

# Tisagenlecleucel and Lisocabtagene Maraleucel: Comparative Efficacy in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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## DISCUSSION AND CONCLUSIONS

- After extensive disease and risk factor adjustment, there is no evidence suggesting significant differences in OS, PFS, and CR between tisa-cel and liso-cel in r/r DLBCL
- Safety outcomes were not compared because adverse event management has evolved with growing clinical experience<sup>11</sup> between the time of conduct of JULIET and TRANSCEND and differed between these 2 trials. Such differences cannot be adjusted for in the MAIC
  - Tocilizumab is now commonly used for lower grades of cytokine release syndrome (CRS). The majority of tocilizumab was initiated for grade 1 or 2 CRS in TRANSCEND (45 of 48 CRS cases with tocilizumab were for grade 1 or 2 CRS); however, it was reserved for grade 3 or 4 CRS in the JULIET trial (16 of 16 CRS cases with tocilizumab were for grade 3 or 4 CRS). Furthermore, CRS grading systems differed between the 2 studies
  - Early use of tocilizumab has been reported to be associated with reduced incidence of severe CRS and neurotoxicity events without affecting the response to CAR-T therapy<sup>12,13</sup>
  - In the real-world, a lower CRS rate was observed for tisa-cel<sup>14</sup> compared to that observed in the JULIET trial
- Compared to a previously reported MAIC,<sup>15</sup> the current study was able to adjust for additional factors known to be associated with differences in efficacy outcomes (ie, age, sex, LDH, use of bridging chemotherapy, number of prior lines of therapy, never achieved CR with prior therapy, SPD, and LVEF) and leads to different conclusions
- Future studies using IPD from either trial with longer follow-up or real-world data will be important for comparisons of the efficacy and safety of tisa-cel and liso-cel for the treatment of r/r DLBCL

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## INTRODUCTION

- Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), comprising up to 40% of total NHL cases globally<sup>1</sup>
- Before the introduction of chimeric antigen receptor (CAR)-T cell therapies, adults with DLBCL who relapsed after or were refractory to (r/r) 2 or more lines of therapy had limited expectation for survival<sup>2</sup>
- Tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel), both CD19 CAR-T cell therapies, have shown efficacy in r/r DLBCL and are approved by the United States Food and Drug Administration as third or later line of therapy for these patients<sup>3,4</sup>
- In the absence of head-to-head randomized controlled trials, this study aimed to compare efficacy outcomes of tisa-cel and liso-cel in r/r DLBCL using the matching-adjusted indirect comparison (MAIC) method

