphocyte depletion at the time of infusion and high peak cell expansion**




PD, progressive disease; PR, partial response; SD, stable disease; Arrow indicates patients with complete lymphocyte depletion at infusion and high peak expansion

**Figure 4. (A) Absolute monocyte counts at the time of infusion stratified by cohorts* and (B) depletion of monocytes at infusion did not associate with response**

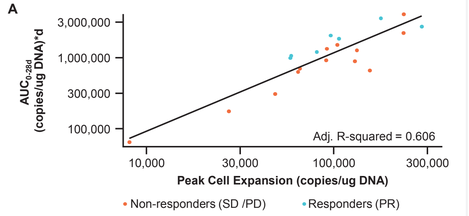


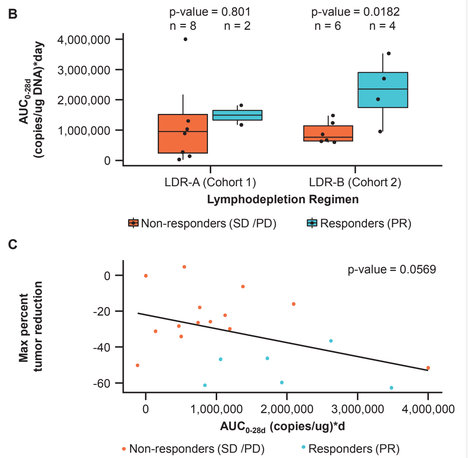

*Monocyte count data at infusion was missing for 5 patients.
LDR, lymphodepletion regimen; PD, progressive disease; PR, partial response; SD, stable disease

### Treatment exposure ($AUC_{0–28d}$) is a better predictor of response than $C_{max}$ and associates with tumor volume reduction

- Higher $C_{max}$ was associated with treatment exposure ($AUC_{0–28d}$) (Adj. R2=0.606) (**Figure 5A**).
- $AUC_{0–28d}$ was a better predictor of response in patients receiving LDR-B (p=0.0182), with $AUC_{0–28d}$ trending towards predicting response in the LDR-A cohort (**Figure 5B**).
- $AUC_{0–28d}$ was associated with tumor volume reduction (p=0.0569) (**Figure 5C**).

**Figure 5. (A) Exposure to lete-cel ($AUC_{0-28d}$) showed association with peak cell expansion, (B) $AUC_{0-28d}$ is a better predictor of response, (C) $AUC_{0-28d}$ associates with tumor volume reduction**



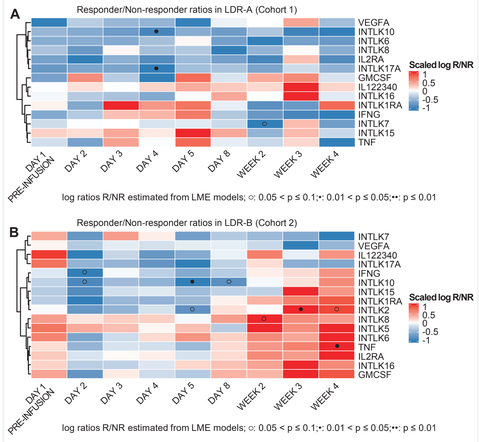




LDR, lymphodepletion; PD, progressive disease; PR, partial response; SD, stable disease.

### Differential expression of cytokines in responders vs. non-responders

- In LDR-A cohort, several cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), IL1 receptor agonist (RA), interferon-gamma (IFN-γ), IL15, and tumor necrosis factor (TNF) were upregulated in the first week following lete-cel infusion in responders when compared with non-responders (**Figure 6A**)
- In LDR-B cohort, responders showed upregulation of IL2, IL5, IL6, IL8, IL15, IL1RA, IL2RA, IL16, and GMCSF after 1 week of lete-cel infusion (**Figure 6B**)

**Figure 6. Heatmap showing differential modulation of cytokine levels in responder vs. non-responders in (A) LDR-A regimen cohort and (B) LDR-B regimen cohort**




GMCSF, granulocyte-macrophage colony-stimulating factor; IFNG, interferon gamma; IL, interleukin; INTLK, interleukin; LDR, lymphodepletion regimen; LME, linear mixed effects models; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

## Conclusions

- The present data supports our previous observations in the Phase I Synovial Sarcoma study (NCT01343043) that complete lymphocyte depletion by LDR at the time of infusion could play an important role for lete-cel expansion and response [4].
- Exposure to lete-cel ($AUC_{0–28d}$) appears to be a better predictor of response than peak expansion ($C_{max}$) and may also associate with tumor volume reduction.
- Several immune modulatory cytokines were upregulated in responders versus non-responders, however, more thorough analyses are warranted to associate these observations to response and/or resistance.


## Disclosures

**GSK , SZ, SS, JK, IE, HF,** and **MN** are current employees of and hold stock/shares in GlaxoSmithKline. **MD** declares honoraria from Adaptimmune, Blueprint, Daiichi Sankyo, Deciphera, and Epizyme. **BAVT** reports a leadership role for Polaris; reports 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, ACXT3102, and for work performed with Accuronix Therapeutics. **NS** reports paid consultancy or advisory roles for Boehringer Ingelheim, Deciphera, Bayer, and Immunicum; has an immediate family member who holds stocks/shares in Pfizer and Johnson and Johnson; and has received research funding from MedImmune/ AstraZeneca, GSK, Karyopharm Therapeutics, Deciphera, Ascentage Pharma, and Daiichi Sankyo/Lilly. **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 paid consulting for Boehringer-Ingelheim and GSK and has received research funding, paid to his institution, from Amgen, Karyopharm Therapeutics, Adaptimmune, Blueprint Medicines, and GSK. **SPDA** reports paid consulting or advisory roles 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 from EMD Serono, Amgen, Incyte, Nektar, BMS, Deciphera, and Merck, paid to her institution.

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