Modeling the efficacy of NY-ESO-1 TCR T cells (letetresgene autoleucel; GSK3377794) in patients with synovial sarcoma: correlations of response with transduced cell kinetics and biomarkers

Poster number: 595

Gyurdieva A[1], Zajic S[1], Chang Y[1], Houseman E[1], Zhong S[1], Kim J[1], Turner DC[1], Johnson L[1], Eleftheriadou I[1], Tress J[1]*, Hasan AN[1], Chiou V[1], Glod J[2], Araujo D[3], Chow W[4], Druta M[5], Demetri G[6], Van Tine BA[7], D'Angelo S[8]

[1]GlaxoSmithKline, Collegeville, PA, USA; [2]National Cancer Institute, Bethesda, MD, USA; [3]University of Texas/MD Anderson Cancer Center, Houston, TX, USA; [4]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [5]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [6]Dana-Farber Cancer Institute and Ludwig Center at Harvard, Boston, MA, USA; [7]Washington University in St. Louis, MO, USA; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; *At time of study

Introduction

- New York esophageal squamous cell carcinoma 1 (NY-ESO-1)–specific T cells (letetresgene autoleucel [lete-cel]; GSK3377794) are autologous CD4+ and CD8+ T cells that have been genetically engineered to express high affinity T-cell receptor (TCR) recognizing NY-ESO-1 antigen in complex with human leukocyte antigen-A*02 (HLA-A*02).
- NY-ESO-1 is a cancer/testis antigen that is expressed in many cancers, including strong expression in ~76% of synovial sarcoma (SS).[1]
- Biomarker analyses of chimeric antigen receptor (CAR) T cells in hematologic malignancies have previously reported increased peak cell expansion or persistence in responders.[2]
- Lymphodepletion regimens (LDR) have been shown to increase cytokines important for T-cell proliferation. Higher LDRs can induce a greater increase in cytokine levels.[3] Higher levels of interleukin-7 (IL-7) and IL-15, have been associated with remission in different hematological disease post treatment with CAR-T,[2,4] but no association of cytokines with response has been shown for TCR T-cell therapy.

Objective

- Study 208466 (NCT01343043) is a Phase I clinical trial of the safety and efficacy of lete-cel in patients with advanced SS (presented in complementary poster #596). The trial was designed to assess efficacy/safety associations between different antigen expression levels and LDR.
- The exploratory objectives included correlations of transduced cell kinetics (exposure–response) and biomarkers in blood and tumors with response are presented here.

Methods

- Patients with unresectable, metastatic, or recurrent SS were enrolled to 4 cohorts based on different NY-ESO-1 expression levels and LDR prior to lete-cel infusion (n=45). NY-ESO-1 criteria, baseline demographics, and clinical characteristics are shown in **Table 1**.
  - Response was assessed per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 (investigator-assessed).

Table 1. Patient baseline demographic and clinical characteristics[a]

Parameter	Cohort 1 (n=12)	Cohort 2 (n=13)	Cohort 3 (n=5)	Cohort 4 (n=15)	Overall[b] (N=45)
NY-ESO-1 expression criteria	≥50% at 2+ or 3+[b]	≥1% at 1+ but not exceeding ≥50% cells at 2+ or 3+	≥50% at 2+ or 3+	≥50% at 2+ or 3+	N/A
Lymphodepleting Regimen	Fludarabine: 30 mg/m² IV x4D Cyclophosphamide: 1800 mg/m² IV x2D		Cyclophosphamide: 1800 mg/m² IV x2D	Fludarabine: 30 mg/m² IV x3D Cyclophosphamide: 600 mg/m² IV x3D	N/A
Sex, n (%)					
Men	6 (50)	7 (54)	3 (60)	8 (53)	24 (53)
Median age (range), years[c]	30 (18–50)	29 (11–73)	25 (15–39)	36 (20–69)	32 (11–73)
Race, n (%)					
Black/African American	0	0	1 (20)	1 (7)	2 (4)
White	11 (92)	10 (77)	4 (80)	14 (93)	39 (87)
Other	1 (8)	3 (23)	0	0	4 (9)
HLA-A status, n (%)					
HLA-A*02:01	10 (83)	13 (100)	5 (100)	14 (93)	42 (93)
HLA-A*02:05	0	0	0	1 (7)	1 (2)
HLA-A*02:06	1 (8)	0	0	0	1 (2)
Other[d]	1 (8)	0	0	0	1 (2)
Disease stage at enrollment, n (%)					
Stage Ib[e]	0	1 (8)	0	1 (7)	2 (4)
Stage III	0	0	0	1 (7)	1 (2)
Stage IV	9 (75)	10 (77)	3 (60)	9 (60)	31 (69)
Other	3 (25)	2 (15)	2 (40)	4 (27)	11 (24)

