Letetresgene Autoleucel in Advanced/Metastatic Myxoid/Round Cell Liposarcoma

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ABSTRACT

PURPOSE The cancer/testis antigen New York esophageal squamous cell carcinoma 1 (NY-ESO-1) is a promising target in myxoid/round cell liposarcoma (MRCLS).

METHODS In this pilot study, we assessed the adoptive T-cell therapy NY-ESO-1c^{259}T letetresgene autoleucel (lete-cel) in patients with human leukocyte antigen (HLA)-A*02:01–, HLA-A*02:05–, and/or HLA-A*02:06–positive advanced/metastatic NY-ESO-1–expressing MRCLS. Patients underwent a reduced-dose (cohort 1) or standard-dose (cohort 2) lymphodepletion regimen (LDR). The primary end point was investigator-assessed overall response rate (ORR). Safety was assessed through adverse event (AE) reports. Correlative biomarker analyses were performed post hoc. The trial is registered at ClinicalTrials.gov (identifier: NCT02992743).

RESULTS Of 23 enrolled patients, 10 in cohort 1 and 10 in cohort 2 received lete-cel. Investigator-assessed ORR was 20% (95% CI, 2.5 to 55.6) and 40% (95% CI, 12.2 to 73.8), median duration of response was 5.3 months (95% CI, 1.9 to 8.7) and 7.5 months (95% CI, 6.0 to not estimable [NE]), and median progression-free survival was 5.4 months (95% CI, 2.0 to 11.5) and 8.7 months (95% CI, 0.9 to NE) in cohorts 1 and 2, respectively. AEs included cytokine release syndrome and cytopenias, consistent with T-cell therapy/LDR. Post hoc correlative biomarkers showed T-cell expansion and persistence in both cohorts.

CONCLUSION To our knowledge, this study is the first demonstrating the clinical promise of lete-cel in HLA-/NY-ESO-1-positive patients with advanced MRCLS.

ACCOMPANYING CONTENT

Editorial, p. 1755

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Myxoid/round cell liposarcoma (MRCLS) accounts for between 15% and 30% of adult liposarcomas and is characterized by low tumor mutational burden and limited immune infiltrates.[1,2] MRCLS is defined by fusion of DNA damage inducible transcript 3 (*DDIT3*) and FUS RNA-binding protein (*FUS*) genes on chromosome regions 12q13 and 16p11, or of *DDIT3* and EWS RNA-binding protein 1 (*EWSR1*) genes on chromosome region 22q12.[3-5] Approximately 33% of MRCLS cases are metastatic at diagnosis or will develop metastatic disease, spreading to lung, abdomen, spine, soft tissue, or bone.[3]

For metastatic MRCLS, doxorubicin-based chemotherapy alone or in combination with ifosfamide is usually the first-line treatment option.[4,6] Second-line and beyond options include trabectedin and eribulin.[4,7] Overall response rates (ORRs) to eribulin in a randomized trial in patients with advanced, locally recurrent or metastatic liposarcoma or leiomyosarcoma were 4% in the overall population and 1.4% in the liposarcoma subgroup.[8] Response rates in clinical trials of trabectedin in previously treated patients with soft tissue sarcomas (not just MRCLS) range between 7% and 10%.[9-11] Although MRCLS is more sensitive to radiation therapy and chemotherapy compared with other soft tissue sarcoma subtypes, current therapies for metastatic MRCLS are not curative and only provide transient clinical benefit in patients.[4,12-14] In a real-world analysis, median overall survival (OS) of patients with advanced/metastatic MRCLS from the start of second-line therapy was approximately 26 months, and response rate to second-line therapy was 13.7%.[15] Thus, there remains an unmet need for novel therapies for MRCLS.[16]

New York esophageal squamous cell carcinoma 1 (NY-ESO-1) is a cancer testis antigen and potential target for adoptive T-cell therapy in MRCLS.[17] Diffuse and high-intensity

CONTEXT

Key Objective

The safety and efficacy of letetresgene autoleucel (lete-cel), an autologous T-cell therapy engineered with a T-cell receptor targeting New York esophageal squamous cell carcinoma 1 (NY-ESO-1), in advanced or metastatic myxoid/round cell liposarcoma (MRCLS) has yet to be defined.

Knowledge Generated

In this pilot study of 20 human leukocyte antigen– and NY-ESO-1–eligible patients who received lete-cel, cytopenias and cytokine release syndrome were the most common adverse events. The overall response rate per RECIST v1.1 by investigators was 20% in cohort 1 and 40% in cohort 2, indicating the clinical promise of lete-cel for advanced or metastatic MRCLS.

Relevance *(G.K. Schwartz)*

Targeting NY-ESO-1 with lete-cel represents a potential breakthrough therapy in patients with MRCLS.*

*Relevance section written by *JCO* Associate Editor Gary K. Schwartz, MD, FASCO.

expression of NY-ESO-1 is observed in 80-90% of patients with metastatic MRCLS.[18] Letetresgene autoleucel (lete-cel) is a novel T-cell receptor therapy recognizing NY-ESO-1 antigen in complex with specific human leukocyte antigen (HLA)-A*02 alleles[19-21] that has shown encouraging antitumor activity in patients with synovial sarcoma (SyS) in previous studies.[20,22,23] Patients with recurrent and/or metastatic SyS with high tumor NY-ESO-1 expression treated with lete-cel and a standard-dose (fludarabine 30 mg/m^2 once daily for 4 days, cyclophosphamide 1,800 mg/m^2 once daily for 2 days) lymphodepletion regimen (LDR) achieved an ORR of 50% compared with 27% with a lower-dose LDR (fludarabine 30 mg/m^2 once daily for 3 days, cyclophosphamide 600 mg/m^2 once daily for 3 days).[24] Generally, standard-dose LDRs create favorable conditions for infused T cells and highlight benefits of a higher cell dose.[24,25]

We conducted a pilot study to evaluate efficacy and safety of lete-cel in patients with advanced or metastatic MRCLS that express NY-ESO-1. Patients were treated with reduced-dose LDR according to the original protocol; however, because of emerging data from the SyS study, the protocol was modified to enroll an additional 10 patients who received standard-dose LDR in a second cohort.

