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# Durable Response After Tisagenlecleucel in Adults With Relapsed/Refractory Follicular Lymphoma: ELARA Trial Update

**Running head (limit 50 characters):** Long-Term Clinical Outcomes From the ELARA Trial

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**Key Points**

- Tisagenlecleucel responses in r/r FL patients remain highly durable a year after primary analysis; no new safety signals were observed
- Low levels of LAG3+CD3+ exhausted T-cells and higher baseline levels of naïve CD8+ T-cells were significantly associated with improved outcomes

## ABSTRACT

Tisagenlecleucel is approved for adults with relapsed/refractory (r/r) follicular lymphoma (FL) in the ≥3rd-line setting. The primary analysis (median follow-up: 17 months) of the Phase II ELARA trial (ClinicalTrials.gov identifier: NCT03568461) reported high response rates and excellent safety profile in extensively pretreated patients with r/r FL. Here we report longer-term efficacy, safety, pharmacokinetic, and exploratory biomarker analyses after a median follow-up of 29 months. As of March 29, 2022, 97 patients with r/r FL (grades 1-3A) after ≥2 lines of therapy or who relapsed after autologous stem cell transplant received tisagenlecleucel infusion ($0.6\text{-}6\times10^8$ CAR+ viable T cells). Bridging chemotherapy was allowed. Baseline clinical factors, tumor microenvironment (TME), blood soluble factors, and circulating blood cells were correlated with clinical response. Cellular kinetics were assessed by quantitative polymerase chain reaction. Median progression-free survival (PFS), duration of response (DOR), and overall survival (OS) were not reached after 29 months median follow-up (IQR, 22.2-37.7). Estimated 24-month PFS, DOR, and OS rates in all patients were 57.4% (95% CI, 46.2-67), 66.4% (95% CI, 54.3-76), and 87.7% (95% CI, 78.3-93.2). Complete response rate and overall response rate were 68.1% (95% CI, 57.7-77.3) and 86.2% (95% CI, 77.5-92.4), respectively. No new safety signals or treatment-related deaths were reported. Low levels of tumor-infiltrating LAG3+CD3+ exhausted T-cells and higher baseline levels of naïve CD8+ T-cells were associated with improved outcomes. Tisagenlecleucel continued to demonstrate highly durable efficacy and a favorable safety profile in this extended follow-up of 29 months in patients with r/r FL enrolled in ELARA.


## INTRODUCTION

Follicular lymphoma (FL) is considered an indolent form of non-Hodgkin lymphoma (NHL) with a relapsing and remitting course.[1,2] There is no clear standard of care (SOC) for

relapsed/refractory (r/r) patients and immunochemotherapy is repeatedly used from first- to later-line settings with diminishing efficacy and the potential for accumulation of toxicities.[3-5] Patients with high-risk disease, such as progression of disease within 24 months from first immunochemotherapy (POD24) and high baseline tumor burden have a poor prognosis and an increased risk of death.[2] Tisagenlecleucel is approved in the United States, the European Union, and Japan for r/r FL in the third-line setting.

In the primary analysis of the single-arm, open-label, Phase II ELARA trial (median follow-up of 17 months; NCT03568461), tisagenlecleucel demonstrated a high overall response rate (ORR; 86%), complete response rate (CRR; 69%), and durable responses (12-month progression-free survival [PFS] rate of 67%) in adult patients with high-risk r/r FL, including patients with POD24 and high tumor burden. Grade ≥3 cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome occurred in ≤1% of patients.[6] This report presents the continued durability of response, longer-term safety, as well as correlative biomarker and pharmacokinetic analyses based on >2-year follow-up data from the ELARA trial of patients treated with tisagenlecleucel.

## METHODS

### Trial design

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 (autoSCT).[6] Detailed study protocol and outcome measures are described in previous reports.[6,7] Eligible patients were ≥18 years with r/r FL (grades 1-3A) after ≥2 lines of prior therapy including an anti-CD20 antibody and an alkylating agent or after autoSCT. Bridging chemotherapy was permitted. After lymphodepleting (LD) chemotherapy, patients received a single dose of tisagenlecleucel (0.6-

$6\times10^8$ CAR+ viable T cells). Trial protocols were reviewed and approved by local institutional review boards; all enrolled patients provided written informed consent.

**Biomarker analyses**

Baseline clinical and disease factors, blood soluble biomarkers, the tumor microenvironment (TME), and circulating blood cells were explored for association with clinical response and PFS. Quantitative tumor burden (total metabolic tumor volume [TMTV]) was assessed by FDG-PET/CT. Expression of exhaustion markers in the TME on tumor-infiltrating T cells (lymphocyte activation gene 3 [LAG3], programmed cell death protein-1 [PD-1], and T-cell immunoglobulin and mucin-domain containing-3 [TIM-3]), monocytes, and myeloid-derived suppressor cells (MDSCs) were measured by fluorescence immunohistochemistry. Baseline tumor tissues were available for 96 of 97 infused patients, 67 of them had quantified values for LAG3+CD3+ biomarker, which were obtained <1 year (in 57 of 67 patients) or >1 year (in 10 of 67 patients) before tisagenlecleucel infusion. Further details including the timing of archival patient tumor biopsies are provided in the Supplemental Data. Peripheral blood samples were obtained prior to LD chemotherapy and prior to infusion, and circulating T, B, and natural killer (NK) cells were quantified (see the Methods section in the Supplemental Data).

**Pharmacokinetics**

Cellular kinetics of tisagenlecleucel in peripheral blood were assessed by measuring transgene levels by quantitative polymerase chain reaction (qPCR).[6,8]

**Statistical analyses**

As previously described, the Kaplan-Meier method was used to estimate PFS, duration of response (DOR), overall survival (OS), and time to next antilymphoma therapy (TTNT).[6] Post-hoc subgroup analyses of response were also completed based on key baseline subgroups.

Univariate and multivariate Cox model analyses were used to explore associations of biomarker and clinical/disease characteristics with PFS. Variables included in the analyses were tumor burden and other clinical factors, TME characteristics, blood T, B, and NK cell counts, cytokines and other soluble clinical lab measurements, as well as peripheral blood T cell immunophenotypes. Correlations between baseline tumor burden and pre-LD serum cytokine levels were quantified using Spearman correlation coefficient. Chimeric antigen receptor (CAR)-T cell in vivo exposure parameters (cellular kinetics) were estimated using noncompartmental methods with Phoenix WinNonlin, version 6.4 (Pharsight Corp., St. Louis, MO). All data analyses were performed by SAS (version 9.4) and RStudio (2022).[9]

**Data sharing statement**

Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The data availability of these trials is according to the criteria and process described on www.clinicalstudydatarequest.com.

## RESULTS

### Baseline characteristics

As of March 29, 2022, 119 patients were screened and 98 patients were enrolled, of whom 97 were infused. Median time from first line of therapy to ELARA enrollment was 59.5 months. The median follow-up time from infusion to data cutoff was 28.9 months (interquartile range [IQR], 22.2–37.7). The median time from enrollment (ie, leukapheresis product accepted) to infusion was 46 days (IQR, 38-57) and the median time from manufacturing process start to final product release from the facility for all enrolled patients (n=98) was 24 days (IQR, 21-30). The efficacy

analysis set included 94 patients who had measurable disease per independent review committee at the time of infusion. Safety analysis was conducted on all 97 patients infused with tisagenlecleucel. Patient demographics and disease characteristics at baseline are shown in **Supplemental Table 1**. At study entry, the median number of prior lines of therapy was 4 (range, 2-13), including prior autoSCT in 36% (35/97); 78% (76/97) of patients were refractory to the last prior antineoplastic treatment (71% [69/97] ≥2 prior regimens) and 63% (61/97) had disease progression within 2 years of initial anti-CD20–containing treatment (POD24 group). Furthermore, 65% (63/97) of patients had bulky disease and 60% (58/97) had a Follicular Lymphoma International Prognostic Index (FLIPI) score ≥3. Overall, 45% (44/97) of patients received bridging therapy. Baseline and disease characteristics more commonly found in patients who required bridging therapy included bulky disease, high FLIPI score, and stage III-IV disease. Tisagenlecleucel was administered in the outpatient setting for 18% of patients.

**Efficacy**

In this updated follow-up, median PFS, DOR, and OS were not reached (**Figures 1A-C**). The estimated 24-month PFS rate for all patients was 57.4% (95% CI, 46.2-67.0). Estimated 24-month DOR of patients in complete response (CR) was 77.8% (95% CI, 64.7, 86.5). Estimated 24-month OS of patients in CR was 87.7% (95% CI, 78.3-93.2). The median TTNT for all patients was not reached and the estimated 24-month TTNT was 69.7% (95% CI, 58.7-78.3; **Figure 1D**). Patients in CR demonstrated better efficacy when compared with the overall ELARA population for each of these efficacy measures. Relapse occurred in 25 (31%) responders. Median time to relapse among responders was 121.5 days (range 43-635). EAS For all patients, the ORR (best overall response of CR or partial response [PR]) was 86.2% (81/94; 95% CI, 77.5-92.4) and CRR was 68.1% (64/94; 95% CI, 57.7-77.3; **Supplemental Table 2**). Of the 31 patients who had an initial PR, 14 converted to a CR within 6 months after infusion. One patient in CR was downgraded to a PR due to a determination that their

confirmatory bone marrow test was performed outside of the strict 14-day testing window, per protocol (**Supplemental Table 2**).

Tisagenlecleucel induced high rates of durable responses in all patients including those with high-risk baseline disease characteristics, such as POD24 (ORR 82%, CRR 59%), high tumor burden by TMTV (ORR 75%, CRR 40%), bulky disease (ORR 85.5%, CRR 64.5%), high FLIPI score (ORR 80.7%, CRR 61.4%), and double refractoriness (ORR 84.6%, CRR 66.2%). A homogeneous treatment effect was observed across all subgroups with no change to response rates (CRR and ORR) when analyzed by risk subgroups (**Supplemental Figure 1**). The estimated 24-month PFS and DOR rates after censoring for new anti-cancer therapy for patients in CR with high (n=20) versus low (n=72) tumor burden were 42.9% (95% CI, 9.8-73.4) versus 78.8% (95% CI, 64.9-87.7) and 42.9% (95% CI, 9.8-73.4) versus 81.8% (95% CI, 67.7-90.1) per independent review committee assessment; due to the low number of patients with high tumor burden, the results should be interpreted with caution.

**Safety**

The safety profile of tisagenlecleucel observed in this long-term follow-up analysis was consistent with published reports.[6,10] No new safety signals or treatment-related mortality were observed. Any-grade infection at any time post infusion occurred in 16 (16.5%) patients, with 9 (9.3%) experiencing grade ≥3; COVID-19 related infections any time post infusion are summarized in **Supplemental Table 3**. By month 6, the probability of resolution (defined as achieving lab results of grade 2 or below) of any cytopenia was 82.0% and for all the cytopenias (leukopenia, anemia, thrombocytopenia, neutropenia, and lymphopenia) ranged from 70% to 100%. At month 24, the probability of resolution was 96.7% for any cytopenia. Any-grade hypogammaglobulinemia was experienced in 11 (11.3%) patients, with 1 (1%) reporting grade ≥3 (**Supplemental Table 4**). Additionally, 2 patients developed serious neurological events >8 weeks after tisagenlecleucel infusion (1 possible progressive multifocal leukoencephalopathy

[onset study day 238] in a patient who had prior grade 4 immune effector cell-associated neurotoxicity syndrome ongoing at the time of death, which was due to euthanasia, and 1 encephalopathy [onset study day 345] ongoing at the time of death due to hemophagocytic lymphohistiocytosis). All other neurological events had resolved at the time of data cutoff. Twenty-two patients (22.7%) received ≥1 new antineoplastic medication after tisagenlecleucel, primarily due to stable disease or progressive disease. Two patients experienced a secondary malignancy during this longer-term follow-up (squamous cell carcinoma and bladder transitional cell carcinoma). Additionally, 3 new deaths occurred during this updated 2-year follow-up period (progressive disease, n=1; serious adverse events, n=2 [urothelial bladder carcinoma and graft-vs-host disease following allogeneic stem cell transplant]). None of the malignancies or deaths were considered related to study treatment. Further details concerning deaths are included in the Supplemental Data.