HLA, human leukocyte antigen; IV, intravenous; NY-ESO-1, New York esophageal antigen-1.

[a]Totals may not sum to 100% due to rounding. [b]One patient had only >30% cells at 3+, which was defined as positive expression (≥3+ in 25% of cells) in the protocol amendment under which the patient was enrolled. [c]At informed consent. [d]Result was ambiguous and assumed to be HLA-A*02:01-positive at >99.99% probability. [e]Stage I patients may have been described as Stage I at diagnosis rather than enrollment.

- Transduced cell kinetics (persistence) were measured by quantitative PCR of transgene vector copies in DNA extracted from peripheral blood mononuclear cells.
- Serum cytokines were measured by Meso Scale Discovery (MSD) immunoassay.
- Gene expression within tumor biopsies was evaluated by Nanostring.
- Post-hoc analyses were evaluated in a hypothesis-driven manner using logistic and linear regression.
  - Potential determinants of peak persistence and clinical response were tested using generalized linear models.

Results

Higher T-cell expansion (persistence) strongly associated with response

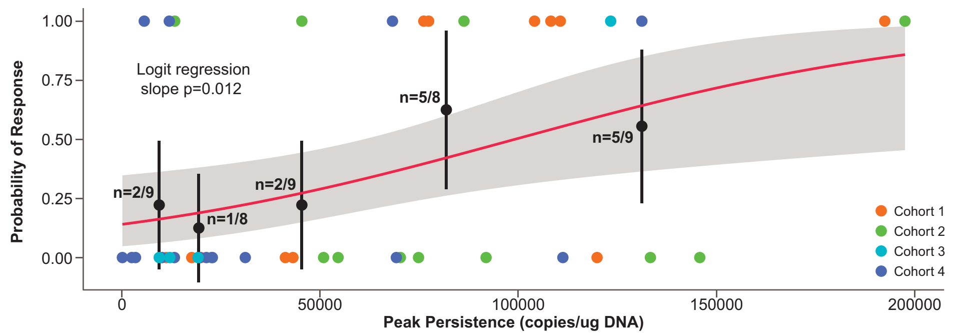
- Patients with responding tumors across cohorts had a higher peak T-cell persistence (p=0.012) (**Table 2** and **Figure 1**).
  - For the median peak persistence of 45,400 copies DNA/µg, the predicted probability of response is 27.3%. If the peak persistence is double (90,900 copies DNA/µg), the predicted probability of response is 46.2%, as illustrated for the range of peak persistence values in **Figure 1**.

