Poster CT-564

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ELARA Trial Update: Long-Term Clinical Outcomes and Correlative Efficacy Analyses of Tisagenlecleucel in Patients with Relapsed/Refractory Follicular Lymphoma

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CONCLUSIONS

- Median DOR, PFS, and OS were not reached in the ELARA trial after >2 years of follow-up
- Tisagenlecleucel induced high rates of durable responses in all patients, including those with high-risk disease characteristics such as POD24 and high baseline tumor burden, superior to published data[11-21]
- Tisagenlecleucel was found to be well tolerated and feasible for outpatient administration
- Exploratory biomarker analyses suggest that a favorable TME (low tumor infiltration of LAG3+ exhausted T cells) and decreased inflammatory status were associated with improved clinical outcomes
- Extended follow-up of >2 years from the ELARA trial continues to demonstrate durable efficacy and a favorable safety profile following tisagenlecleucel in patients with R/R FL

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INTRODUCTION

- Follicular lymphoma (FL) is an indolent lymphoma subtype that often requires multiple lines of treatment[1,2]
- Patients with relapsed high-risk FL (progression of disease within 2 years of initial chemotherapy [POD24], high baseline tumor burden) have a poor prognosis and unmet need for effective therapeutic options[3-5]
- Tisagenlecleucel demonstrated high response rates (overall response rate of 86%, complete response rate [CRR] of 69%)[6] and durable responses (12-month progression-free survival [PFS] rate of 67%)[7] in the ELARA trial
- Here, we present the continued durability of response, long-term safety, and exploratory correlative biomarker analyses of patients with relapsed or refractory (R/R) FL treated with tisagenlecleucel after a median follow-up of 29 months

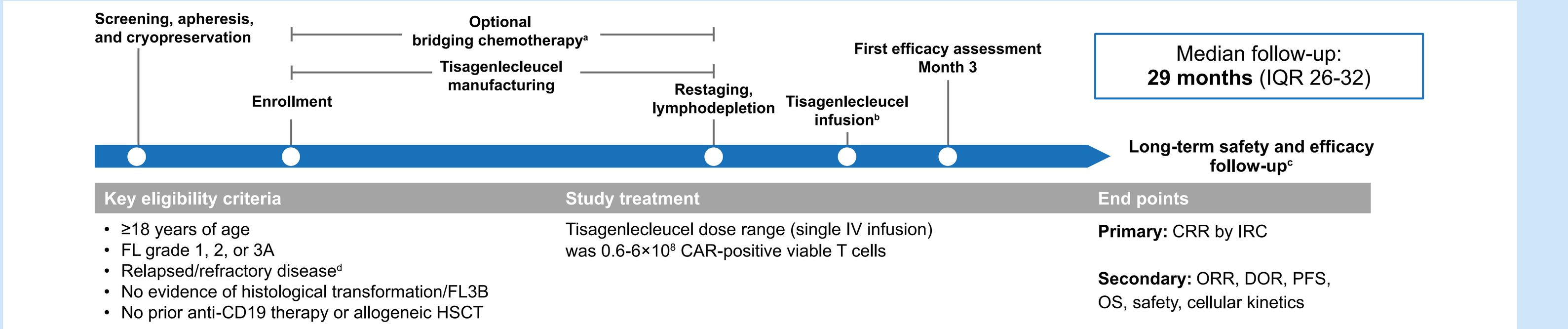
METHODS

- ELARA (NCT03568461) is a Phase II, single-arm, global, multicenter, open-label trial investigating the efficacy and safety outcomes of tisagenlecleucel in adults with R/R FL after ≥2 treatment lines or who relapsed after autologous stem cell transplant (**Figure 1**)
- Eligible patients were ≥18 years of age with R/R FL (grades 1-3A) after ≥2 lines of prior therapy, including an anti-CD20 antibody and an alkylating agent, or after autologous stem cell transplant
- Bridging therapy was allowed and was followed by disease reevaluation before tisagenlecleucel infusion (0.6-6×10^8 chimeric antigen receptor [CAR]-positive viable T cells)
- The primary outcome measure was CRR
- Secondary outcome measures included clinical response and PFS, which were correlated with baseline factors, tumor microenvironment (TME), soluble factors, and circulating blood cells; safety; and cellular kinetics as determined by quantitative polymerase chain reaction measurement of transgene levels