**Biomarker analysis**

Exploratory analyses were performed on long-term efficacy outcomes for patients with several known high-risk disease characteristics. Higher tumor burden at baseline (pre-LD chemotherapy, TMTV >240 mL) was associated with shorter PFS (*P*=0.00016; **Figure 2A**) and DOR in responders (*P*<0.0001; **Figure 2B**). Lower levels of tumor-infiltrating LAG3+ exhausted T cells (<3% of total CD3+ T cells) in the TME were significantly associated with longer PFS (**Figure 2C**) and DOR (**Figure 2D**). No (meaningful/significant) difference was observed for other exhaustion markers such as PD-1 and TIM-3; similarly, no differences were observed for monocyte and MDSCs in the TME (data not shown). Lower tumor necrosis factor (TNF)-α and interleukin (IL)-10 levels were associated with prolonged PFS (**Figure 3A** and **Figure 3B**). Assessment of T and B cells and various cytokines in blood samples showed that baseline tumor burden strongly correlated with pre-LD levels of TNF-α and IL-10 (Spearman correlation = 0.86 and 0.8, respectively; both *P*<0.001; **Figure 3C** and **Figure 3D**). A higher proportion of

circulating naïve CD8+ T cells (≥3.5% of T cells) at baseline was associated with longer PFS (**Figure 4A**) and DOR (**Figure 4B**). Lower baseline tumor volume (≤240 mL) and higher $C_{max}$ (>4000 copies/µg) were associated with longer PFS (**Figure 4C**). Patients with high baseline tumor volume (>240 mL) and high $C_{max}$ (>4000 copies/µg) had PFS that was comparable to patients with low baseline tumor volume (≤240 mL) and low $C_{max}$ (<4000 copies/µg) (**Figure 4C**). Patients with lower tumor volume (≤240 mL) and higher naïve CD8+ T cells (≥3.5% of T cells) at baseline had longer PFS than other subgroups (**Figure 4D**). Higher levels (%) of CD8+ naïve T cells at baseline were associated with ongoing response at 1 year and were observed among the tumor volume and $C_{max}$ subgroups that experienced prolonged PFS (**Figure 4E**). Furthermore, a multivariate analysis showed that nodal area involvement (>4 nodal areas), high tumor volume (>240 mL), and low percentage of naïve CD8+ T cells (<3.5% of T cells) were significantly associated with worse PFS outcomes (**Supplemental Figure 2**).

**Pharmacokinetics**

Among 97 patients evaluable, CAR transgene persistence was detectable for up to 925 days (median, 210 days; range, 13-925 days). The mean area under the concentration-time curve (AUC) from day 0 to day 84 ($AUC_{0\text{-}84d}$) in responders (CR and PR) was similar to nonresponders (stable disease and progressive disease). The geometric mean $AUC_{0\text{-}28d}$ and geometric mean maximum expansion ($C_{max}$) values in responders were nearly 2.4-fold higher compared to nonresponders; however, considering the high interindividual variability, small number of nonresponders, and overlapping expansion ranges observed between responders and nonresponders, the exposure differences should be interpreted with caution (**Supplemental Table 5**). For patients with POD24 or without POD24, the geometric mean $C_{max}$ (geometric mean CV%) was 2700 copies/µg (n=51, 434%) and 9890 copies/µg (n=31, 529%), respectively; however, responses were observed in patients with POD24 despite lower expansion than found in patients without POD24 (**Figure 5A**). Similar to all patients, persistence of CAR transgene in

patients with POD24 was detected up to 925 days (median, 184 days; range, 13-925 days). Lastly, there was a negative association between PD-L1 expression in the TME and expansion (**Figure 5B**). While shorter PFS and DOR were observed in patients with high (median cutoff ≥4%) PD-L1 expression, this was not statistically significant (data not shown).

**Dose-response relationship**

Logistic regression analysis showed no strong evidence of dose-response relationship. A slight trend toward decreased response with lower doses was observed at doses lower than $1.0\times10^8$ cells; however, due to the small number of nonresponders, these findings should be interpreted with caution. Favorable responses were observed across a wide dose range (**Figure 6**). Similarly, dose was not associated with PFS (**Supplemental Figure 3A**) and DOR (**Supplemental Figure 3B**). Baseline characteristics, such as TMTV (**Supplemental Figure 4A**) and POD24 status (**Supplemental Figure 4B**), did not correlate with dose-response.

**DISCUSSION**

Findings from this longer-term update of the ELARA trial continue to demonstrate high response rates and durable remissions with a favorable safety profile in heavily pretreated patients with r/r FL treated with tisagenlecleucel. Median DOR, PFS, OS, and TTNT were not reached after >2 years of follow-up. Durable antitumor efficacy was observed in most patients, including those with high-risk clinical characteristics (POD24, high metabolic tumor volume, bulky disease, double refractory disease, and high FLIPI score). Long-term efficacy in these patients supports use of tisagenlecleucel in a broad population of patients with r/r FL.

These updated data are bolstered by recent findings from retrospective analyses [prior to mosunetuzumab] comparing ELARA with real-world evidence, demonstrating improved efficacy of tisagenlecleucel over other SOC options.[11,12] Patients from ELARA had an estimated 1.4-fold

higher PFS rate at 12 months and an 80% reduction in risk of death compared with SOC.[11] Similarly, comparison of ELARA versus the US Flatiron Health Research Database indicated improved efficacy across CRR (69% versus 18%), 12-month PFS (73% versus 42%), OS (97% versus 85%), and TTNT (86% versus 52%) for tisagenlecleucel compared with SOC.[12] These benefits over SOC were observed regardless of number of previous therapies, requirement for bridging therapy, or POD24 status. Although the median time from study enrollment to infusion was 48 days, median manufacturing time was only 24 days. Numerous factors may influence the time from leukapheresis to infusion during a clinical trial (logistical, disease control, infection) and, given the indolent nature of FL, some physicians took a slightly less aggressive approach to treatment timing. Because turn-around-time was not optimized as a part of the ELARA trial, commercial production is likely to have a faster turn-around-time for patients.

Exploratory biomarker analyses were implemented to provide a better understanding of long-term efficacy outcomes in patients with high-risk disease characteristics. TME composition in pretreatment biopsies collected from patients with FL was assessed by measuring the expression of several exhaustion markers in T cells, monocytes, and MDSCs (data not shown). We found that low expression of LAG3+ on T cells (<3%) was associated with favorable PFS and DOR. Similarly, increased numbers of LAG3+ T cells have been shown to correlate with poor outcomes in patients with FL, whereby LAG3 expression on intratumoral T cells identifies a functionally exhausted subset of T cells with impaired cytokine (IL-2 and IFN-γ) and granule (perforin and granzyme B) production.[13] Inhibition of LAG-3 has shown the capability to restore cytotoxic activity in exhausted T cells and reduce regulating T cells' immune suppression function, thereby enhancing the killing effect on tumors.[14] While the anti-LAG-3 antibody relatlimab has been approved in combination with nivolumab for patients with advanced melanoma,[15] clinical trials are ongoing in patients with classical Hodgkin lymphoma[16,17] and

other indications,[18] and prospective studies would be needed to evaluate the benefit of anti-LAG3 therapies in patients with FL.

We also found that higher levels of TNF-α and IL-10 (at baseline) were associated with lower PFS and DOR. Similar to these findings, high levels of TNF-α correlated with a higher tumor burden, lower CRR, and shorter PFS and OS in patients with FL[19] and diffuse large B-cell lymphoma.[20] TNF-α is thought to influence lymphomagenesis through up-regulation of inflammatory and anti-apoptotic signals, possibly via the nuclear NF-kB pathway.[21] TNF-α may also cooperate with other cytokines, including IL-10, to increase cell proliferation.[22] Macrophages may be the main source of TNF-α, especially when they are exposed to IL-4 and IL-10, both inducing an M2 phenotype characterized by their ability to suppress T-cell adaptive immunity.[23] Altogether, these data suggest that a pre-existing immunosuppressive environment before infusion may hinder effective antitumor function of CAR-T cells.

The prognostic value of high baseline tumor volume in patients with FL and its association with shorter PFS has previously been validated.[24,25] While lower tumor burden prior to tisagenlecleucel infusion may be associated with improved outcomes, the causality is not clear. There are various scenarios where tumor burden cannot be reduced prior to infusion which should not preclude patients with high tumor burden from considering CAR-T cell therapy. Our exploratory analysis revealed that despite high baseline tumor volume, patients with high CAR-T cell expansion ($C_{max}$) had PFS that was comparable to patients with low baseline tumor volume and low $C_{max}$, suggesting that higher CAR-T cell expansion may be able to compensate for high baseline tumor volume. Interestingly, baseline circulating naïve CD8+ cells showed a positive association with $C_{max}$, and the percentage of naïve CD8+ T cells was higher in patients who achieved a CR and had ongoing response ≥1 year. Our analysis has shown that the presence of a higher percentage of circulating naïve CD8+ T cells at baseline was associated with

improved efficacy outcomes. Responses were also observed in patients with POD24 despite lower tisagenlecleucel expansion compared with patients without POD24. No strong evidence suggesting a relationship between dose and overall response was observed. Cellular kinetic analyses showed CAR transgene persistence for up to 925 days in ELARA; however, the relationship between prolonged persistence and long-term clinical efficacy remains unclear, and longer follow-up is needed.

Updated findings from the Phase II ZUMA-5 trial of axicabtagene ciloleucel in patients with r/r indolent NHL (median follow-up of 40.5 months) demonstrated comparable efficacy with ELARA,[26] despite fewer heavily pretreated patients enrolled in ZUMA-5 compared with ELARA (3 versus 4 median lines of prior therapy).[6,27] These findings are consistent with the homogeneous treatment effect seen in ELARA regardless of the number of prior lines of therapy and demonstrates that patient outcomes were still superior to the current non-CAR-T cell therapy standards of care.[11,28-34] Even though difficulties with cross-trial comparisons and variation in follow-up duration between the studies limit definitive conclusions, the safety profile of tisagenlecleucel continues to compare favorably to that of axicabtagene ciloleucel.[26] Notably, both ZUMA-5 and the TRANSCEND-FL Phase II trial allowed the use of bridging therapy at the discretion of the physician. In total, 4% of patients received bridging in ZUMA-5 and 38% to 41% received bridging in TRANSCEND-FL (compared with 45% in ELARA).[6,27,35] The lower frequency of bridging therapy reported in ZUMA-5 may have been a result of the fast product delivery, or could reflect the higher clinical risk profile of the ELARA population. However, this hypothesis remains speculative.