Table 2. Response rate and peak T-cell persistence across cohorts

Cohort N	Response Rate (%)	Median OS (95% CI), months	Mean Transduced T Cell Dose in 10⁹ cells (Min, Max)	Peak T Cell Persistence (vector copies/µg DNA Mean (Std. Dev.)
Cohort 1 n=12	6/12 (50%)	24.3 (8.5–48.8)	4.95 (0.451, 14.4)	76,800 (53,500)
Cohort 2 n=13	4/13 (31%)	9.9 (3.9–19.6)	2.81 (1.60, 5.01)	82,200 (53,600)
Cohort 3 n=5	1/5 (20%)	19.9 (8.8–NA)	3.23 (1.53, 5.00)	41,000 (55,000)
Cohort 4 n=15	4/15 (27%)	Not mature; to be reported later	2.67 (1.00, 4.95)	34,800 (41,100)

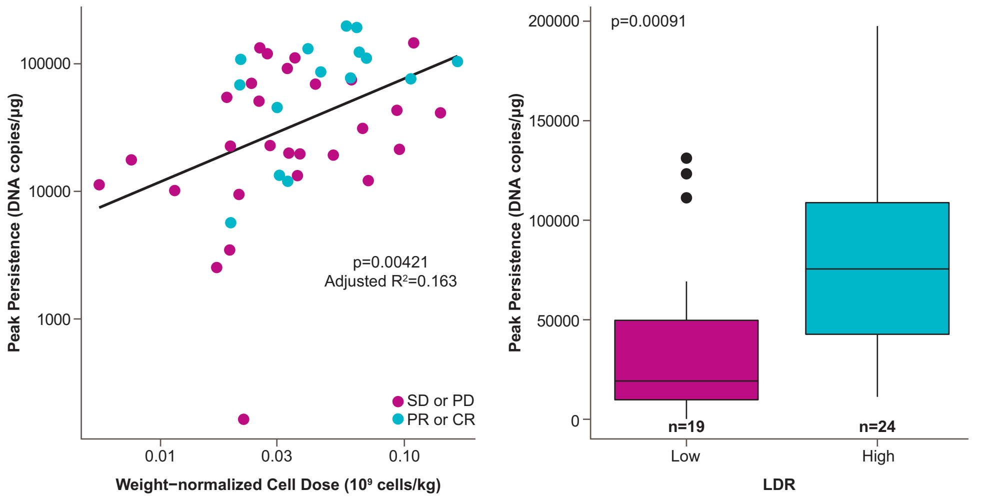
CI, confidence interval; OS, overall survival; Std. Dev., standard deviation.

Figure 1. Association of probability of response with peak persistence



- Higher weight-normalized cell dose (p=0.00421) and LDR (p=0.000910) were associated with C_{max} (maximum transduced T-cell persistence) according to the generalized linear model: C_{max} ~ cell dose + LDR (**Figure 2**). Statistical significance is presented for univariate analysis but remains significant when combined in the model.
  - These relationships allowed for accurate retrospective prediction of probability of response.

Figure 2. Correlation of weight-normalized dose and LDR with peak persistence



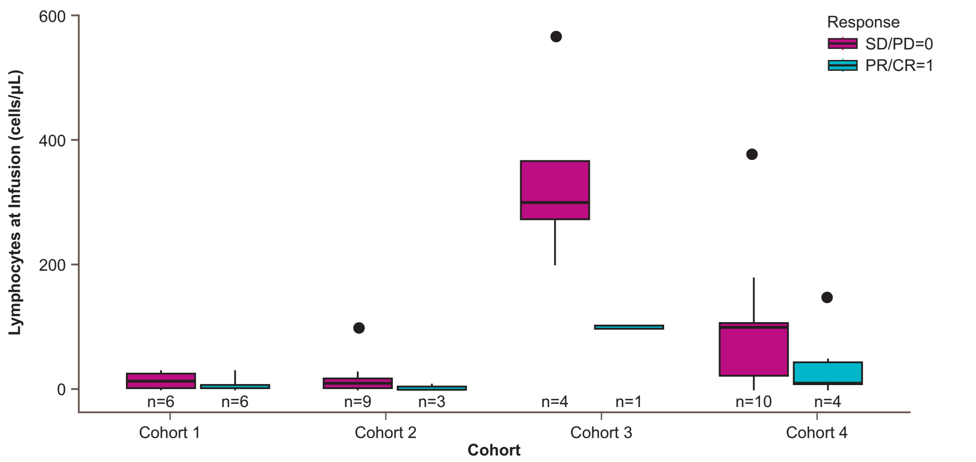
CR, complete response; LDR, lymphodepletion regimen; PD, progressive disease; PR, partial response; SD, stable disease.