METHODS

Study Design

This was a multicenter open-label pilot study (ClinicalTrials.gov identifier: NCT02992743) in patients with MRCLS with HLA-A*02:01, HLA-A*02:05, and/or HLA-A*02:06 alleles, whose tumors expressed NY-ESO-1 antigen (defined by ≥30% of cells that were 2+ or 3+ per immunohistochemistry). Detailed eligibility criteria are shown in the Data Supplement (Tables S1 and S2, online only). Enrollment into the two sequential cohorts was not randomized or stratified.

Leukapheresis was performed to obtain starting material for manufacture of autologous lete-cel. The lete-cel manufacturing process has been described in previous studies.[23] Lete-cel doses were within the range of 1×10^9 to 8×10^9 transduced cells and were administered in a single intravenous infusion as an inpatient procedure.

Before administration of lete-cel, patients in each cohort underwent the following LDR: cohort 1, a reduced-dose LDR comprising fludarabine 90 mg/m^2 (30 mg/m^2 once daily for 3 days) and cyclophosphamide 1,800 mg/m^2 (600 mg/m^2 once daily for 3 days); and cohort 2, a standard-dose LDR comprising fludarabine 120 mg/m^2 (30 mg/m^2 once daily for 4 days) and cyclophosphamide 2,700 mg/m^2 (900 mg/m^2 once daily for 3 days). Cyclophosphamide dose was adjusted to 600 mg/m^2 once daily for patients age 60 years and older.

Patients were monitored for disease progression via magnetic resonance imaging or computed tomography scan at screening; baseline; 4, 8, 12, and 24 weeks; and then every 3 months until progression of disease, death, or 2 years after infusion. Those who were alive on completion or withdrawal from interventional phase were transferred to a separate long-term follow-up (LTFU) study to monitor for delayed adverse events (AEs) for up to 15 years, in accordance with gene therapy clinical trial guidelines.[26,27]

The study protocol and patient informed consent documentation were approved by the site institutional review boards or independent ethics committees. The study complied with all relevant ethical regulations and written informed consent was required from all study patients before study initiation.

End Points and Assessments

The primary efficacy end point was investigator-assessed confirmed ORR determined by RECIST v1.1, defined as proportion of patients with confirmed complete response (CR) or partial response (PR) relative to total number of patients in the analysis population. PR/CR was confirmed if criteria for each were met at a subsequent time point ≥28 days later but before disease progression or initiation of new anticancer therapy. In February 2021, the primary end point was updated to be ORR based upon investigator assessment rather than ORR based upon independent review to ensure consistency between interim and final analyses, and the secondary end point of ORR as assessed by independent review was added.

Secondary efficacy end points included ORR assessed by independent review, and time to response, duration of response, and progression-free survival (PFS) assessed by investigator and independent review. Secondary safety end points were safety and tolerability. Exploratory efficacy end points included investigator-assessed ORR per RECIST v1.1 in patients who received a second treatment, and investigator- and independent reviewer-assessed disease control rate (DCR) with confirmation.

Exploratory biomarker end points included serum cytokine analysis, tumor biopsy assessment, pharmacokinetics, and analysis of expression of the NY-ESO-1 target; however, the study was not powered to evaluate these assessments.

Statistical Analysis

No formal sample size calculations were carried out, and the target of 10 patients receiving lete-cel, with potential expansion with an additional cohort of up to 10 patients, was considered appropriate for evaluating preliminary efficacy and safety in this phase I/II study in patients with a rare disease. Final analyses were carried out after enrollment was complete and all enrolled patients who were to receive lete-cel had done so, including any second infusion in this study. All lete-cel-infused patients were also no longer in follow-up in the study, having either transferred to the separate LTFU protocol, completed 2 years of follow-up on this study, declined LTFU, died, or withdrew (including lost to follow-up).

The modified intention-to-treat (mITT) population, used for all primary efficacy analyses, was defined as all patients who received a T-cell infusion. Comparisons between outcomes in the two independent, sequential cohorts were not planned since enrollment was not stratified or randomized. Additional methodology and statistics can be found in the Data Supplement.

RESULTS

Patients

An overview of study design and treatment/screening visits is shown in the Data Supplement (Fig S1). The study was conducted at six specialist cell therapy centers across the United States between December 6, 2016, and March 22, 2022. Final analysis data cutoff date was May 10, 2022. An updated post hoc OS analysis was conducted on the basis of LTFU data cutoff of January 27, 2023. Sixty-two patients were assessed for eligibility, of whom 37 were positive for eligible HLA alleles and 31 were positive for tumor NY-ESO-1 expression per criteria ≥30% of cells being 2+/3+. There were 39 screen failures, for which the most common reason was not meeting antigen or HLA inclusion criteria. Initial target enrollment was for 10 patients (cohort 1) to undergo reduced-dose lymphodepletion; these patients were leukapheresed between 2017 and 2018. After dosing completion, the study was expanded to enroll a further 10 patients (cohort 2) at standard-dose lymphodepletion (Data Supplement, Fig S1) who were leukapheresed between 2019 and 2020. A total of 23 patients were enrolled; of these, 10 patients in each cohort met mITT criteria and received lete-cel; patient flow details are described in the Data Supplement (Fig S2). Three patients were rescreened for second treatment with lete-cel; one patient (cohort 2) received second infusion of standard LDR + lete-cel, detailed in the Data Supplement. Baseline characteristics and demographics of the mITT population are shown in Table 1. Of note, 90% and 67% of patients in cohorts 1 and 2 had stage IV disease at the time of screening (although all were metastatic at the time of treatment), with a median of 2.5 and one line of systemic therapy before leukapheresis, respectively. Seventy percent and 30% of patients, respectively, in cohorts 1 and 2 received chemotherapy between leukapheresis and lymphodepletion. Eight patients in cohort 1 and five patients in cohort 2 received previous ifosfamide chemotherapy.