The comparable efficacy and lower rates of severe cytokine release syndrome and neurological events reported in ELARA versus ZUMA-5 reported in a matching-adjusted indirect comparison[36] support the feasibility of tisagenlecleucel outpatient administration. Of the 30

clinical trial sites, only 4 in the United States and 1 in Australia allowed outpatient infusions. In total, 18% percent of patients in ELARA were infused in the outpatient setting, 12 of the 17 patients infused in the outpatient setting were in the United States. Patients infused in the outpatient setting generally had favorable Eastern Cooperative Oncology Group (ECOG) performance status, favorable FLIPI scores, and less bulky disease at baseline. Findings from a recent report of the ELARA trial after a median follow-up of 20 months showed that compared with inpatients, outpatients had higher proportions of patients with grade 3A FL, primary refractory disease, and >5 lines of prior therapy; 41% of patients treated in the outpatient setting did not require hospitalization within 30 days; and no patients required intensive care unit admission.[37]

Our biomarker findings provide evidence for prognostic markers of PFS; however, the criteria used to select patients who are likely to benefit from tisagenlecleucel encompasses a broad range of factors that cannot be fully addressed with these data. Nonetheless, these findings suggest improved tisagenlecleucel efficacy with a favorable TME (lower LAG3+ exhausted T cells) and decreased inflammatory status (lower TNF-α and IL-10). Additional correlative analyses are needed to understand how these findings could inform clinical decision-making. As more treatment options become available for patients with r/r FL setting, the question of how to individualize the sequencing of therapy to achieve the best possible outcomes remains, especially in patients who relapse following CAR-T cell therapy. Long-term follow-up and real-world data are needed to help to identify the optimal sequencing for these patients and to understand the influence previous treatment regimens and patient-related criteria may have on available treatment options. Overall, extended follow-up of >2 years from ELARA demonstrates that tisagenlecleucel continues to provide substantial clinical benefit with a remarkable safety profile in adult patients with r/r FL (including patients with high-risk characteristics for whom effective therapeutic options are currently unavailable), suggesting a potential new SOC.

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## DISCLOSURE OF CONFLICTS OF INTEREST

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**FIGURE LEGENDS**

**Figure 1. Kaplan-Meier curves for secondary endpoints in r/r FL patients who received tisagenlecleucel infusion.** (**A**) PFS, (**B**) DOR, (**C**) OS, and (**D**) TTNT in the EAS (n=94). PFS, DOR, OS by BOR curves are per IRC assessment. TTNT curve is per local assessment. Censoring times are shown as squares. BOR, best overall response; CR, complete response; DOR, duration of response; EAS, efficacy analysis set; FL, follicular lymphoma; IRC, independent review committee; NE, not estimable; OS, overall survival; PFS, progression-free survival; PR, partial response; r/r, relapsed/refractory; TTNT, time to start of new lymphoma therapy.

**Figure 2. Association between baseline TMTV and tumor-infiltrated LAG3+ T cells with PFS and DOR.** (**A**) Kaplan-Meier plots of PFS by TMTV. (**B**) Kaplan-Meier plots of DOR by TMTV. (**C**) Kaplan-Meier plots of PFS associated with %LAG3+CD3+ cells in baseline tumors. (**D**). Kaplan-Meier plots of DOR associated with %LAG3+CD3+ cells in baseline tumors. A cutoff (240 mL) where most separation between PFS and DOR was derived and results are shown here. CD, cluster of differentiation; DOR, duration of response; LAG3, lymphocyte activation gene 3; NE, not estimable; PFS, progression-free survival; TMTV, total metabolic tumor volume.

**Figure 3. Lower pre-LD serum TNF-α and IL-10 levels correlated with lower tumor volume and prolonged PFS.** (**A**) TNF-α and PFS. (**B**) IL-10 and PFS. (**C**) TNF-α versus tumor volume. (**D**) IL-10 versus tumor volume. IL, interleukin; LD, lymphodepleting; NE, not estimable; PFS, progression-free survival; TNF, tumor necrosis factor.

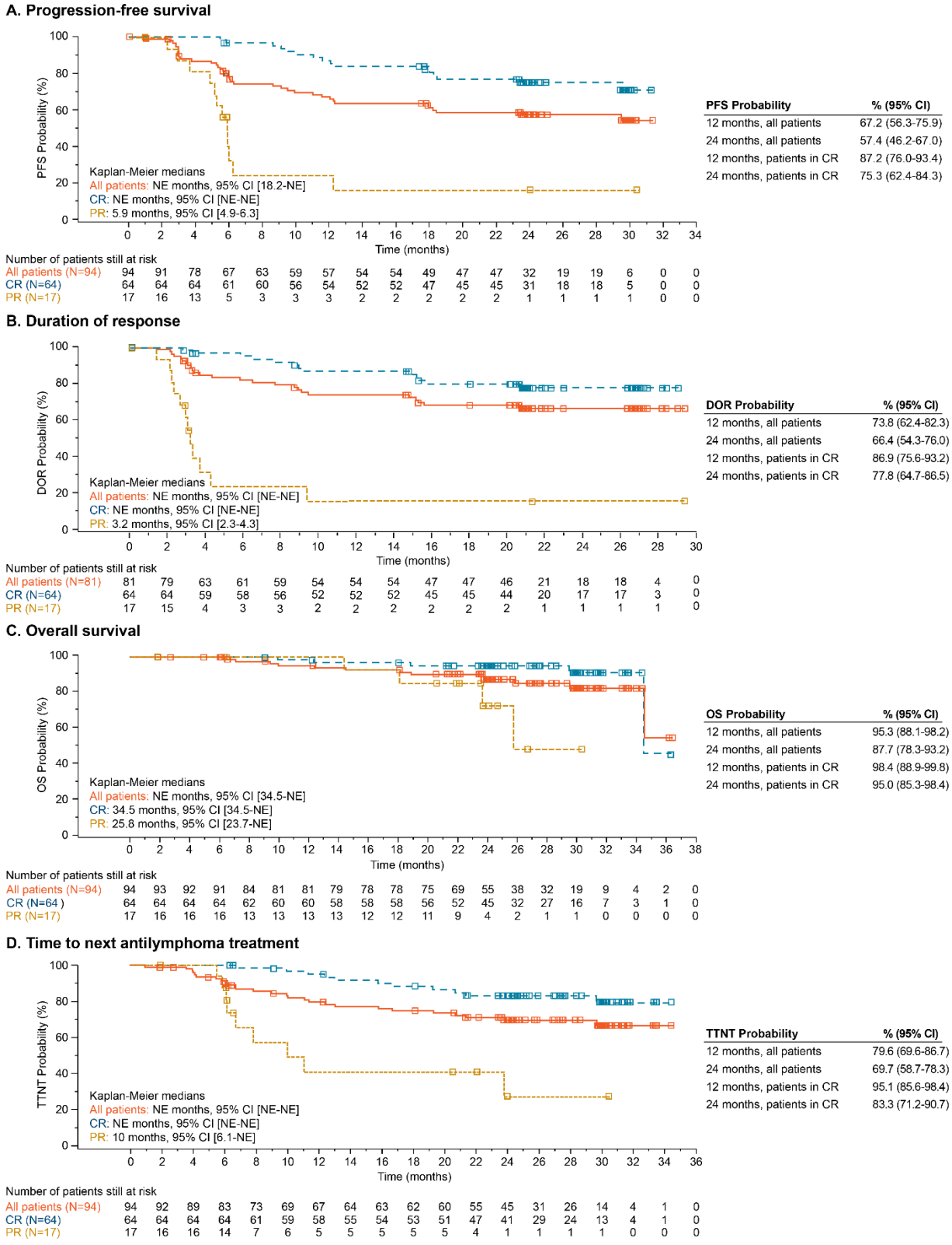
**Figure 4. Lower tumor volume, high $C_{max}$, and high naïve CD8+ T cells at baseline were associated with prolonged PFS.** (**A**) PFS by percentage of naïve CD8+ T cells. (**B**) DOR by

percentage of naïve CD8+ T cells. Significant associations between naive CD8+ cells and DOR ($p = 0.044$) and PFS ($p = 0.014$) were observed when using median (2.14%) as cutoff (data not shown). A cutoff (3.5%) where most separation between PFS and DOR was derived and results are shown here. (**C**) PFS by tumor volume and $C_{max}$. (**D**) PFS by TMTV and percentage of naïve CD8+ T cells. (**E**) Naïve CD8+ T cells by tumor volume and $C_{max}$. CD, cluster of differentiation; $C_{max}$, maximum transgene level; DOR, duration of response; NE, not estimable; PFS, progression-free survival; TMTV, total metabolic tumor volume; TV, tumor volume.

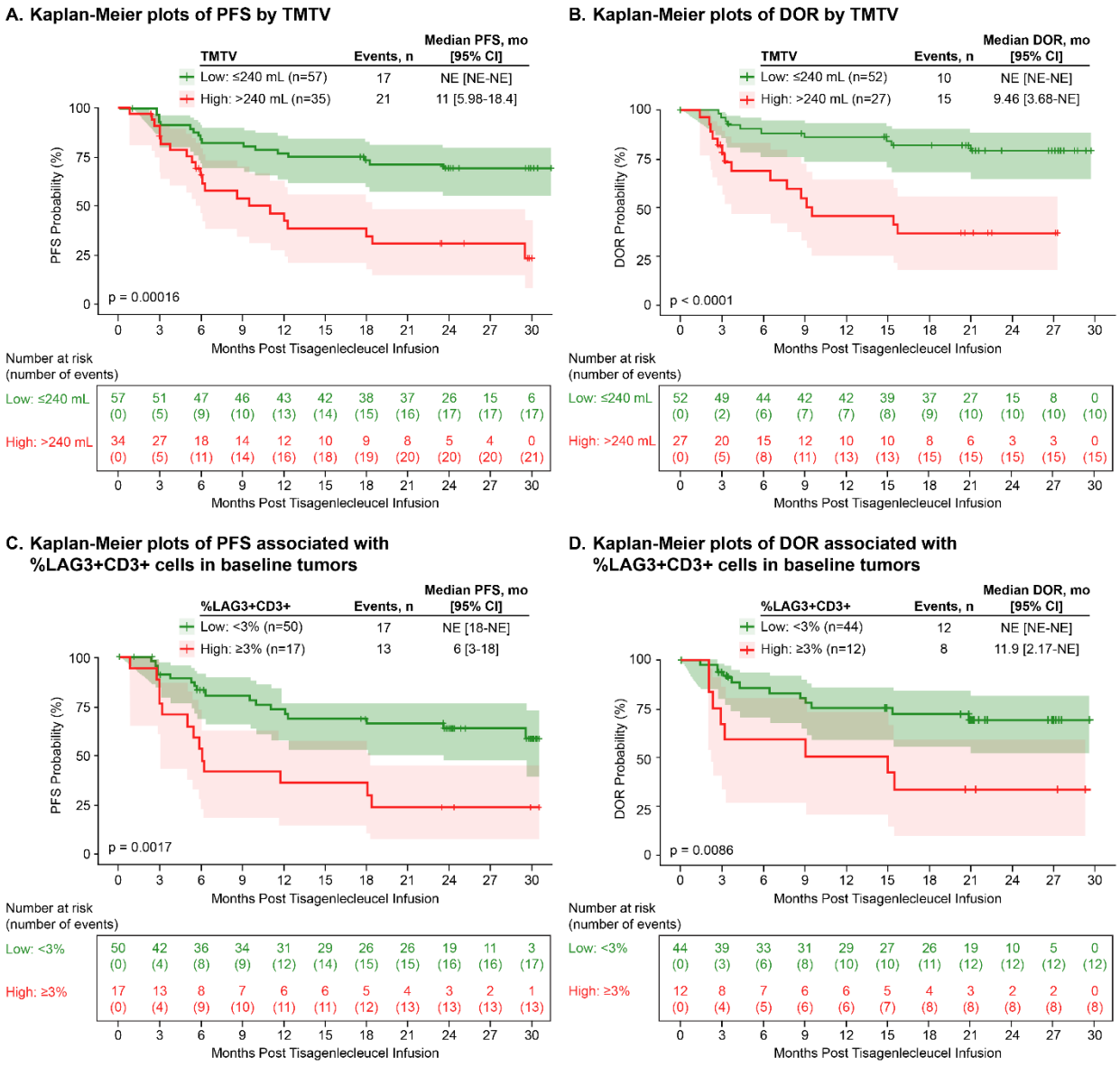
**Figure 5. Pharmacokinetic analysis.** (**A**) qPCR cellular kinetic parameters by POD24 in tisagenlecleucel infused set. (**B**) Association of $C_{max}$ with PD-L1 in patients based on total metabolic tumor volume. CAR, chimeric antigen receptor; $C_{max}$, maximum transgene level; CR, complete response; NA, not available; NR, no response; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1; POD24, progression of disease within 24 months from first immunochemotherapy; PR, partial response; qPCR, quantitative polymerase chain reaction; R, response; SD, stable disease; TME, tumor microenvironment; TMTV, total metabolic tumor volume; UNK, unknown.

