Background NCT02992743 is an open-label pilot study of lete-cel, a New York esophageal squamous cell carcinoma 1 (NY-ESO-1)-specific autologous T-cell therapy, expressing a high-affinity T-cell receptor (TCR) that recognizes the NY-ESO-1 antigen epitope in complex with specific human leukocyte antigen (HLA) alleles of group A*02. Lete-cel exhibited anti-tumor activity and an acceptable safety profile in patients with advanced MRCLS. Previously, the association of T-cell kinetics with response and elevated inflammatory cytokine levels has been shown in responders. This abstract presents additional data on potential biomarkers of response and non-response to lete-cel in patients with advanced MRCLS.

Methods Twenty patients with advanced MRCLS received either reduced-dose (Cohort 1 [C1]; n=10; 30 mg/m² fludarabine for 3 days + 600 mg/m² cyclophosphamide for 3 days) or standard-dose (Cohort 2 [C2]; n=10; 30 mg/m² fludarabine for 4 days + 900 mg/m² cyclophosphamide for 3 days) lymphodepletion prior to lete-cel infusion (median transduced T-cell dose = 4.6 × 10^9). Key eligibility criteria were: ≥18 years of age; HLA-A*02:01 and/or 05 and/or 06; advanced or metastatic NY-ESO-1-positive MRCLS (>30% of cells 2+/3+ by immunohistochemistry); prior anthracycline treatment; and measurable disease. Investigator-assessed objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was the primary efficacy endpoint. For T-cell kinetics, a quantitative polymerase chain reaction assay was used to assess transgene vector copies in DNA from peripheral blood mononuclear cells collected longitudinally during the trial. Serum cytokines were measured by Meso Scale Discovery platform. Whole-transcriptome sequencing was performed on pre- and post-infusion tumor samples. Statistical methods specific to data modalities were used for post-hoc correlative analyses.

Results T-cell persistence at Week 4 was significantly higher (P=0.0067) in responders (n=5) than in non-responders (n=13). Lete-cel peak cell expansion was associated with maximum levels of interferon-γ (IFN-γ; r=0.56, P=0.03) and interleukin-15 (IL-15; r=0.55, P=0.02) post-infusion. Preliminary gene expression data from the tumors collected at baseline showed enrichment of metabolic pathways in responders and epithelial–mesenchymal transition and fibroblast activation in non-responders.

Conclusions These data suggest that higher lete-cel persistence and the association of lete-cel expansion with cytokine upregulation post-infusion, as well as tumor-intrinsic transcriptional features, may have a role in lete-cel response in patients with advanced MRCLS.

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REFERENCES

Ethics Approval The study protocol and patient informed consent documentation were approved by center Institutional Review Boards (or Independent Ethics Committees and other site-level committees, as deemed appropriate by the institution).

Consent The study protocol and patient informed consent documentation were approved by center Institutional Review Boards (or Independent Ethics Committees and other site-level committees, as deemed appropriate by the institution).