Statistical analysis

- The Kaplan-Meier method was used to estimate PFS, duration of response (DOR), overall survival (OS), and time to next antilymphoma therapy (TTNT)
- Univariate and multivariate Cox model analyses were used to correlate biomarker and clinical/disease characteristics with response and PFS
- The Spearman correlation was used to estimate the baseline tumor burden with pre-lymphodepleting chemotherapy serum cytokine levels
- CAR-T cell in vivo exposure parameters (cellular kinetics) were estimated using noncompartmental methods

Figure 1. ELARA Study Design



CAR, chimeric antigen receptor; CD, cluster of differentiation; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; FL3B, FL grade 3B; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; IRC, independent review committee; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[a]Disease was reassessed prior to infusion for all patients requiring bridging therapy. [b]Infusion was conducted on an in- or outpatient basis at investigator discretion. [c]Every 3 months until Month 12, and every 6 months until end of study. [d]Refractory to second or greater line of systemic therapy (including an anti-CD20 antibody and alkylating agent) or relapsed within 6 months after second or greater line of therapy or after an autologous HSCT.

RESULTS

- As of March 29, 2022, a total of 97 patients received tisagenlecleucel; 18% (17/97) of patients received tisagenlecleucel in the outpatient setting

Tisagenlecleucel induced high rates of durable responses in all patients, including those with high-risk disease characteristics

- Among 94 efficacy evaluable patients (median follow-up, 28.9 months), CRR was 68% (95% CI, 58-77) and overall response rate was 86% (95% CI, 78-92) (**Table 1**), which were consistent with the primary analysis[6]
- High rates of durable responses were observed in most patients in high-risk disease subgroups who have poor prognosis with current non–CAR-T cell therapies (**Table 2**)

Table 1. Clinical Response Among Efficacy Evaluable Patients Who Received Tisagenlecleucel

Endpoint in Efficacy Analysis Set (IRC Assessment)	% (95% CI) N=94
CRR[a]	68 (58-77)[b]
ORR[c]	86 (78-92)[b]

Table 2. Clinical Response Among High-Risk Patients Who Received Tisagenlecleucel

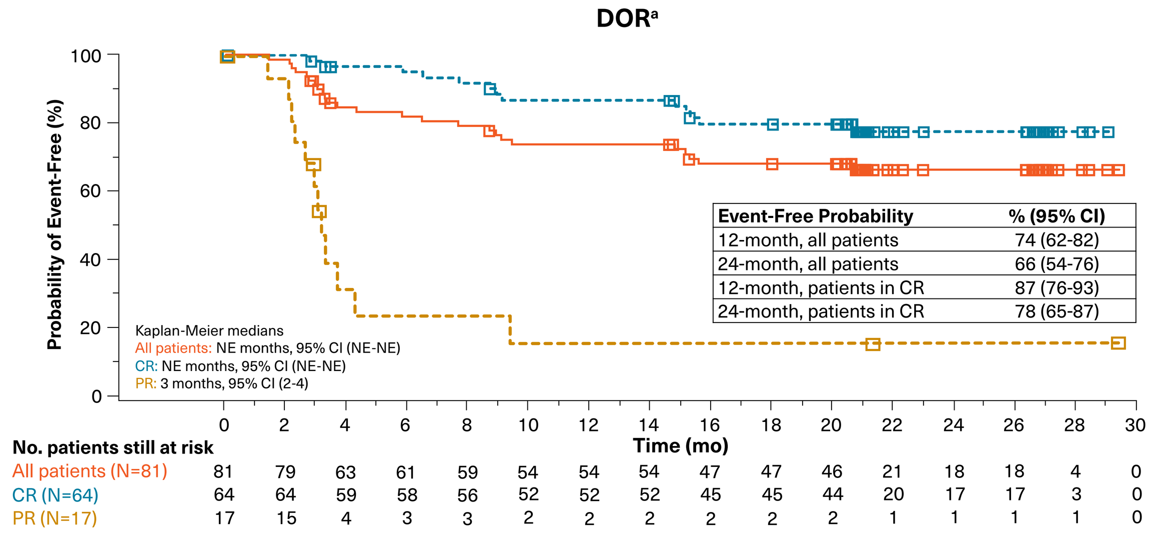
Baseline Disease Characteristic	All Patients n (%) N=97	CRR % (95% CI)	ORR % (95% CI)
POD24	61 (63)	59 (46-71)	82 (70-91)
High metabolic tumor volume[d]	20 (21)	40 (19-64)	75 (51-91)
Bulky disease[e]	62 (64)	65 (51-76)	86 (74-93)
Double refractory	65 (67)	66 (53-77)	85 (74-92)
High FLIPI (≥3)	57 (59)	61 (48-74)	81 (68-90)