## METHODS

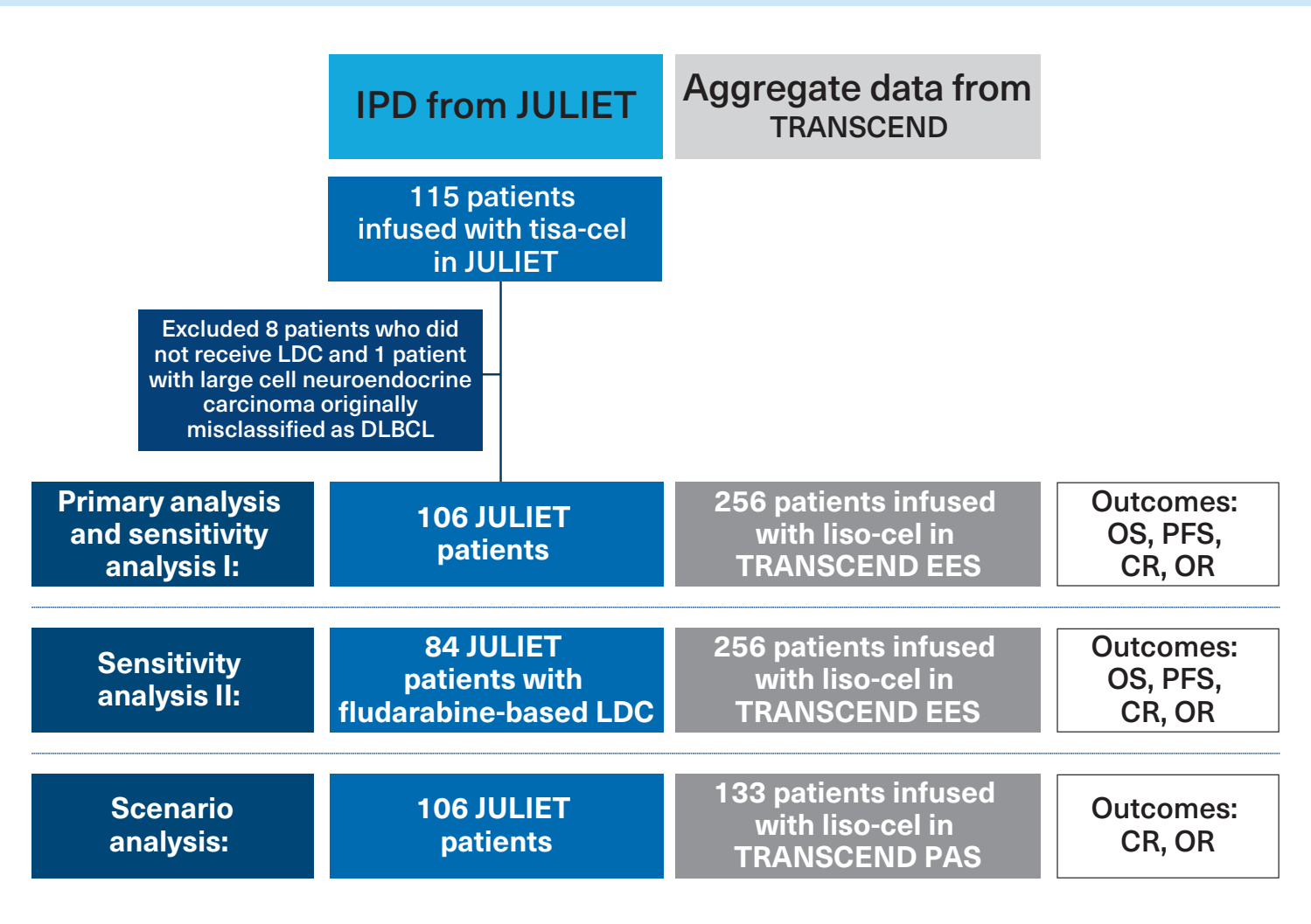
### Data Source

- Tisa-cel: Individual patient-level data (IPD) from the JULIET trial (NCT02445248; 02/2020 datacut)<sup>5,6</sup> (**Figure 1**)
- Liso-cel: Published aggregate data from the TRANSCEND NHL 001 trial (NCT02631044; 08/2019 datacut)<sup>7</sup> (**Figure 1**)

### Analysis

- MAIC<sup>8-10</sup> used a propensity score model to assign statistical weights to JULIET patients based on clinically relevant baseline factors to match the patient population in TRANSCEND
- Sample selections are described in **Figure 1**
- The baseline factors available in both trials, confirmed as relevant by clinical experts, were adjusted for the MAIC in primary analysis, sensitivity analysis II, and scenario analysis (**Table 1**). Sensitivity analysis I only adjusted for baseline factors that were significantly different between JULIET and TRANSCEND EES (ie, age, histology, Eastern Cooperative Oncology Group performance status [ECOG PS], prior stem cell transplant [SCT], and use of bridging therapy)
- For complete response (CR) and overall response (OR) rates, weighted Wald tests were used to compare the differences in response rates after MAIC. For progression-free survival (PFS) and overall survival (OS), weighted Cox proportional hazards models were used for hazard ratio (HR) estimation after MAIC

Figure 1. Data Source and Patient Populations



CR, complete response; DLBCL, diffuse large B-cell lymphoma; EES, efficacy-evaluable set; IPD, individual patient-level data; LDC, lymphodepleting chemotherapy; OR, overall response; OS, overall survival; PAS, primary analysis set; PFS, progression-free survival.

## RESULTS

### Baseline Characteristics

- Before MAIC adjustment, JULIET had significantly higher proportions of patients younger than age 65 years, with DLBCL histology, ECOG PS of 0, prior SCT, and bridging chemotherapy (all  $P<0.05$ ) compared to the TRANSCEND EES (**Table 2**)
- After MAIC adjustment, baseline characteristics were balanced. The effective sample size for JULIET after weighting was N=29

Table 2. Baseline Characteristics of JULIET (N=106) Patients and the TRANSCEND EES (N=256), Before and After Matching

|                                      | Before Matching |           |         | After Matching |           |         |
|--------------------------------------|-----------------|-----------|---------|----------------|-----------|---------|
|                                      | JULIET          | TRANSCEND | P value | JULIET         | TRANSCEND | P value |
| Age <65                              | 76.4%           | 57.8%     | <0.01*  | 57.8%          | 57.8%     | 1.00    |
| Male                                 | 61.3%           | 66.0%     | 0.47    | 66.0%          | 66.0%     | 1.00    |
| HGBCL                                | 14.2%           | 12.9%     | 0.88    | 12.9%          | 12.9%     | 1.00    |
| DLBCL                                | 66.0%           | 51.2%     | <0.05*  | 51.2%          | 51.2%     | 1.00    |
| ECOG PS of 0                         | 57.5%           | 40.9%     | <0.01*  | 40.9%          | 40.9%     | 1.00    |
| 40% ≤ LVEF <50%                      | 1.9%            | 4.8%      | 0.37    | 4.8%           | 4.8%      | 1.00    |
| SPD (≥50 cm <sup>2</sup> )           | 22.6%           | 28.3%     | 0.31    | 28.3%          | 28.3%     | 1.00    |
| LDH (≥500 U/L)                       | 17.0%           | 22.3%     | 0.32    | 22.3%          | 22.3%     | 1.00    |
| Prior ASCT                           | 47.2%           | 34.0%     | <0.05*  | 34.0%          | 34.0%     | 1.00    |
| Prior lines of therapy ≥3            | 49.1%           | 51.7%     | 0.75    | 51.7%          | 51.7%     | 1.00    |
| Received bridging                    | 89.6%           | 58.6%     | <0.01*  | 58.6%          | 58.6%     | 1.00    |
| Refractory                           | 73.6%           | 66.8%     | 0.25    | 66.8%          | 66.8%     | 1.00    |
| Never achieved CR with prior therapy | 44.3%           | 44.2%     | 1.00    | 44.2%          | 44.2%     | 1.00    |

\* $P<0.05$   
ASCT, autologous stem cell transplant; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EES, efficacy-evaluable set; HGBCL, high-grade B-cell lymphoma; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; SPD, sum of product diameter.