Efficacy End Points per Investigator (cohort 1)

The primary end point was ORR per RECIST v1.1 by investigator assessment. In cohort 1, ORR with confirmation was 20% (95% CI, 2.5 to 55.6; Table 2). Best overall response (with confirmation) was PR in two patients (20%) and stable disease (SD) in the remaining eight patients (80%), of which five patients experienced SD duration of ≥12 weeks (Table 2). Median time to response (TTR) was 1.9 months in cohort 1 (with the two responses at 0.9 and 2.8 months). Median duration of response (DOR) was 5.3 months (95% CI, 1.9 to 8.7); median PFS was 5.4 months (95% CI, 2.0 to 11.5; Fig 1). DCR with confirmation was 70% (95% CI, 34.8 to 93.3). Median OS in cohort 1 was 33.2 months (95% CI, 5.3 to 40.9), with eight of 10 patients having died, one having withdrawn, and one patient being in follow-up for >5 years. Median OS follow-up for cohort 1 was 62.4 months (95% CI, 4.9 to 62.4).

Efficacy End Points per Investigator (cohort 2)

In cohort 2, confirmed ORR was 40% (95% CI, 12.2 to 73.8). Best confirmed overall response was PR in four patients (40%). SD was noted in one patient with duration <12 weeks and in four patients with duration ≥12 weeks (Table 2). One patient had progressive disease (PD) as best confirmed

TABLE 1. Patient Demographic Characteristics and Disease Characteristics

Parameter	Cohort 1: Reduced-Dose LDR (n = 10)	Cohort 2: Standard-Dose LDR (n = 10)
Sex, No. (%)		
Female	4 (40)	3 (30)
Male	6 (60)	7 (70)
Age, years, median[a]	52.5	41.0
Race, No. (%)		
White	9 (90)	10 (100)
Black	1 (10)	0
Disease stage at screening[b]		
No.	10	9[c]
Stage IIIb, No. (%)	1 (10)	3 (33)
Stage IV, No. (%)	9 (90)	6 (67)
Range of tumor cells positive for NY-ESO-1 (2+/3+ per IHC)[d]	30-100	70-100
Range of *H* score for NY-ESO-1 expression	110-300	185-300
Percent of round cells, median (range)	22.5 (0-30) (n = 6)	16 (0-90) (n = 9)
Previous systemic therapy,[e,f] No. (%)	10 (100)	10 (100)
Median lines of systemic therapy before leukapheresis[e]	2.5	1
Type of chemotherapy before leukapheresis, No. (%)[e]		
Doxorubicin-based	8 (80)	8 (80)
Doxorubicin/ifosfamide	5 (50)	3 (30)
Trabectedin	7 (70)	4 (40)
Type of chemotherapy before diagnosis of advanced/metastatic disease (neoadjuvant/adjuvant), No. (%)		
Doxorubicin-based	4 (40)	2 (20)
Doxorubicin/ifosfamide	4 (40)	2 (20)
Previous systemic therapy between apheresis and lymphodepletion,[g] No. (%)		
Chemotherapy	7 (70)	3 (30)
No chemotherapy	3 (30)	7 (70)
Type of bridging chemotherapy,[g] No. (%)		
Doxorubicin	3 (30)	2 (20)
Trabectedin	4 (40)	1 (10)
Eribulin	1 (10)	—
Transduced T cells in 10^9 cells, median No.	4.7	4.6

Abbreviations: *H* score, histoscore; IHC, immunohistochemistry; LDR, lymphodepletion regimen; NY-ESO-1, New York esophageal squamous cell carcinoma 1.

[a]Age was derived using T-cell infusion date as the reference date.

[b]All patients were metastatic before lymphodepletion and T-cell infusion.

[c]The stage at screening for one patient was not reported, although this patient was noted to have metastatic disease via scans before lymphodepletion.

[d]Post hoc analysis.

[e]After diagnosis of advanced/metastatic disease. One patient in cohort 1 received doxorubicin/ifosfamide for neoadjuvant/adjuvant treatment and for advanced/metastatic disease.

[f]Before leukapheresis. All patients received previous doxorubicin-based chemotherapy.

[g]Bridging therapy plus continuation of previous anticancer therapy. In cohort 1, one patient received two bridging therapies, eribulin and doxorubicin. In cohort 2, one patient received a combination of doxorubicin and ifosfamide.

overall response. Median TTR was 1.9 months in cohort 2 (range, 1.9-2.8). Median DOR was 7.5 months (95% CI, 6.0 to not estimable [NE]); median PFS was 8.7 months (95% CI, 0.9 to NE; Fig 1). DCR with confirmation was 80% (95% CI, 44.4 to 97.5). Owing to the sequential nature of the cohorts, follow-up time was shorter for cohort 2 than for cohort 1. In cohort 2, four of 10 patients had died, two were lost to follow-up, and four were still alive on January 27, 2023; OS data from this cohort were therefore not mature (Table 2). Patients from cohort 2 are being monitored for survival under a separate LTFU study. Median OS follow-up for cohort 2 was 30.4 months (95% CI, 12.9 to 36.8), with