BM, bone marrow; CR, complete response; CRR, CR rate; FLIPI, Follicular Lymphoma International Prognostic Index; IRC, independent review committee; ORR, overall response rate; POD24, progression of disease within 2 years of initial chemotherapy; PR, partial response; TMTV, total metabolic tumor volume.
[a]One patient in CR downgraded to PR due to confirmatory BM biopsy performed out of window. [b]The 95% exact Clopper-Pearson CIs are displayed. As the primary endpoint was met at interim analysis (<0.0001, at 1-sided 0.0025 level to reject the null hypothesis: CRR ≤15%), no formal significance testing was conducted at extended follow-up analysis. [c]ORR is defined as the proportion of patients with a best overall disease response of CR or PR. [d]TMTV >510 cm^3. [e]Any nodal or extranodal tumor mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm.

Median DOR, PFS, and OS were not reached after >2 years of follow-up

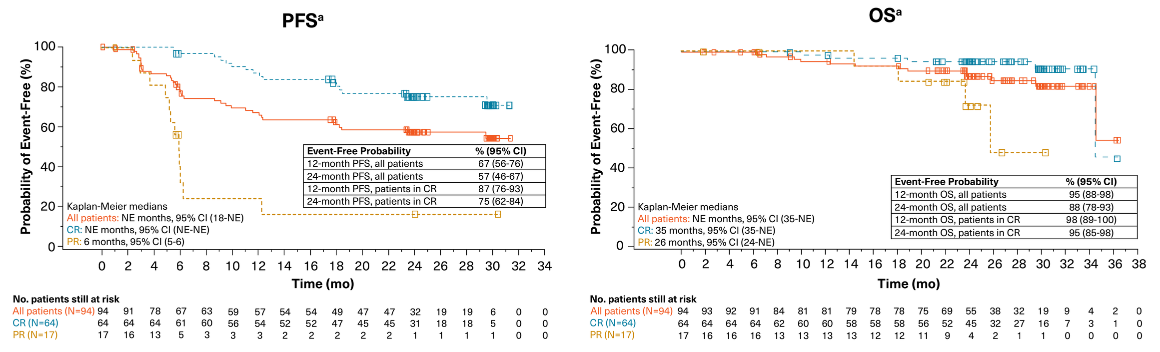
- In this updated follow-up, median DOR, PFS, and OS were not reached
- The estimated 24-month DOR of all patients in complete response was 78% (95% CI, 65-87; **Figure 2**)
  - None of the patients received reinfusion of tisagenlecleucel; 1 patient received subsequent antineoplastic treatment while in remission
- The estimated 24-month PFS and OS rates for all patients were 57% (95% CI, 46-67) and 88% (95% CI, 78-93), respectively (**Figure 3**)

Figure 2. Duration of Response Among Patients Who Received Tisagenlecleucel



CR, complete response; DOR, duration of response; IRC, independent review committee; NE, not estimable; PR, partial response.
[a]DOR is per IRC assessment. Censoring times are shown as squares.