**Figure 6. Linear regression analysis of dose-response relationship.** CR, complete response, PR partial response.

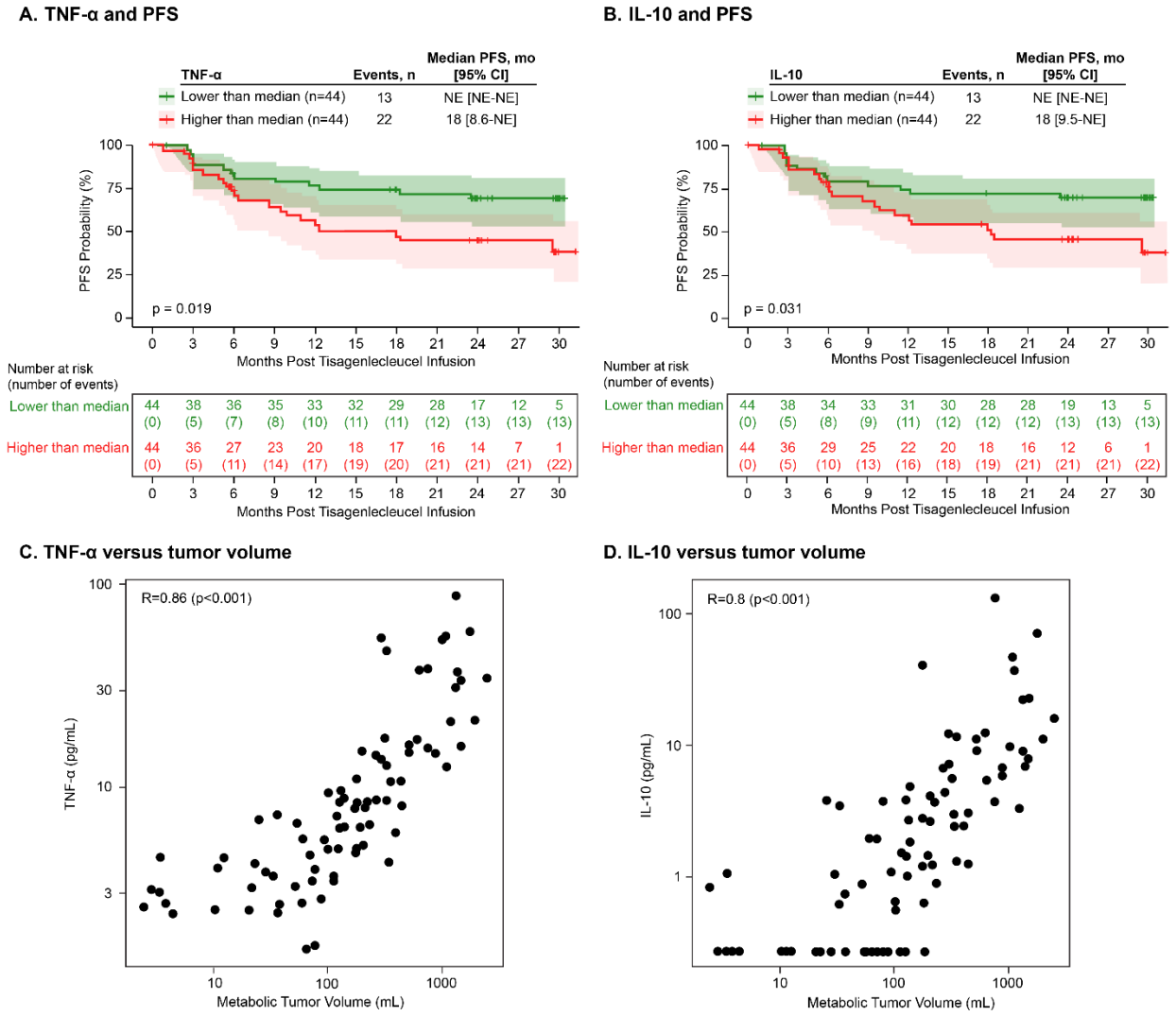
# Figure 1.


A. Progression-free survival
PFS Probability (%)
Kaplan-Meier medians
All patients: NE months, 95% CI [18.2-NE]
CR: NE months, 95% CI [NE-NE]
PR: 5.9 months, 95% CI [4.9-6.3]
Time (months)
Number of patients still at risk
All patients (N=94) 94 91 78 67 63 59 57 54 54 49 47 47 32 19 19 6 0 0
CR (N=64) 64 64 64 61 60 56 54 52 52 47 45 45 31 18 18 5 0 0
PR (N=17) 17 16 13 5 3 3 3 2 2 2 2 2 1 1 1 1 0 0
PFS Probability % (95% CI)
12 months, all patients 67.2 (56.3-75.9)
24 months, all patients 57.4 (46.2-67.0)
12 months, patients in CR 87.2 (76.0-93.4)
24 months, patients in CR 75.3 (62.4-84.3)
B. Duration of response
DOR Probability (%)
Kaplan-Meier medians
All patients: NE months, 95% CI [NE-NE]
CR: NE months, 95% CI [NE-NE]
PR: 3.2 months, 95% CI [2.3-4.3]
Time (months)
Number of patients still at risk
All patients (N=81) 81 79 63 61 59 54 54 54 47 47 46 21 18 18 4 0
CR (N=64) 64 64 59 58 56 52 52 52 45 45 44 20 17 17 3 0
PR (N=17) 17 15 4 3 3 2 2 2 2 2 2 1 1 1 1 0
DOR Probability % (95% CI)
12 months, all patients 73.8 (62.4-82.3)
24 months, all patients 66.4 (54.3-76.0)
12 months, patients in CR 86.9 (75.6-93.2)
24 months, patients in CR 77.8 (64.7-86.5)
C. Overall survival
OS Probability (%)
Kaplan-Meier medians
All patients: NE months, 95% CI [34.5-NE]
CR: 34.5 months, 95% CI [34.5-NE]
PR: 25.8 months, 95% CI [23.7-NE]
Time (months)
Number of patients still at risk
All patients (N=94) 94 93 92 91 84 81 81 79 78 78 75 69 55 38 32 19 9 4 2 0
CR (N=64 ) 64 64 64 64 62 60 60 58 58 58 56 52 45 32 27 16 7 3 1 0
PR (N=17) 17 16 16 16 13 13 13 13 12 12 11 9 4 2 1 1 0 0 0 0
OS Probability % (95% CI)
12 months, all patients 95.3 (88.1-98.2)
24 months, all patients 87.7 (78.3-93.2)
12 months, patients in CR 98.4 (88.9-99.8)
24 months, patients in CR 95.0 (85.3-98.4)
D. Time to next antilymphoma treatment
TTNT Probability (%)
Kaplan-Meier medians
All patients: NE months, 95% CI [NE-NE]
CR: NE months, 95% CI [NE-NE]
PR: 10 months, 95% CI [6.1-NE]
Time (months)
Number of patients still at risk
All patients (N=94) 94 92 89 83 73 69 67 64 63 62 60 55 45 31 26 14 4 1 0
CR (N=64) 64 64 64 64 61 59 58 55 54 53 51 47 41 29 24 13 4 1 0
PR (N=17) 17 16 16 14 7 6 5 5 5 5 5 4 1 1 1 1 0 0 0
TTNT Probability % (95% CI)
12 months, all patients 79.6 (69.6-86.7)
24 months, all patients 69.7 (58.7-78.3)
12 months, patients in CR 95.1 (85.6-98.4)
24 months, patients in CR 83.3 (71.2-90.7)

## Figure 2.


A. Kaplan-Meier plots of PFS by TMTV
TMTV
Events, n
Median PFS, mo [95% CI]
Low: ≤240 mL (n=57)
17
NE [NE-NE]
High: >240 mL (n=35)
21
11 [5.98-18.4]
PFS Probability (%)
p = 0.00016
Months Post Tisagenlecleucel Infusion
Number at risk (number of events)
Low: ≤240 mL
57 (0) 51 (5) 47 (9) 46 (10) 43 (13) 42 (14) 38 (15) 37 (16) 26 (17) 15 (17) 6 (17)
High: >240 mL
34 (0) 27 (5) 18 (11) 14 (14) 12 (16) 10 (18) 9 (19) 8 (20) 5 (20) 4 (20) 0 (21)
B. Kaplan-Meier plots of DOR by TMTV
TMTV
Events, n
Median DOR, mo [95% CI]
Low: ≤240 mL (n=52)
10
NE [NE-NE]
High: >240 mL (n=27)
15
9.46 [3.68-NE]
DOR Probability (%)
p < 0.0001
Months Post Tisagenlecleucel Infusion
Number at risk (number of events)
Low: ≤240 mL
52 (0) 49 (2) 44 (6) 42 (7) 42 (7) 39 (8) 37 (9) 27 (10) 15 (10) 8 (10) 0 (10)
High: >240 mL
27 (0) 20 (5) 15 (8) 12 (11) 10 (13) 10 (13) 8 (15) 6 (15) 3 (15) 3 (15) 0 (15)
C. Kaplan-Meier plots of PFS associated with %LAG3+CD3+ cells in baseline tumors
%LAG3+CD3+
Events, n
Median PFS, mo [95% CI]
Low: <3% (n=50)
17
NE [18-NE]
High: ≥3% (n=17)
13
6 [3-18]
PFS Probability (%)
p = 0.0017
Months Post Tisagenlecleucel Infusion
Number at risk (number of events)
Low: <3%
50 (0) 42 (4) 36 (8) 34 (9) 31 (12) 29 (14) 26 (15) 26 (15) 19 (16) 11 (16) 3 (17)
High: ≥3%
17 (0) 13 (4) 8 (9) 7 (10) 6 (11) 6 (11) 5 (12) 4 (13) 3 (13) 2 (13) 1 (13)
D. Kaplan-Meier plots of DOR associated with %LAG3+CD3+ cells in baseline tumors
%LAG3+CD3+
Events, n
Median DOR, mo [95% CI]
Low: <3% (n=44)
12
NE [NE-NE]
High: ≥3% (n=12)
8
11.9 [2.17-NE]
DOR Probability (%)
p = 0.0086
Months Post Tisagenlecleucel Infusion
Number at risk (number of events)
Low: <3%
44 (0) 39 (3) 33 (6) 31 (8) 29 (10) 27 (10) 26 (11) 19 (12) 10 (12) 5 (12) 0 (12)
High: ≥3%
12 (0) 8 (4) 7 (5) 6 (6) 6 (6) 5 (7) 4 (8) 3 (8) 2 (8) 2 (8) 0 (8)