TABLE 2. Summary of Efficacy End Points, per Investigator and Independent Reviewer Assessment

	Investigator-Assessed		Independent Reviewer–Assessed	
Parameter	Cohort 1 (n = 10)	Cohort 2 (n = 10)	Cohort 1 (n = 10)	Cohort 2 (n = 10)
ORR,[a] % (95% CI)	20 (2.5 to 55.6)	40 (12.2 to 73.8)	20 (2.5 to 55.6)	40 (12.2 to 73.8)
DCR, % (95% CI)	70 (34.8 to 93.3)	80 (44.4 to 97.5)	60 (26.2 to 87.8)	70 (34.8 to 93.3)
Best overall response				
PR	2/10	4/10	2/10	4/10
SD	8/10	5/10	8/10	3/10
≥12 weeks	5/10	4/10	4/10	3/10
<12 weeks	3/10	1/10	4/10	0/10
PD	0/10	1/10	0/10	0/10
NE	0/10	0/10	0/10	3/10
TTR, months, median (range)	1.9 (0.9-2.8)	1.9 (1.9-2.8)	2.4 (1.8-2.9)	1.9 (1.0-2.0)
DOR, months, median (95% CI)	5.3 (1.9 to 8.7)	7.5 (6.0 to NE)	NE[b]	7.2 (4.6 to NE)
PFS, months, median (95% CI)	5.4 (2.0 to 11.5)	8.7 (0.9 to NE)	4.7 (2.8 to NE)	9.0 (5.3 to NE)
OS, months, median (95% CI)	33.2 (5.3 to 40.9)	NE[c]	NA	NA
Probability of OS at 12 months, % (95% CI)	67 (28 to 88)	90 (47 to 99)	NA	NA
Probability of OS at 24 months, % (95% CI)	56 (20 to 80)	51 (16 to 79)	NA	NA
Probability of OS at 30 months, % (95% CI)	56 (20 to 80)	51 (16 to 79)	NA	NA
Probability of OS at 60 months, % (95% CI)	11 (1 to 39)	NE	NA	NA
OS follow-up, months, median (95% CI)[d]	62.4 (4.9 to 62.4)	30.4 (12.9 to 36.8)	NA	NA

Abbreviations: DCR, disease control rate; DOR, duration of response; NA, not applicable; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.
[a]Responses were not in the same patients according to investigator versus independent review, see the Data Supplement (Table S3).
[b]Both responders were censored at 1.0 and 1.9 months, with no further follow-up.
[c]Post hoc analyses for OS estimates were conducted on the basis of data from the long-term follow-up study as of January 27, 2023. The OS estimates for cohort 2 were not mature at that time.
[d]Estimates on the basis of reverse Kaplan-Meier methodology.

probability of survival at 12, 24, and 30 months being 90% (95% CI, 47 to 99), 51% (95% CI, 16 to 79), and 51% (95% CI, 16 to 79), respectively.

Efficacy End Points per Independent Reviewer

Although ORR with confirmation was consistent between treatment groups regardless of whether they were investigator- or independent reviewer–assessed, there was variation in how patients were identified as responders. There was 80% concordance in cohort 1 and 60% concordance in cohort 2 between investigator- and independent reviewer-assessed ORRs. In cohort 1, one patient was identified as a responder by both investigator and independent reviewer. In cohort 2, there were three patients identified as responders in both assessments (Data Supplement, Table S3).

Results per independent review for both cohorts can be found in Table 2 and the Data Supplement (Fig S3). Results per independent review for cohort 1 were similar to results per investigator assessment; in cohort 2, best overall response was PR in four patients (40%) and SD was noted as best overall response (with confirmation) in three patients (30%). Per independent review, both responders in cohort 1 had their DOR censored at 1.0 and 1.9 months.

Safety

All patients experienced at least one treatment-emergent AE (TEAE). Common TEAEs in cohort 1 (occurring in ≥90% of patients) were lymphopenia (100%), leukopenia (90%), and neutropenia (90%). Common TEAEs in cohort 2 (occurring in ≥90% of patients) were leukopenia (100%), cytokine release syndrome (CRS; 100%), and anemia (90%). Rates of common grade ≥3 TEAEs in both cohorts were similar (Table 3).

CRS, an AE of special interest, occurred in 60% and 100% of patients in cohorts 1 and 2, respectively, with one patient in cohort 1 and three patients in cohort 2 having a grade ≥3 event. First onset of CRS was within 5 days of infusion, with median duration of 7 days (range, 1-11) in cohort 1 and 7.5 days (range, 3-25) in cohort 2. All events resolved. All patients with grade 3 CRS received tocilizumab as supportive treatment (one patient in cohort 1 and three patients in cohort 2).

Common treatment-emergent serious adverse events (SAEs) included CRS and rash/maculopapular rash (Data Supplement, Table S4). One patient experienced a potentially treatment-related fatality (cardiac arrest); this occurred on