High LDR refers to Cohorts 1 and 2 where patients received high doses of fludarabine and cyclophosphamide; low LDR refers to Cohorts 3 and 4 where patients received high doses of cyclophosphamide ONLY (Cohort 3) or a combination regime with a low dose of cyclophosphamide (Cohort 4).

Decreased lymphocyte counts and higher IL-15 levels prior to infusion correlate to response

- Low LDR, especially without the use of Fludarabine (Flu), was associated with higher endogenous (residual) lymphocyte counts on the day of dosing, which trended with lack of response within and across cohorts (**Figure 3**).
  - Most patients with responding tumors had less than 10 cells/µL prior to T-cell infusion (two responders in Cohorts 3 and 4 had 100–150 cells/µL).

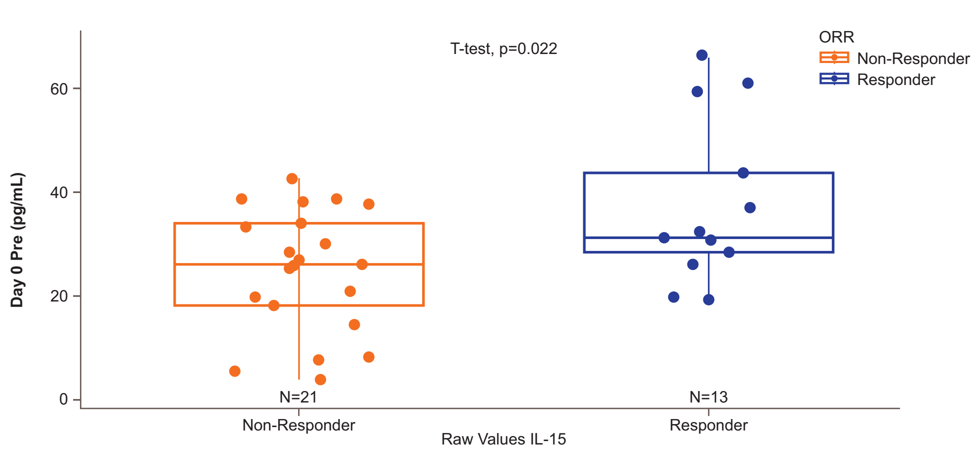
Figure 3. Endogenous lymphocyte counts across cohorts and correlation to response



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

- Use of Flu in the LDR has been shown to increase IL-15 levels and higher IL-15 prior to lete-cel infusion correlated with clinical response (p=0.022) (**Figure 4**).
  - There was no significant difference in IL-7 levels prior to infusion between responders and non-responders (Welch's 2-sample t-test p-value=0.393, Ratio of Responder/Non-Responder geometric mean=1.18, 95% CI: 0.79–1.77).
- The only responder within Cohort 3 had the lowest levels of endogenous lymphocytes and the highest levels of IL-15 pre-infusion (20 pg/mL) as compared to the rest of Cohort 3.