## Figure 3.


A. TNF-α and PFS
TNF-α
Events, n
Median PFS, mo [95% CI]
Lower than median (n=44) 13 NE [NE-NE]
Higher than median (n=44) 22 18 [8.6-NE]
PFS Probability (%)
p = 0.019
Months Post Tisagenlecleucel Infusion
Number at risk (number of events)
Lower than median 44 (0) 38 (5) 36 (7) 35 (8) 33 (10) 32 (11) 29 (11) 28 (12) 17 (13) 12 (13) 5 (13)
Higher than median 44 (0) 36 (5) 27 (11) 14 (14) 20 (17) 18 (19) 17 (20) 16 (21) 14 (21) 7 (21) 1 (22)
B. IL-10 and PFS
IL-10
Events, n
Median PFS, mo [95% CI]
Lower than median (n=44) 13 NE [NE-NE]
Higher than median (n=44) 22 18 [9.5-NE]
PFS Probability (%)
p = 0.031
Months Post Tisagenlecleucel Infusion
Number at risk (number of events)
Lower than median 44 (0) 38 (5) 34 (8) 33 (9) 31 (11) 30 (12) 28 (12) 28 (12) 19 (13) 13 (13) 5 (13)
Higher than median 44 (0) 36 (5) 29 (10) 25 (13) 22 (16) 20 (18) 18 (19) 16 (21) 12 (21) 6 (21) 1 (22)
C. TNF-α versus tumor volume
R=0.86 (p<0.001)
TNF-α (pg/mL)
Metabolic Tumor Volume (mL)
D. IL-10 versus tumor volume
R=0.8 (p<0.001)
IL-10 (pg/mL)
Metabolic Tumor Volume (mL)

## Figure 4.

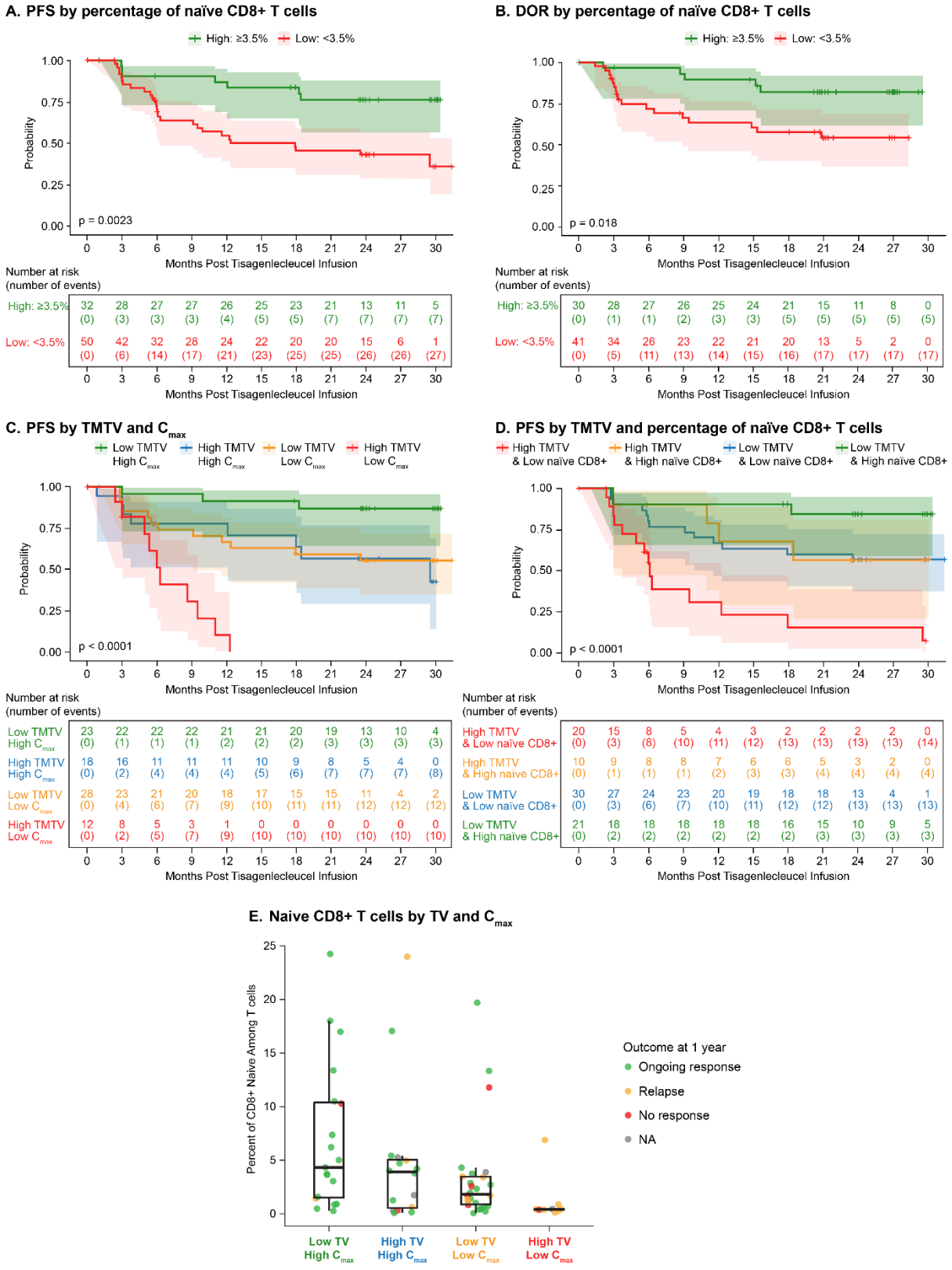

A. PFS by percentage of naïve CD8+ T cells
High: ≥3.5%
Low: <3.5%
Probability
p = 0.0023
Months Post Tisagenlecleucel Infusion
Number at risk
(number of events)
High: ≥3.5% 32 (0) 28 (3) 27 (3) 27 (3) 26 (4) 25 (5) 23 (5) 21 (7) 13 (7) 11 (7) 5 (7)
Low: <3.5% 50 (0) 42 (6) 32 (14) 28 (17) 24 (21) 22 (23) 20 (25) 20 (25) 15 (26) 6 (26) 1 (27)
B. DOR by percentage of naïve CD8+ T cells
p = 0.018
Number at risk
(number of events)
High: ≥3.5% 30 (0) 28 (1) 27 (1) 26 (2) 25 (3) 24 (3) 21 (5) 15 (5) 11 (5) 8 (5) 0 (5)
Low: <3.5% 41 (0) 34 (5) 26 (11) 23 (13) 22 (14) 21 (15) 20 (16) 13 (17) 5 (17) 2 (17) 0 (17)
C. PFS by TMTV and Cmax
Low TMTV High Cmax
High TMTV High Cmax
Low TMTV Low Cmax
High TMTV Low Cmax
p < 0.0001
Number at risk
(number of events)
Low TMTV High Cmax 23 (0) 22 (1) 22 (1) 22 (1) 21 (2) 21 (2) 20 (2) 19 (3) 13 (3) 10 (3) 4 (3)
High TMTV High Cmax 18 (0) 16 (2) 11 (4) 11 (4) 11 (4) 10 (5) 9 (6) 8 (7) 5 (7) 4 (7) 0 (8)
Low TMTV Low Cmax 28 (0) 23 (4) 21 (6) 20 (7) 18 (9) 17 (10) 15 (11) 15 (11) 11 (12) 4 (12) 2 (12)
High TMTV Low Cmax 12 (0) 8 (2) 5 (5) 3 (7) 1 (9) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10)
D. PFS by TMTV and percentage of naïve CD8+ T cells
High TMTV & Low naïve CD8+
High TMTV & High naïve CD8+
Low TMTV & Low naïve CD8+
Low TMTV & High naïve CD8+
p < 0.0001
Number at risk
(number of events)
High TMTV & Low naïve CD8+ 20 (0) 15 (3) 8 (8) 5 (10) 4 (11) 3 (12) 2 (13) 2 (13) 2 (13) 2 (13) 0 (14)
High TMTV & High naive CD8+ 10 (0) 9 (1) 8 (1) 8 (1) 7 (2) 6 (3) 6 (3) 5 (4) 3 (4) 2 (4) 0 (4)
Low TMTV & Low naïve CD8+ 30 (0) 27 (3) 24 (6) 23 (7) 20 (10) 19 (11) 18 (12) 18 (12) 13 (13) 4 (13) 1 (13)
Low TMTV & High naïve CD8+ 21 (0) 18 (2) 18 (2) 18 (2) 18 (2) 18 (2) 16 (2) 15 (3) 10 (3) 9 (3) 5 (3)
E. Naive CD8+ T cells by TV and Cmax
Percent of CD8+ Naive Among T cells
Low TV High Cmax
High TV High Cmax
Low TV Low Cmax
High TV Low Cmax
Outcome at 1 year
Ongoing response
Relapse
No response
NA

**Figure 5.**

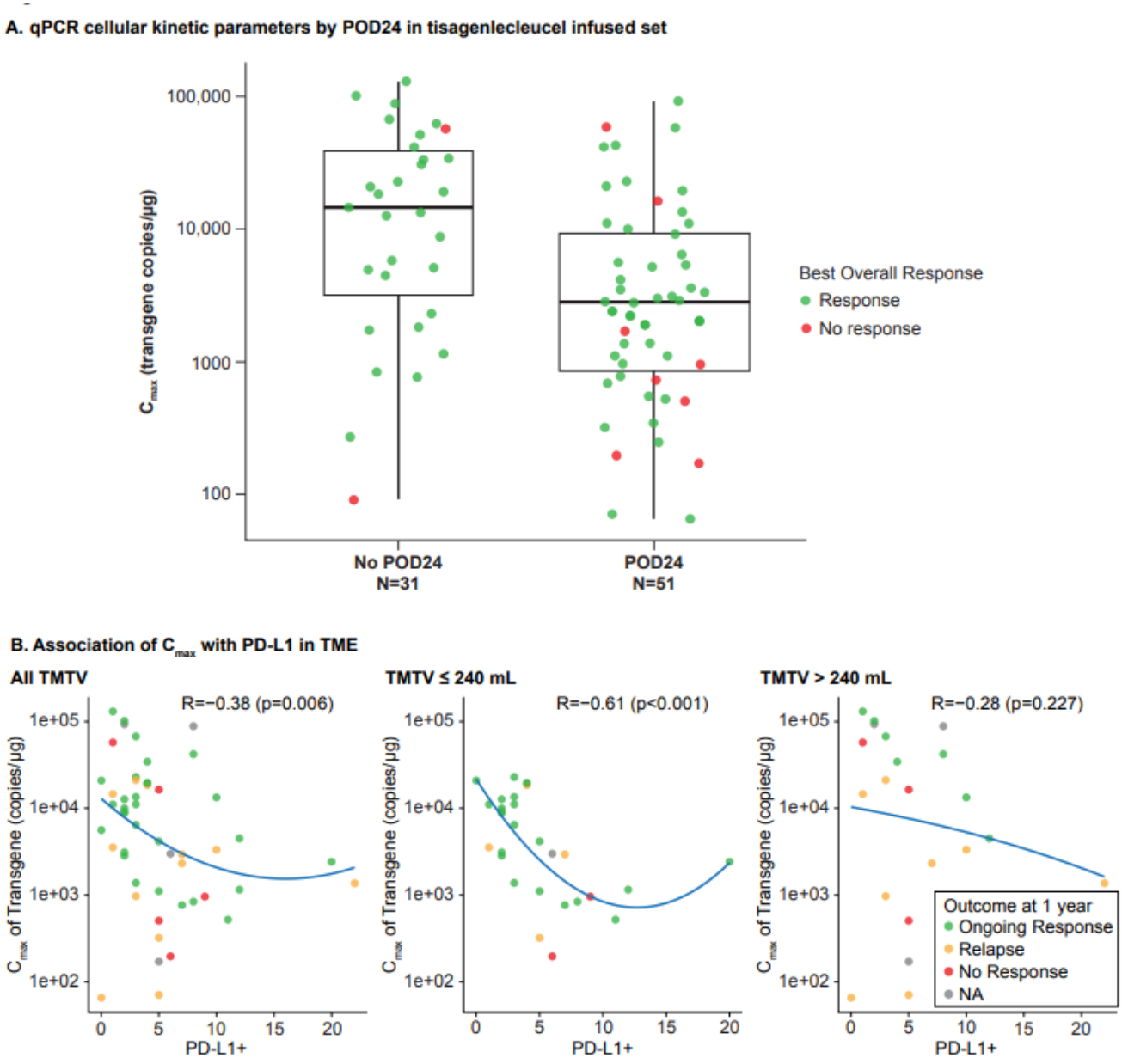
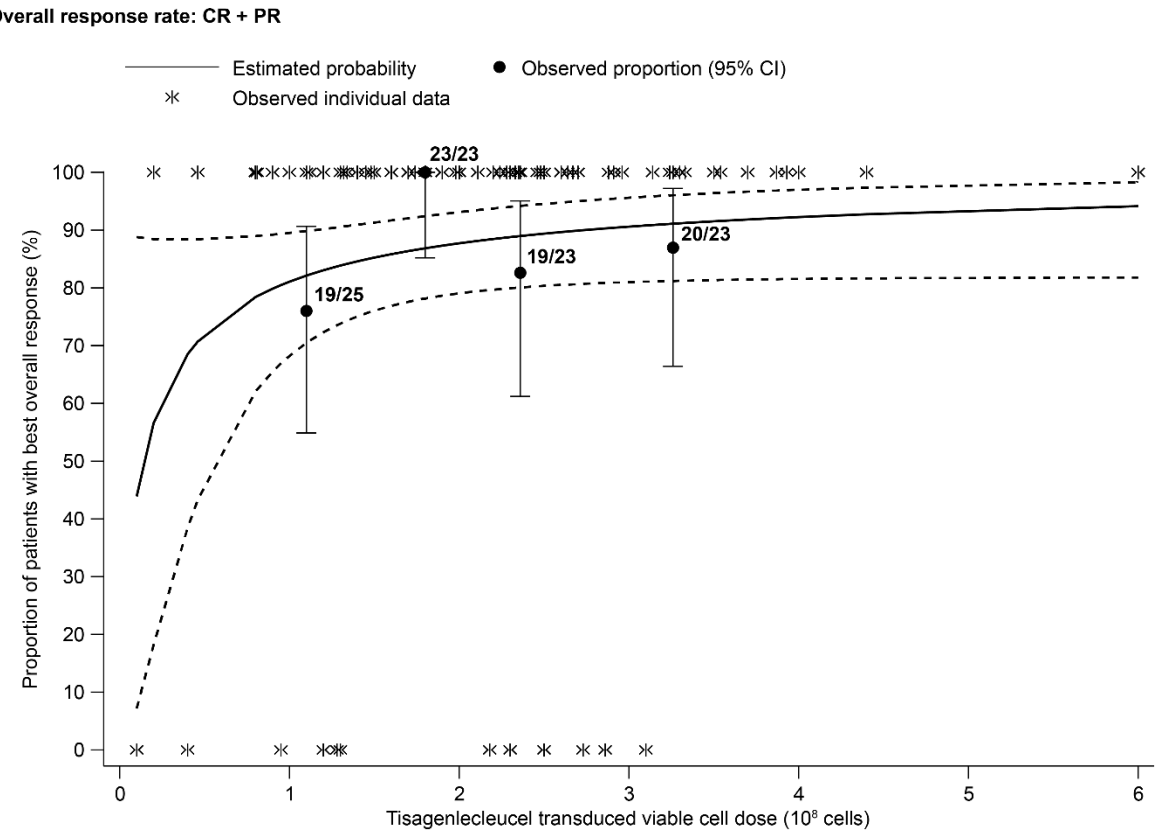