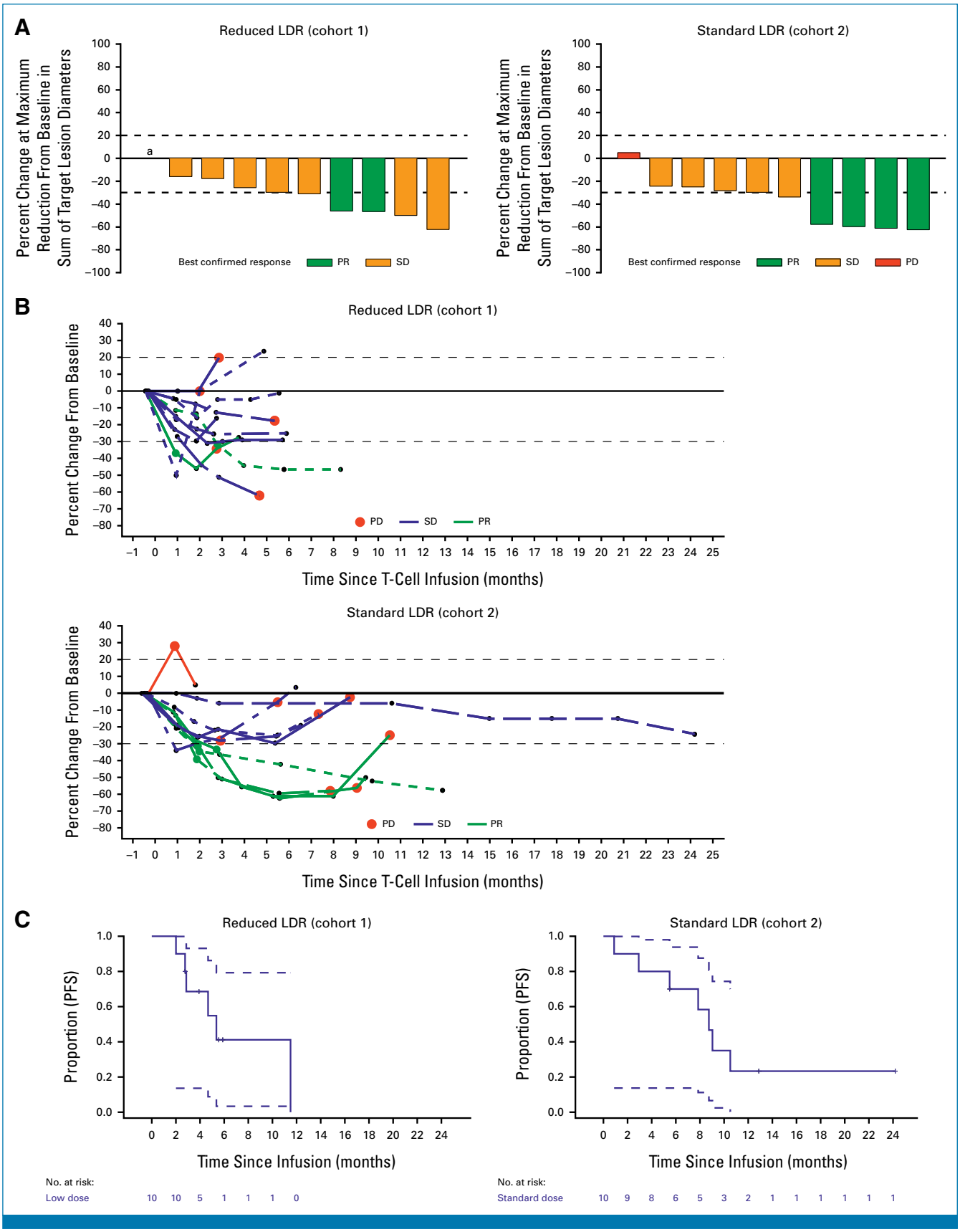

FIG 1. Efficacy end points per investigator. (A) Investigator-assessed maximum percent reduction from baseline in sum of target lesion diameters by LDR (mITT population), excluding second treatment. (B) Investigator-assessed percent change from baseline in sum of target lesion diameters by LDR (mITT population), excluding second treatment. Color of lines indicates best response (with confirmation): red for PD, blue for SD, and green for PR. The red dots indicate overall response at that assessment was PD. The green dots indicate first confirmed

FIG 1. (Continued). response. Initial responses of PR in four patients were not confirmed ≥28 days later. One patient assessment at 11.5 months not shown because one target lesion was not assessed. (C) Kaplan-Meier estimates of investigator-assessed PFS (RECIST 1.1 criteria; mITT population), excluding second treatment. + marks indicate censored patients; dashed line represents 95% Hall-Wellner confidence bands. [a]Patient's maximum reduction from baseline in sum of target lesions = 0%. LDR, lymphodepletion regimen; mITT, modified intention-to-treat; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

day 161 after T-cell infusion and after the patient had developed PD in the setting of hypotension because of poor oral intake and renal insufficiency, and treatment with radiation and pazopanib for a new metastatic spine lesion. The three other deaths in the mITT population occurred after the patients had ended the interventional phase due to PD and were not treatment-related (two due to cancer and one due to disseminated intravascular coagulation).

On the basis of laboratory data, hematopoietic cytopenia occurred at grade 4 in all patients. Representative data from four patients are shown in the Data Supplement (Fig S4). Cases of persistent cytopenias at week 4 were observed in 30% of patients in cohort 1, with two recovering to grade 2 or better within 1.2-1.4 months after T-cell infusion, and 40% of patients in cohort 2, with all recovering to grade 2 or better within 0.9-2.3 months. Before week 4, numbers of patients with grade ≥3 neutropenia, anemia, and thrombocytopenia across both cohorts were 19, 13, and 13, respectively. Of these, four had persistent neutropenia (all of whom recovered within 1.0-2.3 months), two had persistent anemia (both in cohort 2 and who recovered in 0.9 and 2.2 months, respectively), and five had persistent thrombocytopenia (all but one recovered within 0.9-1.4 months, with one death) at week 4. None of the patients experienced late-onset neutropenia, anemia, or thrombocytopenia after week 4 (Table 4).

Rash/rash maculopapular was a common grade ≥3 treatment-emergent SAE, affecting 30% of patients in cohort 2; treatment-related rash/rash maculopapular occurred in 20% of patients in cohort 2. No graft-versus-host disease, immune effector cell–associated neurotoxicity syndrome, or Guillain-Barré syndrome was reported.