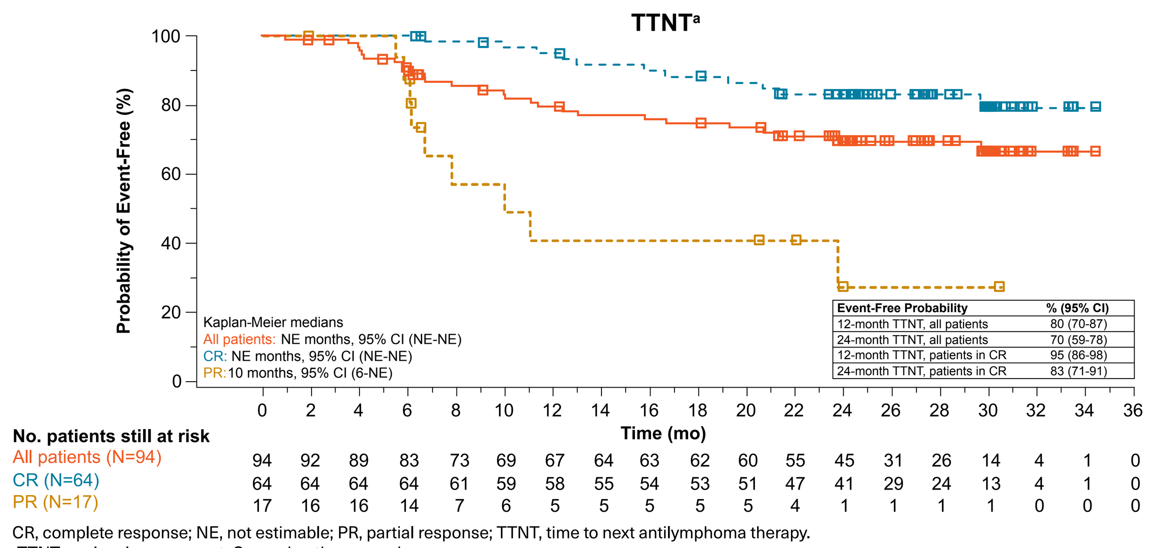
Figure 3. Median PFS and OS of Patients Who Received Tisagenlecleucel



BOR, best overall response; CR, complete response; IRC, independent review committee; NE, not estimable; OS, overall survival; PFS, progression-free survival; PR, partial response.
[a]PFS and OS by BOR curves are per IRC assessment. Censoring times are shown as squares.

- The median TTNT for all patients was not reached and the estimated 24-month TTNT was 70% (95% CI, 59-78; **Figure 4**)

Figure 4. Time to Start of New Antilymphoma Therapy Among Patients Who Received Tisagenlecleucel



CR, complete response; NE, not estimable; PR, partial response; TTNT, time to next antilymphoma therapy.
[a]TTNT per local assessment. Censoring times are shown as squares.

Tisagenlecleucel was well tolerated

- Adverse events were consistent with the known safety profile of tisagenlecleucel (**Table 3**)
  - No new safety signals were reported in this long-term analysis
  - One patient developed hemophagocytic lymphohistiocytosis (HLH) >1 year after receiving tisagenlecleucel
    - The patient did not have cytokine release syndrome during or immediately preceding HLH; the fatal HLH event occurred on Day 375 and was considered drug related by the physician
  - Two patients experienced a secondary malignancy during this longer-term follow-up (squamous cell carcinoma and bladder transitional cell carcinoma); neither was considered related to study treatment
  - Rate of all-grade serious neurological events was 8%; 2% were grade ≥3
  - The 17 patients (18%) who received tisagenlecleucel in the outpatient setting did not require admission to the intensive care unit, and one-third did not require hospitalization for adverse event management
  - Twenty-two patients (23%) received ≥1 new antineoplastic medication after tisagenlecleucel
  - Three new deaths (total to date n=13) occurred during extended follow-up; none were treatment related
    - Causes included progressive disease (n=1) and serious adverse events (urothelial bladder carcinoma and graft-vs-host disease following allogeneic stem cell transplant [n=2])