A. qPCR cellular kinetic parameters by POD24 in tisagenlecleucel infused set
100,000
10,000
1000
100
$C_{max}$ (transgene copies/µg)
No POD24
N=31
POD24
N=51
Best Overall Response
Response
No response
B. Association of $C_{max}$ with PD-L1 in TME
All TMTV
R=−0.38 (p=0.006)
TMTV ≤ 240 mL
R=−0.61 (p<0.001)
TMTV > 240 mL
R=−0.28 (p=0.227)
1e+05
1e+04
1e+03
1e+02
$C_{max}$ of Transgene (copies/µg)
0
5
10
15
20
PD-L1+
Outcome at 1 year
Ongoing Response
Relapse
No Response
NA

**Figure 6.**


Overall response rate: CR + PR
Estimated probability
Observed proportion (95% CI)
Observed individual data
23/23
19/23
20/23
19/25
Proportion of patients with best overall response (%)
Tisagenlecleucel transduced viable cell dose ($10^8$ cells)

# SUPPLEMENTAL DATA

## Durable Response After Tisagenlecleucel in Adults With Relapsed/Refractory Follicular Lymphoma: ELARA Trial Update

**Table of Contents**

## METHODS

### Biomarker analyses

*Cytokine analysis:* Approximately 5.0 mL of blood was collected at different time points for cytokine analysis. Serum was prepared within 4 hours of blood collection by centrifuging the samples at 860 RCF for 10 minutes and stored at –70°C. Tubes containing 500 µL frozen serum aliquots were shipped to BioAgilytix (Durham, NC) for analysis via pro-inflammatory multiplex panel according to manufacturer's instructions.

*T-, B-, and natural killer cell counts:* Approximately 5.0 mL of blood was collected at different time points in speckled Cyto-Chex® tubes and sent ambient to LabCorp for the measurement of T-, B-, and natural killer cell counts via flow cytometry.

*Immunophenotyping:* Approximately 5.0 mL of blood was collected for the immunophenotypic characterization by flow cytometry. Immunophenotyping was performed by Navigate BioPharma (Carlsbad, CA). Proportions of T-cell subsets, including naïve T cells, were identified by maturation markers (CCR7/CD45RA/CD45RO) and then correlated with clinical outcome. Naïve CD8+ T cells were separated into high vs low groups by using 3.5% as cutoff.

*Fluorescent immunohistochemistry analysis:* Formalin-fixed paraffin-embedded blocks and/or 4-µm-thick slides were sent to Navigate BioPharma (Carlsbad, CA) for the quantification of CD19 as well as T-cell markers (e.g., CD3, LAG3) expression on baseline tumor biopsies. Fluorescent images were acquired on the PhenoImager HT (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®.[1,2] LAG3 positive CD3 T cells were separated into high (highest quantile) vs low (three lower quantiles) groups by using 3% as cutoff.

*Immunohistochemistry analysis:* Quantification of CD19 baseline expression baseline tumor biopsies (formalin-fixed paraffin-embedded blocks and/or 4-µm-thick slides) was performed using immunohistochemistry method. Samples were sent to NeoGenomics Laboratories (Aliso Viejo, CA) and tested with CD19 antibody (Dako, M7296) on the Ventana Ultra platform according to vendor instructions.

**Timing of archival patient tumor biopsies samples for LAG3+ progression-free survival/duration of response analysis**

Of the 97 patients infused with tisagenlecleucel, 96 submitted central biopsies for analysis. One additional patient did not submit central sample; however, local assessment confirmed follicular lymphoma grade 3A and archival tumor biopsy from 2014 diagnosis was available at site. Thirty-five patients submitted newly obtained tumor biopsies (i.e., collected after patient informed consent was obtained) and 61 submitted archival tumor biopsies (i.e., collected prior to ELARA screening). For archival samples, the median time from biopsy to tisagenlecleucel infusion was 127 days (interquartile range [IQR], 98-210 days), with only 13 patients having a biopsy collected >1 year prior to tisagenlecleucel infusion. For all infused patients, the median time from biopsy to tisagenlecleucel infusion was 108 days (IQR, 81-166 days).

### Statistical analyses

Efficacy outcomes were measured in all patients who received infusion of tisagenlecleucel and had measurable disease at baseline as per independent review committee. Safety outcomes were assessed in all patients who received tisagenlecleucel. The cellular kinetic analysis set included all patients who received tisagenlecleucel infusion and provided ≥1 cellular kinetic parameter.

## RESULTS

### Baseline characteristics

Baseline characteristics for all patients who received tisagenlecleucel infusion are shown in **Supplemental Table 1.**

### Efficacy

Among all patients in the efficacy analysis set, the overall response rate was 90.4% (85/94; 95% CI, 82.6-95.5) according to local assessment, with a complete response rate of 73.4% (69/94; 95% CI, 63.3-82.0). The concordance rate between local and independent review committee assessments was high (86.2%).

### Safety

Similar to previous reports, of the 97 patients evaluated for safety, 99% (96/97) of patients experienced any-grade adverse events (AEs) at any time post infusion and 81.4% (79/97) patients had grade ≥3 AEs, most commonly neutropenia (43.3%). The incidence of any-grade cytokine release syndrome (CRS) was 48.5% (47/97) and no

CRS grade ≥3 any time post infusion was suspected to be tisagenlecleucel related. One patient died (Day 375) after developing hemophagocytic lymphohistiocytosis (HLH) >1 year post tisagenlecleucel infusion. However, the patient did not have CRS during or immediately preceding HLH.

Treatment-related grade ≥3 AEs occurred in 48.5% (47/97) patients. Serious AEs were experienced by 46.4% (45/97) of patients and serious AEs suspected to be related to study drug were reported in 28.9% (28/97) of patients. Any-grade and grade ≥3 AEs of special interest were experienced by 95.9% (93/97) and 79.4% (77/97) patients, respectively, regardless of tisagenlecleucel relationship any time post infusion. All-grade and grade ≥3 AEs of special interest suspected to be related to tisagenlecleucel any time post infusion were reported in 75.3% (73/97) and 46.4% (45/97) patients, respectively.

*Neurological Events:* Any-grade serious neurological events any time post infusion, regardless of tisagenlecleucel relationship, included encephalopathy (3.1%), tremor (3.1%), dyskinesia (1%), and muscular weakness (1%). Any-grade serious neurological adverse reactions any time post infusion, regardless of tisagenlecleucel relationship, occurred in 12 (12.4%) patients; 3 (3.1%) experienced grade ≥3 (**Supplemental Table 3**). Median onset from infusion to first neurological event was 8.5 days (range, 4-345) post infusion. Immune effector cell-associated neurotoxicity syndrome of any grade occurred in 4/97 (4.1%) patients, while 1 patient had grade ≥3 immune effector cell-associated neurotoxicity syndrome (**Supplemental Table 3**).

*Deaths:* A total of 13 (13.4%) deaths that occurred >30 days after tisagenlecleucel infusion have been reported (study indication, n=7; other causes, n=6 [HLH on Day 375, euthanasia due to worsening neurological symptoms in a patient with possible progressive multifocal leukoencephalopathy on Day 302, post-allogenic stem cell transplant complications on Day 1049, urothelial bladder cell carcinoma (G3) on Day 784, metastatic squamous cell carcinoma on Day 897; and pneumonia on Day 721). No deaths occurred within 30 days after tisagenlecleucel infusion.

**REFERENCES**

1. Dolled-Filhart M, Gustavson M, Camp RL, et al: Automated analysis of tissue microarrays. *Methods Mol Biol*. 2010;664:151-162.
2. Johnson DB, Bordeaux J, Kim JY, et al: Quantitative spatial profiling of PD-1/PD-L1 interaction and HLA-DR/IDO-1 predicts improved outcomes of anti–PD-1 therapies in metastatic melanoma. *Clin Cancer Res*. 2018;24(21):5250-5260.