Exploratory Biomarker End Points

Exploratory analyses evaluated pharmacokinetics and functionality of lete-cel in the periphery. T-cell persistence levels at week 4 were higher in responders (P = .00677; Fig 2A). Across both cohorts, geometric mean maximum concentration (C_{max}; peak cell expansion; Fig 2B) and area under the time curve from days 0 to 28 ($AUC_{(0-28d)}$) values were numerically higher in responders versus nonresponders. In cohort 2, between responders and nonresponders, $AUC_{(0-28d)}$ was a better predictor of response than

TABLE 3. Incidence of Grade ≥3 TEAEs Occurring in ≥10% of Patients Across Cohorts, Regardless of Attribution

	Cohort 1: Reduced-Dose LDR (n = 10), No. (%)		Cohort 2: Standard-Dose LDR (n = 10), No. (%)	
TEAE	Total	Grade ≥3	Total	Grade ≥3
Any event	10 (100)	10 (100)	10 (100)	10 (100)
Leukopenia/WBC decreased[a]	9 (90)	9 (90)	10 (100)	10 (100)
Lymphopenia/lymphocyte count decreased[a]	10 (100)	10 (100)	7 (70)	7 (70)
Neutropenia/neutrophil count decreased[a]	9 (90)	9 (90)	6 (60)	6 (60)
Anemia/RBC count decreased[a]	7 (70)	4 (40)	9 (90)	8 (80)
Thrombocytopenia/platelet count decreased[a]	8 (80)	6 (60)	8 (80)	6 (60)
Hypophosphatemia	6 (60)	5 (50)	8 (80)	6 (60)
Febrile neutropenia	2 (20)	1 (10)	4 (40)	4 (40)
Cytokine release syndrome[b]	6 (60)	1 (10)	10 (100)	3 (30)
Rash/rash maculopapular[a]	2 (20)	0	3 (30)	3 (30)
Hyponatremia	1 (10)	1 (10)	2 (20)	1 (10)
Leukocytosis	2 (20)	2 (20)	0	0
Pyrexia	8 (80)	1 (10)	7 (70)	1 (10)

NOTE. TEAEs occurred during or after lymphodepletion.
Abbreviations: CRS, cytokine release syndrome; LDR, lymphodepletion regimen; TEAE, treatment-emergent adverse event.
[a]Preferred terms have been combined.
[b]One patient with grade 3 CRS received tocilizumab in cohort 1 and three patients with grade 3 CRS received tocilizumab in cohort 2. One patient in cohort 2 received tocilizumab for grade 1 CRS.

TABLE 4. Cytopenia AESIs on the Basis of Laboratory Values

Cytopenia AESI	Cohort 1: Reduced-Dose LDR (n = 10)	Cohort 2: Standard-Dose LDR (n = 10)
Neutropenia		
Patients with grade ≥3 before week 4, No. (%)[a]	9 (90)	10 (100)
Patients with persistent neutropenia at week 4, No.[b]	2	2
Recovered, No. (%)[c]	2 (100)	2 (100)
Time to resolution, months, range	1.2-1.3	1.0-2.3
Late-onset neutropenia after week 4, No.	0	0
Anemia		
Patients with grade ≥3 before week 4, No. (%)[a]	4 (40)	9 (90)
Patients with persistent anemia at week 4, No.[b]	0	2
Recovered, No. (%)[c]	0	2 (100)
Time to resolution, months, range	NA	0.9-2.2
Late-onset anemia after week 4, No.	0	0
Thrombocytopenia		
Patients with grade ≥3 before week 4, No. (%)[a]	6 (60)	7 (70)
Patients with persistent thrombocytopenia at week 4, No.[b]	2	3
Recovered, No. (%)[c]	1 (50)	3 (100)
Time to resolution, months, range	1.4-7.5[d]	0.9-1.4
Late-onset thrombocytopenia after week 4, No.	0	0

Abbreviations: AESI, adverse event of special interest; LDR, lymphodepletion regimen; NA, not available.
[a]Events occurring within 4 weeks after T-cell infusion.
[b]Events at last value within 4 weeks of first T-cell infusion. Persistent cytopenia analysis was conducted as a post hoc analysis.
[c]Recovery is defined as the first time the event resolves to grade 2 or below; week 4 is defined as days 25-31, inclusive.
[d]Patient did not recover and was censored at their last laboratory assessment.

in cohort 1 ($P = .0182$ in cohort 2 was statistically significant *v* $P = .801$ in cohort 1; Fig 2C). There was a significant association between normalized transduced cell dose (10^9/kg) and C_{max} ($P = .0197$; Fig 2D). $AUC_{(0-28d)}$ and C_{max} were well correlated ($P = .0000319$, adjusted $R^2 = 0.606$; Fig 2E). Cytokine analysis showed that lete-cel induces cytokines crucial for T-cell activation, growth, and activity; however, there was no association between cytokine upregulation and response in either cohort (Data Supplement, Fig S5). We observed that C_{max} was associated with maximum levels of interleukin (IL)-7, IL-122340, and IL-2 receptor alpha at day 1 before infusion (Data Supplement, Fig S6A) and with interferon (IFN)-γ ($r = 0.56$; $P = .03$) and IL-15 ($r = 0.55$; $P = .02$) after infusion (Data Supplement, Fig S6B). Target expression analysis of all treated patients revealed high NY-ESO-1 expression (median *P* score, 97%); however, target antigen levels did not correlate with response (Data Supplement, Fig S7A). Gene expression and tumor mutation profiling (Data Supplement, Fig S8) and gene set enrichment analysis (Data Supplement, Fig S9) in responders and nonresponders along with additional results for exploratory end points can be found in the Data Supplement.