Table 3. Adverse Events of Special Interest

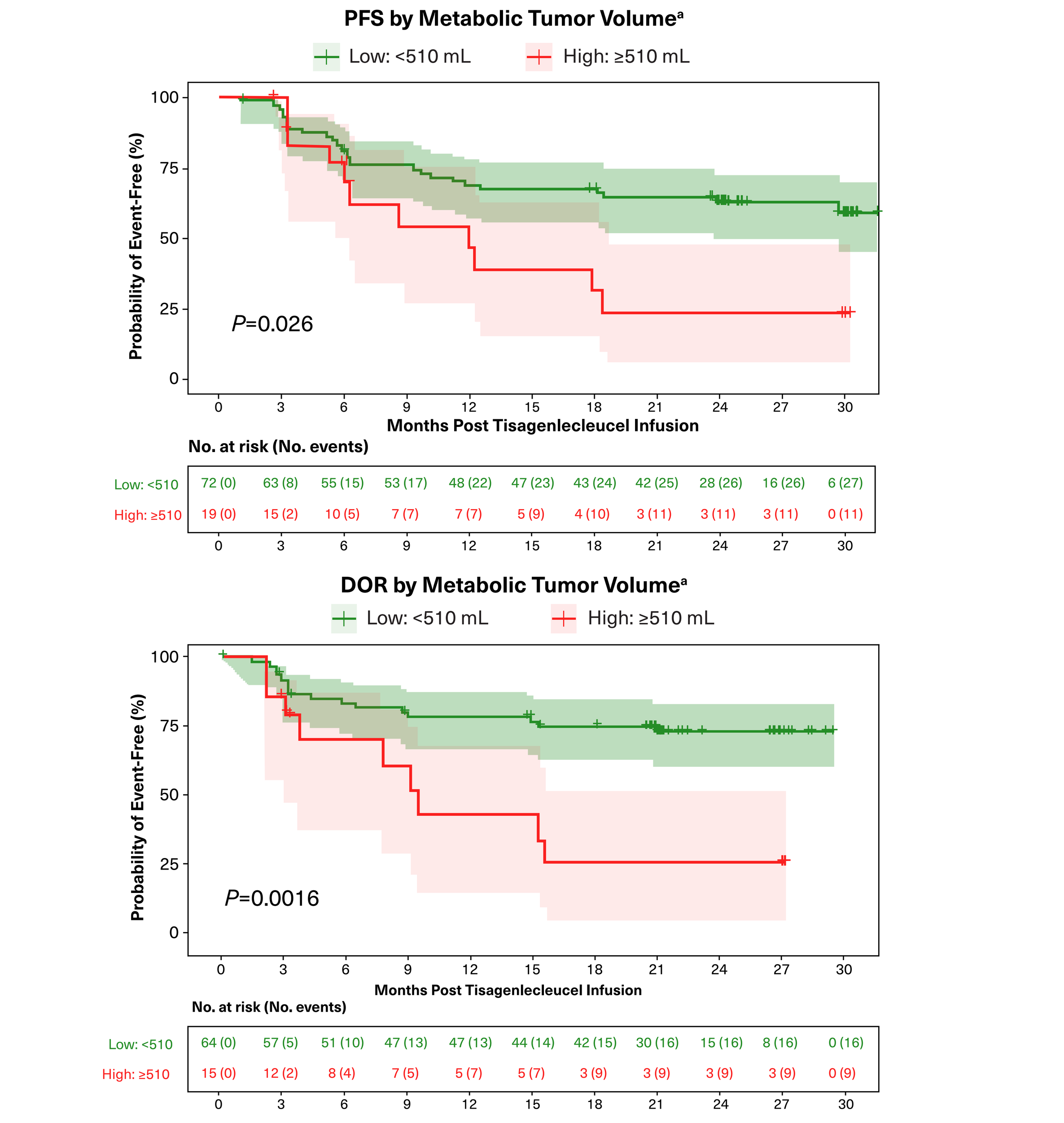
Selected Adverse Events Anytime Post Infusion[a]	Safety Analysis Set[b] (N=97) All Grade, n (%)	Safety Analysis Set[b] (N=97) Grade ≥3, n (%)
No. patients with at least 1 AE	73 (75)	45 (46)
CRS[c,d]	47 (49)	0
Hematological disorders including cytopenias	45 (46)	43 (44)
Neutropenia	23 (24)	23 (24)
Anemia	13 (13)	7 (7)
Thrombocytopenia	6 (6)	5 (5)
Infections[e]	16 (17)	9 (9)
Hypogammaglobulinemia	11 (11)	1 (1)
Serious neurological adverse events	8 (8)	2 (2)
ICANS	4 (4)	1 (1)
Encephalopathy	3 (3)	1 (1)
Dyskinesia	1 (1)	0
Muscular weakness	1 (1)	0
Tremor	1 (1)	0
Deaths >30 days post infusion		13 (13)[f]
Deaths during the long-term follow-up		3 (3)[g]