## SUPPLEMENTAL TABLES

### Supplemental Table 1. Baseline Patient Demographics, Disease History, and Clinical Characteristics

| Parameter | Infused Patients (N=97) |
|---|---|
| Median age (range), years | 57 (29-73) |
| ≥65 years, n (%) | 24 (24.7) |
| Male, n (%) | 64 (66.0) |
| ECOG PS ≥1 prior to infusion, n (%) | 42 (43.3) |
| Stage at study entry III-IV, n (%) | 83 (85.6) |
| Bone marrow involvement, n (%) | 37 (38.1) |
| Bulky disease,[a] n (%) | 63 (64.9) |
| FLIPI high at study entry (≥3), n (%) | 58 (59.8) |
| Median no. of prior therapies (range) | 4 (2-13) |
| ≥3 lines | 73 (75.2) |
| ≥5 lines | 27 (27.8) |
| POD24 from first anti-CD20 mAb-containing therapy,[b] n (%) | 61 (62.9) |
| Refractory disease[c] to last line of therapy, n (%) | 76 (78.3) |
| Best response SD/PD | |
| Refractory to ≥2 regimens, n (%) | 69 (71.1) |
| Double refractory[d]: Anti-CD20 mAb + alkylating agent | 66 (68.0) |

| Parameter | Infused Patients (N=97) |
|---|---|
| Refractory to PI3K inhibitors | 14 (14.4) |
| Prior autologous HSCT, n (%) | 35 (36.1) |
| Relapsed ≤12 months after autologous HSCT | 15 (15.5) |
| Median DOR from last line of therapy, months (n=35) | 7.5 |
| Received bridging chemotherapy | 44 (45.4) |

[a]Bulky disease defined per IRC as imaging showing 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. [b]POD24: Patients primary refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb-containing treatment. [c]Refractory is defined as failure to respond to previous treatment (SD/PD as best response) or PD within 6 months of prior therapy completion. [d]Double refractory is defined as no response or progressed <6 months after treatment with monoclonal anti-CD20 antibodies and alkylating agents.

CD, cluster of differentiation; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; HSCT, hematopoietic stem cell transplant; IRC, independent review committee; mAb, monoclonal antibody; PD, progressive disease; PI3K, phosphatidylinositol 3-kinase; POD24, progression of disease within 24 months from first immunochemotherapy; SD, stable disease.

**Supplemental Table 2. Best Overall Response**

| | IRC Assessment |
|---|---|
| **Best Overall Response, n (%)** | |
| Overall response rate (ORR: CR+PR) | 81 (86.2)<br>95% CI, 77.5-92.4 |
| CR | 64[a] (68.1)<br>95% CI, 57.72-77.3 |
| PR | 17 (18.1) |
| SD | 3 (3.2) |
| PD | 9 (9.6) |
| UNK[b] | 1 (1.1) |

[a]One patient in CR downgraded to PR due to a determination that their confirmatory bone marrow test was performed outside of the strict 14-day testing window, per protocol. [b]This patient received a lower dose than the assigned range of CAR-positive viable T cells. The investigator started a new anticancer treatment before Month 3.

CAR, chimeric antigen receptor; CR, complete response; IRC, independent review committee; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; UNK, unknown.

**Supplemental Table 3. COVID-19 AEs, Anytime Post Infusion**

| | All Patients,[a] N=97 | |
|---|---|---|
| | All Grades, n (%) | Grade ≥3, n (%) |
| COVID-19 | 8 (8.2) | 3 (3.1) |
| COVID-19 pneumonia | 1 (1.0) | 1 (1.0) |
| Post-acute COVID-19 syndrome | 1 (1.0) | 0 |

[a]All patients infused with tisagenlecleucel.

AE, adverse event.

**Supplemental Table 4. Selected AESI, Anytime Post Infusion Suspected to Be Related to Tisagenlecleucel**

| | All Patients,[a] N=97 | |
|---|---|---|
| | All Grades, n (%) | Grade ≥3, n (%) |
| No. of patients with at least 1 AE | 73 (75.3) | 45 (46.4) |
| CRS[b,c] | 47 (48.5) | 0 |
| Hematological disorders including cytopenias | 45 (46.4) | 43 (44.3) |
| Neutropenia | 23 (23.7) | 23 (23.7) |
| Anemia | 13 (13.4) | 7 (7.2) |
| Thrombocytopenia | 6 (6.2) | 5 (5.2) |
| Infections | 16 (16.5) | 9 (9.3) |
| Hypogammaglobulinemia | 11 (11.3) | 1 (1) |
| Serious neurological adverse events | 8 (8.2) | 2 (2.1) |
| ICANS | 4 (4.1) | 1 (1) |
| Encephalopathy | 3 (3.1) | 1 (1) |
| Dyskinesia | 1 (1) | 0 |
| Muscular weakness | 1 (1) | 0 |
| Tremor | 1 (1) | 0 |

[a]All patients infused with tisagenlecleucel. [b]CRS was graded using Lee scale 2014. [c]Refers to first CRS episode only.

AE, adverse event; AESI, AE of special interest; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

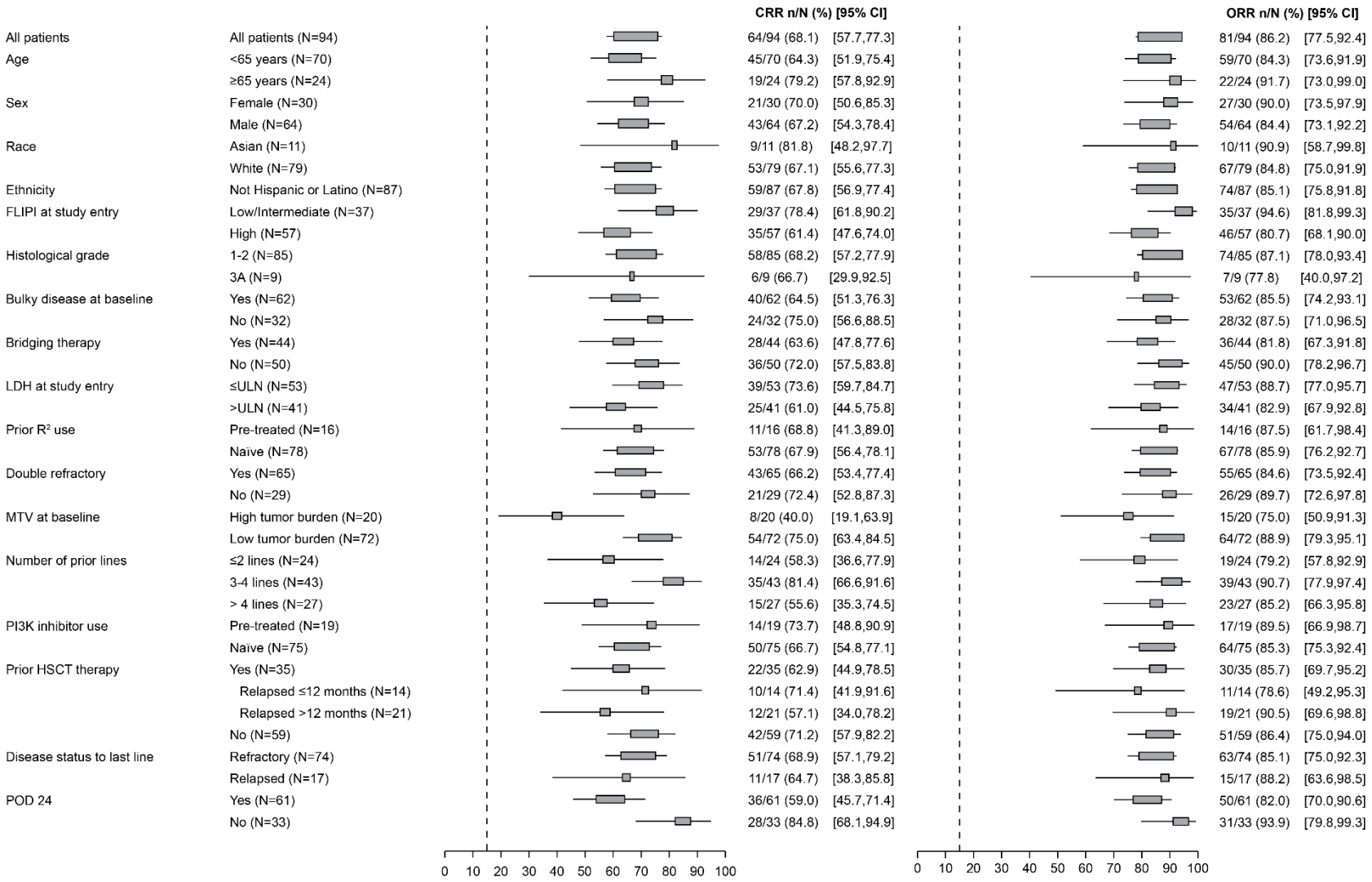
**Supplemental Table 5. Summary of Cellular Kinetic Parameters by Response at Month 3**

| Parameter | Statistics | CR/PR (N=78) | SD/PD/Unknown (N=13) | All Patients (N=91) |
|---|---|---|---|---|
| $AUC_{0\text{-}28d}$, (copies/µg × days) | n | 67 | 9 | 76 |
| | Geo-mean | 51,600 | 20,100 | 46,200 |
| | Geo-CV% | 308 | 7220 | 454 |
| | Fold difference (responders over nonresponders) | | 2.6 | |
| $AUC_{0\text{-}84d}$, (copies/µg × days) | n | 66 | 8 | 74 |
| | Geo-mean | 80,500 | 67,100 | 78,900 |
| | Geo-CV% | 273 | 555 | 289 |
| | Fold difference (responders over nonresponders) | | 1.2 | |
| $AUC_{0\text{-}180d}$, (copies/µg × days) | n | 64 | 6 | 70 |
| | Geo-mean | 105,000 | 89,200 | 104,000 |
| | Geo-CV% | 250 | 496 | 260 |
| | Fold difference (responders over nonresponders) | | 1.2 | |
| $C_{max}$, copies/µg | n | 71 | 11 | 82 |
| | Geo-mean | 4950 | 2100 | 4410 |
| | Geo-CV% | 472 | 1610 | 565 |
| | Fold difference (responders over nonresponders) | | 2.4 | |
| $T_{max}$, days | n | 71 | 11 | 82 |
| | Median | 10.0 | 13.1 | 10.7 |
| | Min, max | 1.91, 562 | 7.73, 54.8 | 1.91, 562 |
| $T_{last}$, days | n | 75 | 12 | 87 |
| | Median | 336 | 107 | 210 |
| | Min, max | 13.0, 925 | 18.7, 918 | 13.0, 925 |

n, number of patients with nonmissing values. Geo-CV% = sqrt (exp (variance for log transformed data)-1) × 100.