Figure 4. Correlation of IL-15 levels pre-infusion to response

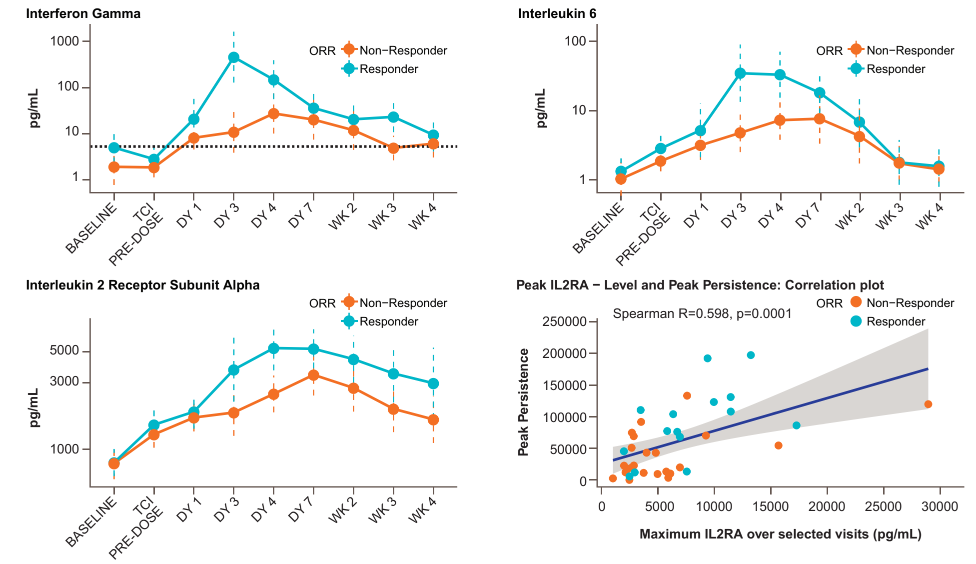


IL, interleukin; ORR, overall response rate.

Pro-inflammatory cytokines are identified as PD markers and IL-2RA shows PK/PD relationship

- Post lete-cel infusion, the concentrations of interferon-gamma (IFNγ), IL-6, and IL-2RA within the first week were increased in patients with responding vs non-responding tumors (**Figure 5**).
  - These cytokines are indicative of immune cell activation and typically peak by Day 3 or 4 in responders and then gradually decreased to pre-infusion levels by Week 4.
- The peak expression of IL-2RA showed a linear correlation to C_{max} (**Figure 5**).

Figure 5. Cytokine upregulation in responders within the first week and correlation of IL-2RA to peak persistence

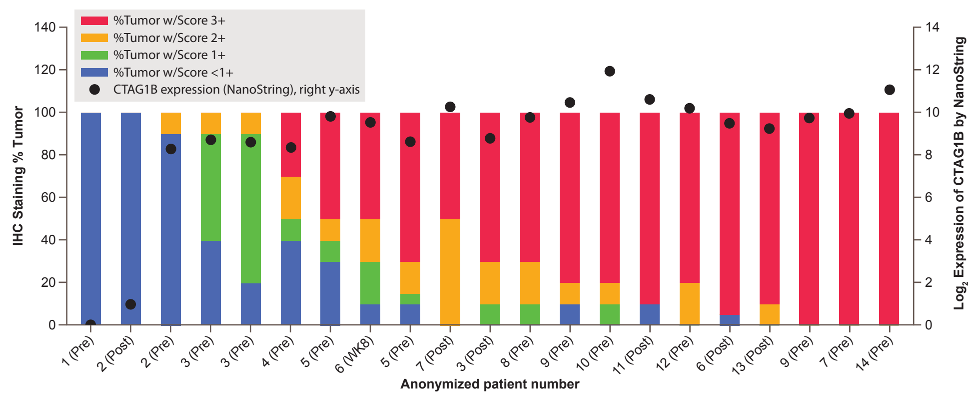


DY, day; WK, week; ORR, overall response rate.

Good correlation between NY-ESO-1 mRNA and protein expression in tumor biopsies

- This suggests that RNA-based techniques could be used for selection purposes in the future (**Figure 6**).

Figure 6. Correlation between NY-ESO-1 mRNA and protein expression



Patient 3: 2 blocks from same biopsy tested; patient 5: 2 different biopsies tested at screening and baseline. CTAG1B, cancer/testis antigen 1B; IHC, immunohistochemistry; NY-ESO-1, New York esophageal squamous cell carcinoma 1.