AE, adverse event; alloSCT, allogeneic stem cell transplant; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; PD, progressive disease; SAE, serious adverse event; SARS-COV2, severe acute respiratory syndrome coronavirus 2.
[a]Table summarizes selected AEs anytime post infusion suspected to be related to tisagenlecleucel. [b]All patients infused with tisagenlecleucel. [c]CRS was graded using Lee scale 2014. [d]Refers to first CRS episode only. [e]Eight patients had SARS-COV-2 infection at the time of data cutoff. [f]Out of total 13 deaths (study indication=7; other=6). [g]Three were new deaths that occurred during this longer-term follow-up period (PD, n=1; SAE, n=2, [urothelial bladder carcinoma and post alloSCT complications]).

A favorable TME and decreased inflammatory status were associated with improved clinical outcomes

- Exploratory analyses were performed on long-term efficacy outcomes in patients with several known high-risk disease characteristics
- Higher baseline tumor burden, POD24, and >4 nodal areas at inclusion correlated significantly with lower efficacy
  - Higher tumor burden at baseline (pre-lymphodepleting chemotherapy, total metabolic tumor volume ≥510 mL) was associated with shorter PFS (*P*=0.026) and DOR in responders (*P*=0.0016; **Figure 5**)

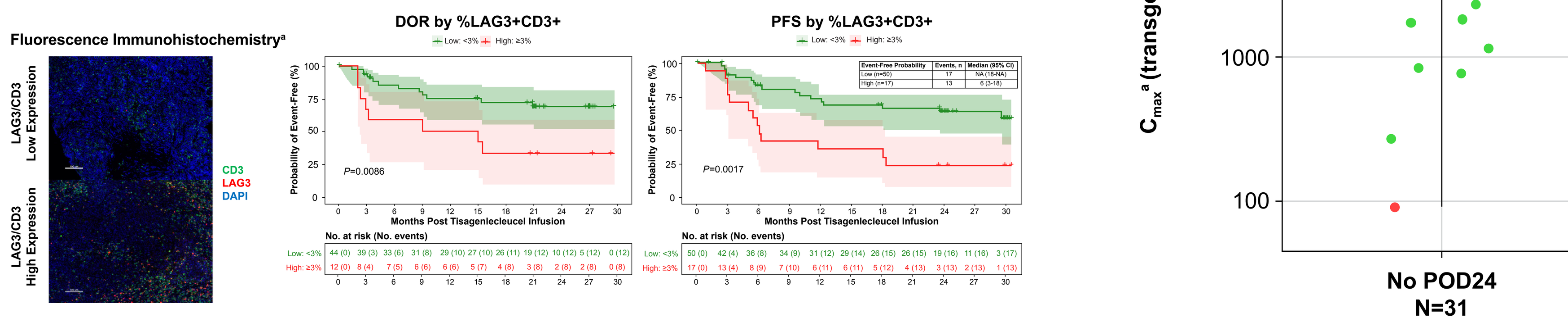
Figure 5. PFS and DOR of Patients Who Received Tisagenlecleucel According to Baseline Tumor Burden



DOR, duration of response; PFS, progression-free survival; TMTV, total metabolic tumor volume.
[a]Low risk = TMTV <510 cm^3 and high risk = TMTV ≥510 cm^3.