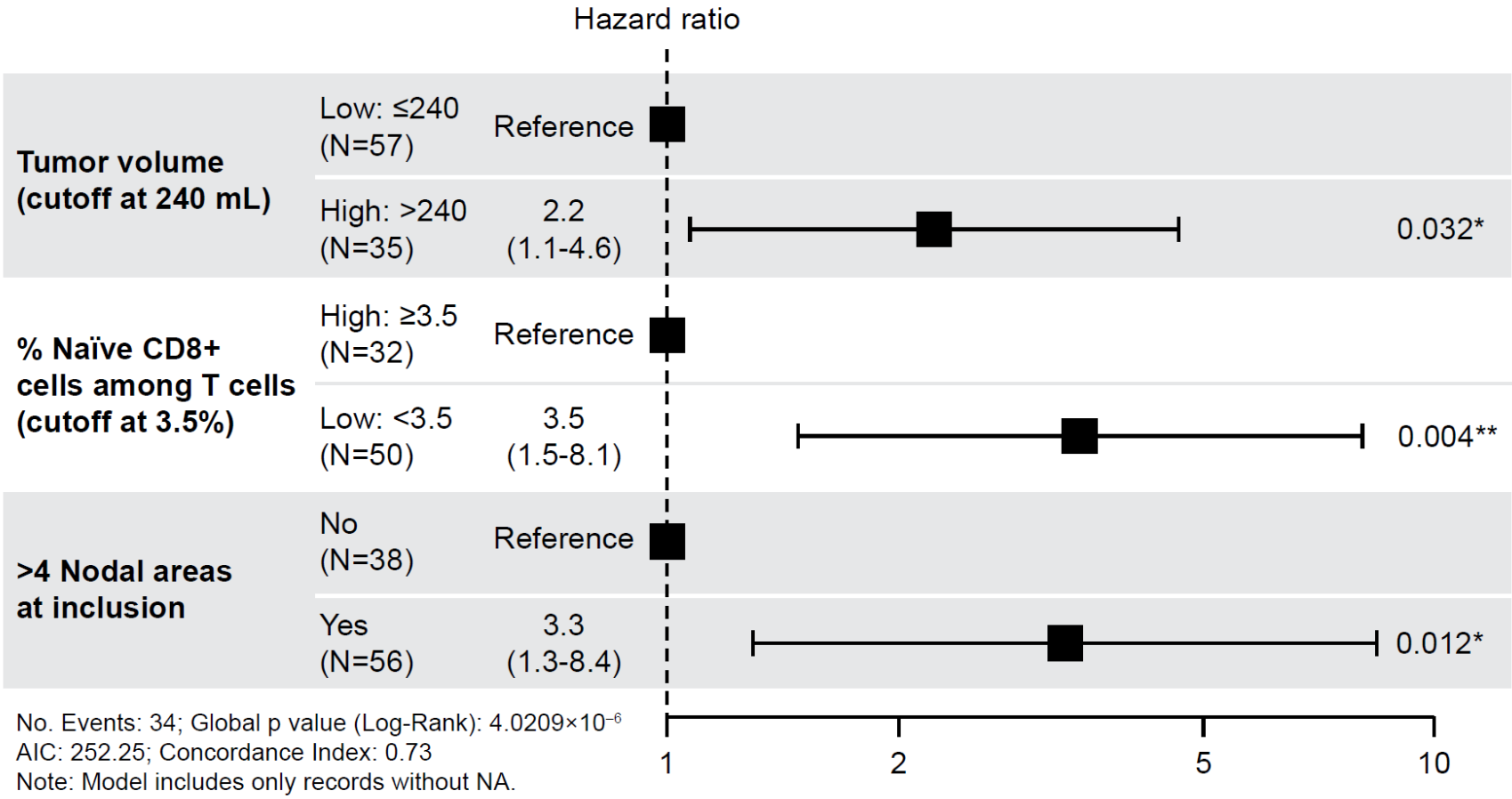
AUC, area under the curve; $C_{max}$, maximum transgene level; CR, complete response; CV, coefficient of variation; exp, exponent; Geo, geometric; max, maximum; min, minimum; PD, progressive disease; PR, partial response; SD, stable disease; $T_{last}$, time to last quantifiable concentration following dosing; $T_{max}$, time to maximum transgene level.

## SUPPLEMENTAL FIGURES



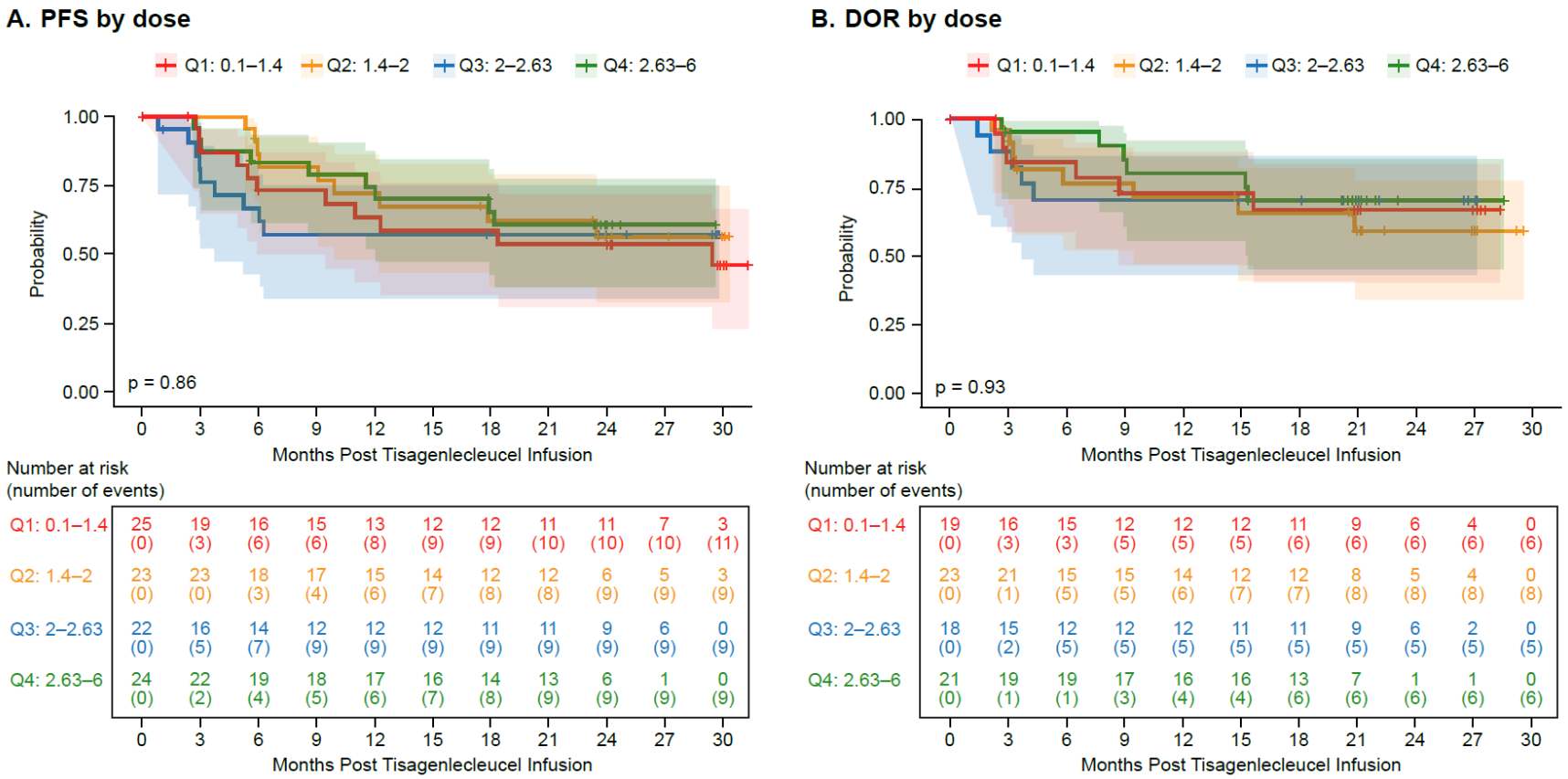
**Supplemental Figure 1. Best response of CRR and ORR according to subgroup (EAS population).**

Forest plot showing the effect of tisagenlecleucel treatment across major demographic and prognostic subgroups. Red boxes indicate key findings in high-risk prognostic subgroups in relation to CRR and ORR. [a]Patients primarily refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb-containing treatment. CD, cluster of differentiation; CRR, complete response rate; EAS, efficacy analysis set; FLIPI, Follicular Lymphoma International Prognostic Index; HSCT, hematopoietic stem cell transplant; LDH, lactate dehydrogenase; mAb, monoclonal antibody; MTV, metabolic tumor volume; ORR, overall response rate; PI3K, phosphatidylinositol 3-kinase; POD24, progression of disease within 24 months from first immunochemotherapy; $R^2$, lenalidomide + rituximab; ULN, upper limit of normal; US, United States.



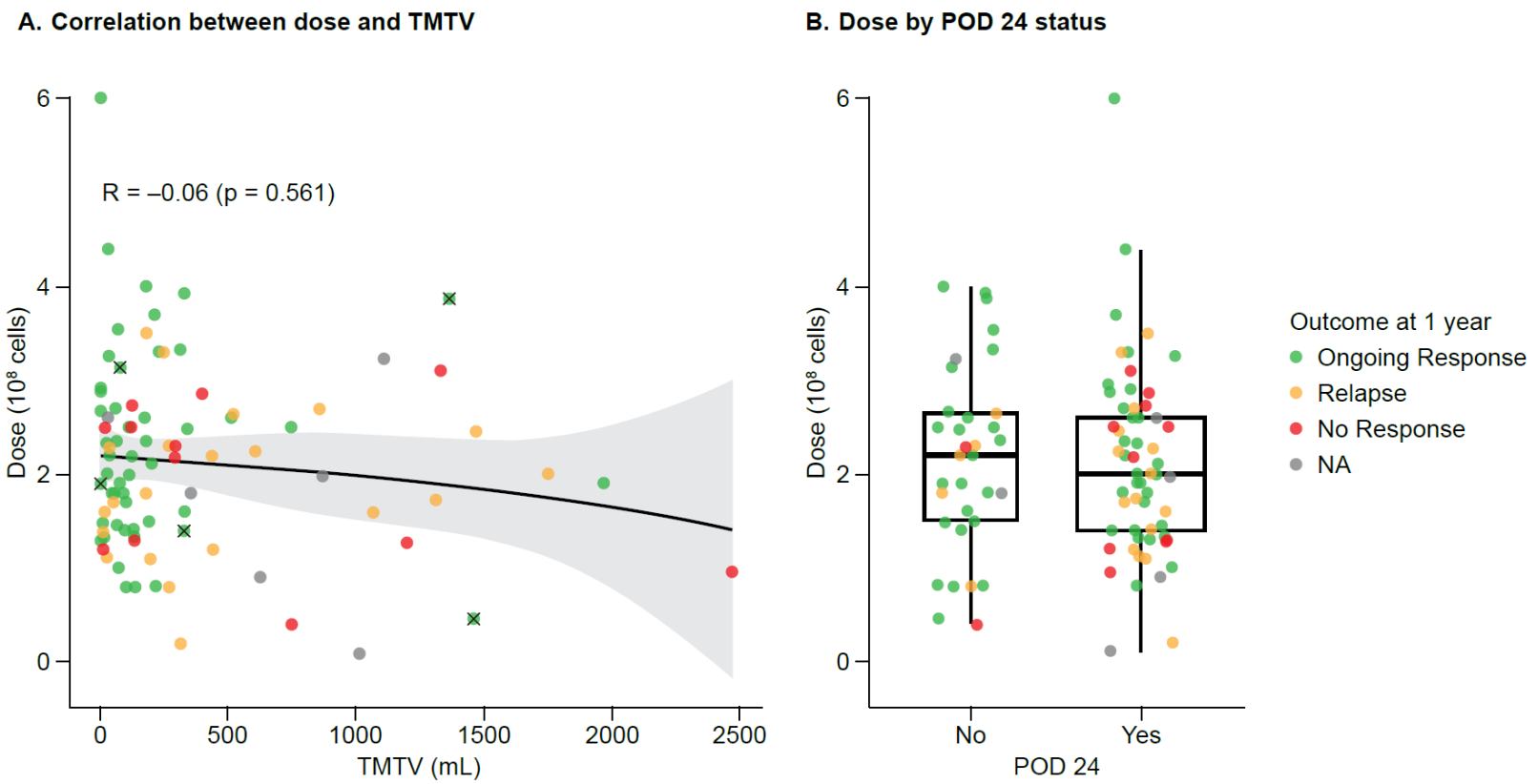

**Supplemental Figure 2. Multivariate analysis of clinical factors significantly associated with PFS.**

AIC, Akaike information criteria; CD, cluster of differentiation; NA, not available; PFS, progression-free survival.




**Supplemental Figure 3. Dose was not significantly associated with clinical outcomes.**

(**A**) PFS by dose. (**B**) DOR by dose. DOR, duration of response; PFS, progression-free survival; Q, quarter.




**Supplemental Figure 4. Dose did not show strong correlations with baseline variables.**

(A) Correlation between dose and TMTV. (B) Dose by POD 24 status. NA, not available; POD 24, progression of disease within 24 months from first immunochemotherapy; TMTV, total metabolic tumor volume.