Conclusions

- **Similar to CAR T-cell therapies in hematologic malignancies, exposure–response analysis of study (NCT01343043) reveals that peak cell persistence is associated with TCR T-cell response in solid tumors. Moreover, efficacy appears to be driven by weight-normalized cell dose and LDR via C_{max}.**
- **A higher dose and an LDR consisting of high doses of fludarabine and cyclophosphamide may offer opportunities with to maximise anti-tumor efficacy in individual patients and across populations.**
- **Biomarker correlation analysis indicates that LDR impacts the level of IL-15 pre-infusion, which correlates with response directly.**
- **Post infusion of lete-cel, IFNγ, IL-6, and IL-2RA levels appear to be promising pharmacodynamic markers.**

References

1. Lai JP, et al. *Mod Pathol* 2012;6:854–8.
2. Kochenderfer JN, et al. *J Clin Oncol* 2017;35(16):1803–13.
3. Ramachandran I, et al. *J Immunother Cancer* 2019;7:276–90.
4. Hirayama AV, et al. *Blood* 2019;133(17):1876–87.

Acknowledgments

Funding: This study (208466) was funded by GlaxoSmithKline and Adaptimmune.

Presenting author email: alexandra.x.gyurdieva@gsk.com

Ethics statement

This study was approved by the appropriate institutional review boards and independent ethics committees.

Disclosures

AG is an employee of GSK and holds stock/stock options in GSK and Amgen. **SZhong**, **SZajic**, **DCT**, **LAJ**, **JK**, **IE**, and **VLC** are employees of and hold stock/stock options in GSK. **JT** is a former employee of GSK and holds stock/stock options in GSK. **YC** and **EAH** are employees of GSK. **ANH** is an employee of and holds stock/stock options in GSK and receives royalties from Atara Biotherapeutics. **DA** and **JG** have nothing to disclose. **WC** declares paid consultancy for GSK; other financial/material support from AdvenChen. **MD** declares honoraria from Adaptimmune, Blueprint, Daiichi Sankyo, Deciphera, and Epizyme. **GDD** declares scientific consultancy with research funding to Dana Farber from AbbVie, Adaptimmune, Bayer, Daiichi-Sankyo, Epizyme, GSK, Ignyta, Janssen, LOXO Oncology, Mirati, Novartis, Pfizer, PharmaMar, Roche/Genentech, and ZioPharm; paid consultancy for GSK, EMD-Serono, ICON plc, MEDSCAPE, MJ Hennessey/OncLive, Polaris Pharmaceuticals, Sanofi, and WCG/Arsenal Capital; consultancy/scientific advisory board membership with minor equity holding for Bessor Pharmaceuticals, Caprion/HistoGeneX, Caris Life Sciences, Champions Biotechnology, Erasca Pharmaceuticals, G1 Therapeutics, and RELAY Therapeutic; board membership and scientific advisory board consultancy with minor equity holding for Blueprint Medicines, Merrimack Pharmaceuticals (ended Oct 2019), and Translate BIO; royalties from Novartis to institute (Dana-Farber) for use of patent of imatinib in GIST; non-financial interests in AACR Science Policy and Government Affairs Committee Chair, Alexandria Summit, and McCann Health. **BAVT** holds board membership/committee appointment for Polaris; declares paid consultancy for Adaptimmune, Caris, CytRx, Daiichi Sankyo, Deciphera, Epizyme, Immune Design, Janssen, Lilly, Novartis, and Pfizer; speakers bureau/paid presentations for Adaptimmune, Caris, GSK, Janssen, Lilly, and Novartis; research funding from GSK, Merck, Pfizer, and Tracon; travel support from GSK. **SPDA** reports paid consultancy for Amgen, EMD Serono, GSK, Immune Design, Immunocore, Incyte, and Nektar; research support from Bristol-Myers Squibb, Deciphera, and Merck; other financial/material support from Adaptimmune.

Please find the online version of this poster by scanning the QR code or via tago.ca/sitc2. Copies of this poster obtained through QR code are for personal use only and may not be reproduced without written permission of the authors.

Presented at Society for Immunotherapy of Cancer, 35th Annual Meeting, Virtual Format, November 9–14, 2020