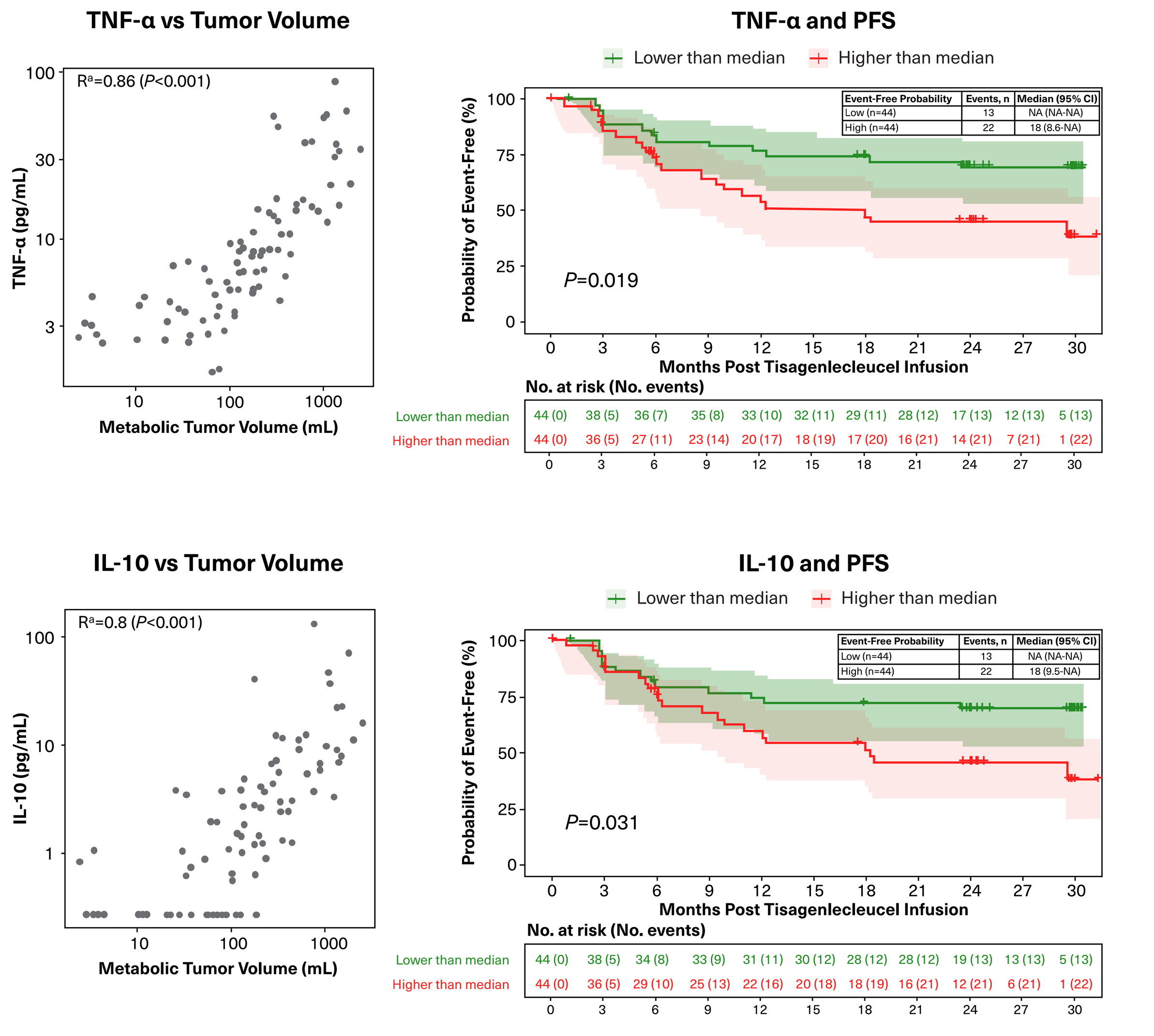
- Lower levels of lymphocyte-activation gene (LAG) 3+ exhausted T cells in the TME, interleukin (IL)-10, and tumor necrosis factor (TNF)-α correlated with longer PFS
  - Lower levels of LAG3+ exhausted T cells (<3% of total T cells), which represents a favorable TME[8], was significantly associated with longer DOR and PFS (**Figure 6**)
  - Lower TNF-α and IL-10 levels, representative of lower inflammation, were associated with prolonged PFS (**Figure 7**)
- In an exploratory analysis, POD24, nodal area involvement, tumor volume, and LAG3+ % among T cells in TME remained prognostic for PFS separation in a multivariate Cox model
  - The multivariate Cox analysis included clinical factors, clinical lab measurements, TME characteristics, cytokines, soluble factors, and blood T, B, and natural killer cell counts

Figure 6. PFS and DOR of Patients Who Received Tisagenlecleucel According to Tumor-Infiltrated LAG3+ Exhausted T Cells