DISCUSSION

Because lete-cel has previously shown promising activity in SyS,[20] this study aimed to evaluate its efficacy and safety in advanced MRCLS. This study demonstrated meaningful clinical benefit of lete-cel in patients with HLA-A*02:01 or 05 or 06/NY-ESO-1-positive disease. Patients treated with standard-dose LDR (cohort 2) before lete-cel infusion had an ORR of 40%, with 40% of patients experiencing SD at ≥12 weeks, whereas those treated with reduced-dose LDR (cohort 1) had an ORR of 20%, with 50% of patients experiencing SD at ≥12 weeks. Of note, more patients enrolled in cohort 1 had stage IV disease, higher number of previous lines of chemotherapy in the metastatic setting, and more required bridging chemotherapy between leukapheresis and LDR compared with patients enrolled in cohort 2, suggesting a group with more advanced disease at baseline. Follow-up times also differed between the two sequential, independent cohorts. Eight patients in cohort 1, including the two responders, and five patients in cohort 2, including three of the four responders, had previous treatment with ifosfamide, a standard treatment for MRCLS. Although it is difficult to draw conclusions because of the small sample size, the responses (and duration of response) observed here with lete-cel, in patients with previous exposure to ifosfamide, suggest that the cyclophosphamide component of the LDR has limited impact on overall responses observed.

Selection of LDR components and doses implemented in this study was driven by previous evidence. Ideal LDR for T-cell-based therapies in solid tumors is not known; however, relevance of fludarabine-containing regimens is well established.[20,28] A fludarabine plus cyclophosphamide