AQUA, automated quantitative analysis; CD, cluster of differentiation; DAPI, 4′,6-diamidino-2-phenylindole; DOR, duration of response; LAG, lymphocyte-activation gene; PD-1, programmed cell death protein 1; PFS, progression-free survival; TIM, T-cell immunoglobulin and mucin domain-3.
[a]Archival tumor biopsies were available for 67 of 97 infused patients. TME (CD19 expression, total CD3+ T cells and exhausted subsets expressing PD-1, TIM3, and LAG3, and myeloid-derived suppressor cells) was characterized by fluorescence immunohistochemistry. Fluorescent images were acquired via PhenoImagerHT (Akoya Biosciences) at ×20 using various channels, including DAPI, Opal 520, Opal 570, and Opal 620, depending on the biomarker. Images were analyzed by proprietary analysis algorithms AQUA®.[9,10]

Figure 7. Pre-LD Serum TNF-α and IL-10 Levels Correlated with Tumor Volume and PFS

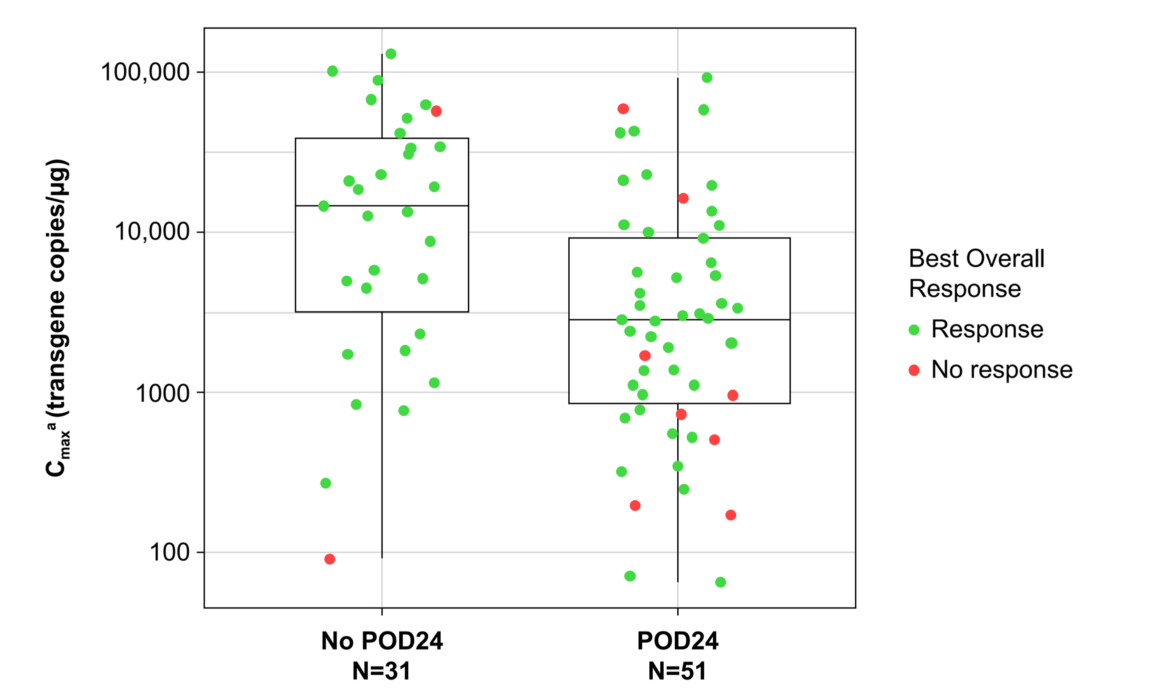


IL, interleukin; LD, lymphodepleting; PFS, progression-free survival; TNF, tumor necrosis factor.
[a]R: Spearman correlation coefficient.

Responses were observed in POD24 patients despite lower expansion than non-POD24 patients

- Persistence of the CAR transgene was observed for up to 925 days (median, 210 days; range, 13-925 days); observed persistence is expected to increase with extended follow-up
- Lower in vivo expansion in patients with POD24 did not meaningfully affect response rates (**Figure 8**)

Figure 8. Cellular Kinetics in POD24 and Non-POD24 Patients



C_{max}, maximum concentration; CR, complete response; IQR, interquartile range; POD24, progression of disease within 2 years of initial chemotherapy; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease.
Note: Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively.
Response: CR/PR; No response: SD/PD/Unknown.
[a]C_{max} (geometric mean maximum expansion) was defined as the maximum (peak) observed in peripheral blood after single dose administration (copies/μg).

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