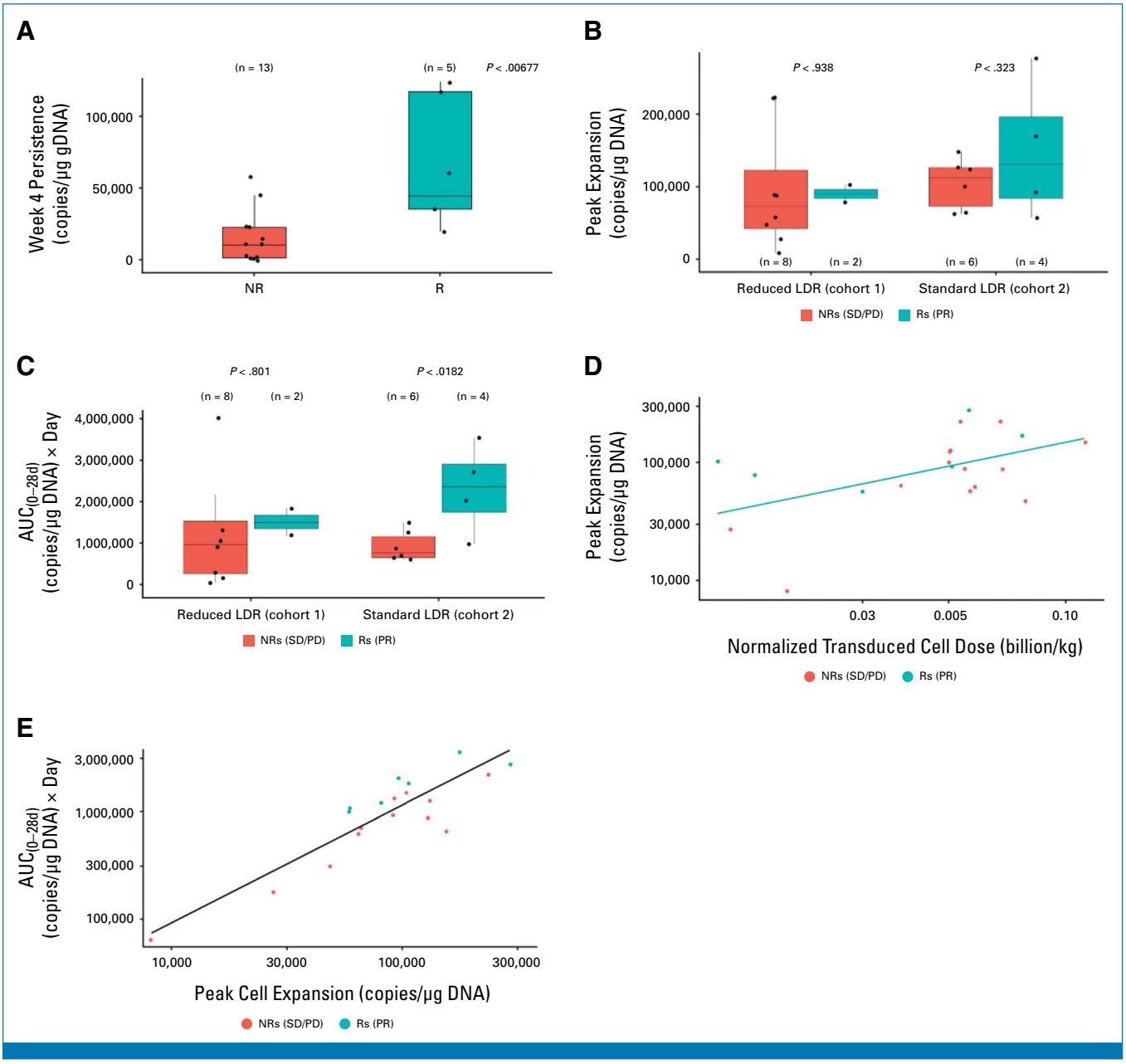

FIG 2. Biomarker correlates. (A) Persistence levels. Responders showed higher persistence of lete-cel at week four when compared with nonresponders. (B) Geometric mean C_{max} (peak cell expansion). (C) $AUC_{(0\text{-}28d)}$ was a better predictor of response in patients receiving standard LDR (cohort 2). (D) Association of normalized transduced cell dose (10^9/kg) with C_{max} ($P = .0197$). (E) Association of $AUC_{(0\text{-}28d)}$ with C_{max} ($P = .0000319$, adj. $R^2 = 0.606$). *P* values are two sided and calculated with logistic regression. Boxplots: center line, median; box limits, upper and lower quartiles; whiskers, 1.5 × IQR; all data points shown. adj, adjusted; $AUC_{(0\text{-}28d)}$, area under the time curve from days 0 to 28; C_{max}, maximum concentration; gDNA, genomic DNA; LDR, lymphodepletion regimen; lete-cel, letetresgene autoleucel; NR, nonresponder; PD, progressive disease; PR, partial response; R, responder; SD, stable disease.

LDR has been previously shown to elicit better efficacy, T-cell expansion, and persistence, as well as a manageable safety profile, compared with a cyclophosphamide-alone regimen in SyS.[20] In this study, higher geometric peak cell expansion and persistence in standard-dose LDR correlated with response, consistent with data from the SyS study, although limited by sample size. Previous studies also highlight how standard-dose LDR achieves both the lymphodepleting and conditioning effects necessary for optimal T-cell engraftment and persistence after infusion, per serum IL-7 and IL-15 levels.[21,24] Cytokine analyses in this study did not show statistically significant differences in IL-7 and IL-15 levels in responders versus nonresponders in either cohort; however, we did observe a correlation between C_{max} and peak levels of IFN-γ and IL-15 after infusion when cohorts were combined. These

observations suggest that multiple cytokines may be involved in supporting lete-cel engraftment and expansion.

Mechanisms of resistance to T-cell therapy in sarcoma are yet to be defined. In hematologic malignancies, decreased or loss of antigen expression has been described. Post-progression loss of tumor NY-ESO-1 expression in a patient with pleomorphic sarcoma previously treated with NY-ESO-1 targeting TCR lymphocytes and dendritic cell vaccination, and nivolumab has been observed[29]; however, this was not seen in patients with SyS treated with lete-cel.[24,30-32] In our current report, in two of the three patients who were reevaluated for a second lete-cel infusion, one had loss of tumor NY-ESO-1 expression, and another had approximately 50% decreased expression of NY-ESO-1. Although this could be reflective of heterogeneity of this disease, or tumor site biopsied, decreased target expression requires further evaluation as a mechanism of resistance, particularly because NY-ESO-1 expression is typically found to be high and homogeneous in MRCLS. In patients with SyS treated with lete-cel, decreases in HLA-A expression and genes involved in antigen presentation may be mechanisms of antigen escape.[24] The relevance of the beta-2-microglobulin loss-of-function mutation in one patient in this study also requires further investigation, particularly given a similar finding in patients treated with T-cell receptor T cells targeting human papillomavirus 16 E7.[33] These data may provide insights on strategies to optimize duration of responses, such as strategies that can upregulate antigen presentation, as well as antigen expression.

Clinical factors of benefit to lete-cel in MRCLS appear similar to those seen with afamitresgene autoleucel (afami-cel; an autologous T-cell receptor therapy targeting the cancer/testis antigen melanoma-associated antigen A4 [MAGE-A4]), including lower disease burden and less use of bridging therapy.[34] Integration of T-cell therapy earlier in treatment may also be beneficial, as demonstrated by the use of immunotherapy in patients with advanced malignancies. In this study, NY-ESO-1 expression levels did not correlate with response ($P = .58$). It is important to note the small sample size and that all treated patients had high NY-ESO-1 expression levels (P score, 97%), which may not allow clear differentiation of antigen expression levels between responders and nonresponders.[35] However, this may provide insight into the ORR of 25% by independent review seen with afami-cel in MRCLS, because MAGE-A4 expression tends to be lower compared with NY-ESO-1 expression.[34]

In both cohorts, we observed a manageable safety profile for lete-cel, consistent with previous reports.[36] In this study, most common SAEs were CRS, cytopenias (thrombocytopenia, neutropenia, and anemia), and rash. Of note, standard-dose LDR was associated with higher incidence of CRS versus reduced-dose LDR; however, there were no significant differences in median time to onset and median duration of each CRS episode. Tocilizumab administration was more common in cohort 2, potentially because of a greater number of patients experiencing CRS grade ≥2. All patients experienced at least one grade 4 cytopenia.

To the best of our knowledge, this was the first clinical trial reporting primary efficacy and safety for adoptive T-cell therapies specifically in advanced MRCLS. Although MRCLS remains a chemosensitive disease, once metastatic, it is not curable.[9,37] In the afami-cel study, 25% of eight patients with advanced MRCLS responded at final analysis of cohort 1.[34] The ORRs of 20% in cohort 1 and 40% in cohort 2 demonstrated in this study suggest lete-cel may be a promising treatment in the recurrent metastatic/advanced MRCLS setting.

Overall, this was a pilot study with a small sample size, limiting our interpretation of translational correlates between responder and nonresponder groups. Although the present data provide valuable insights into the potential for clinical benefit with lete-cel after LDR in advanced MRCLS, further investigation is needed to understand mechanisms of response and/or resistance. The findings from this small study were promising enough to prompt a larger phase II study that is currently underway in patients with advanced MRCLS and SyS (ClinicalTrials.gov identifier: NCT03967223). The primary efficacy end point of the phase II study has been met at the planned interim analysis, and further work will help define prognostic factors of efficacy.[38]

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