### Acknowledgments

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### Disclosures

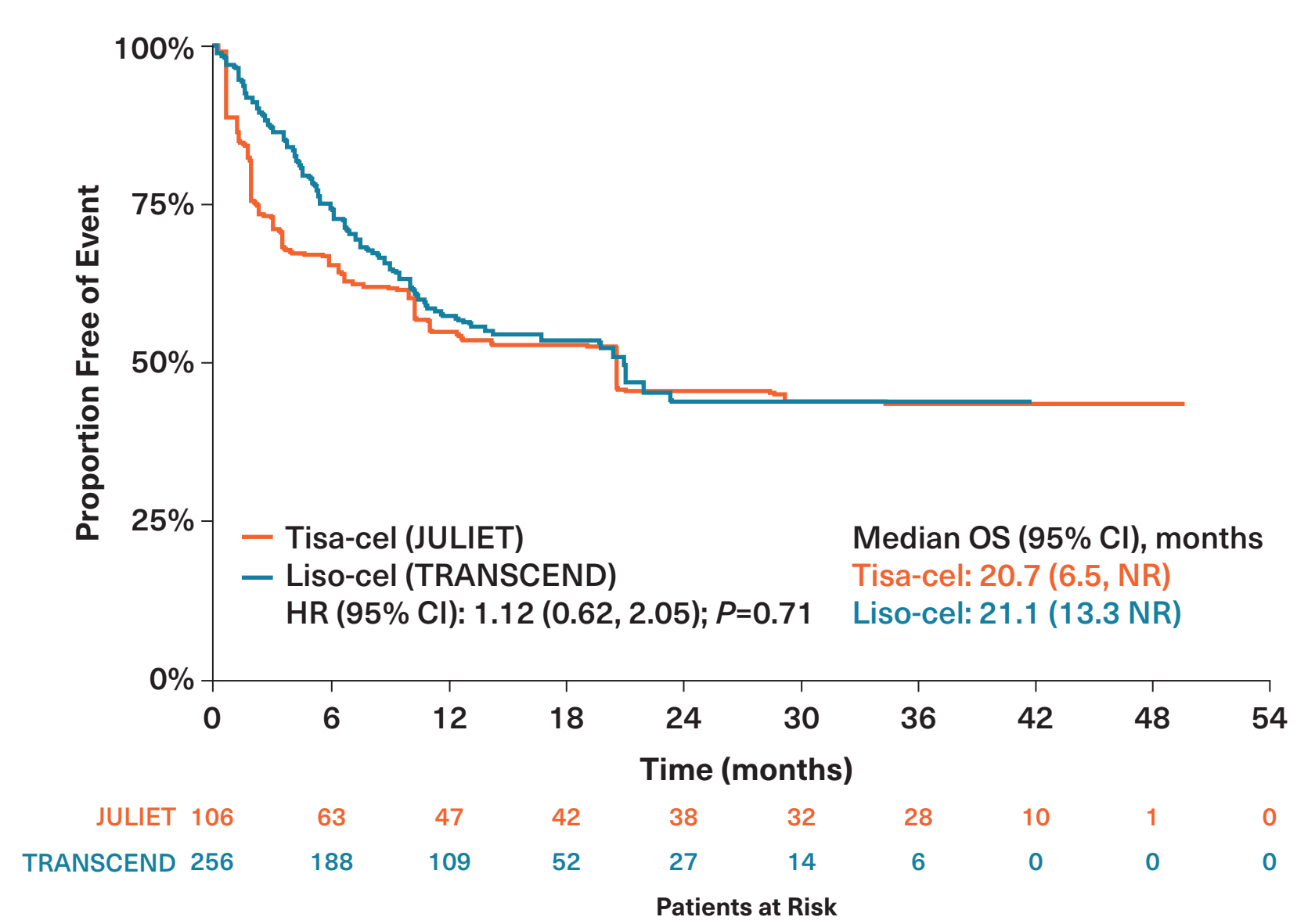
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### Comparison of OS

- OS was comparable between tisa-cel and liso-cel (**Figure 2**)
  - Before MAIC: HR of tisa-cel vs liso-cel (95% CI) = 1.29 (0.95, 1.76),  $P=0.10$
  - After MAIC: HR of tisa-cel vs liso-cel (95% CI) = 1.12 (0.62, 2.05),  $P=0.71$

Figure 2. OS Curves for JULIET Patients and the TRANSCEND EES, After Matching



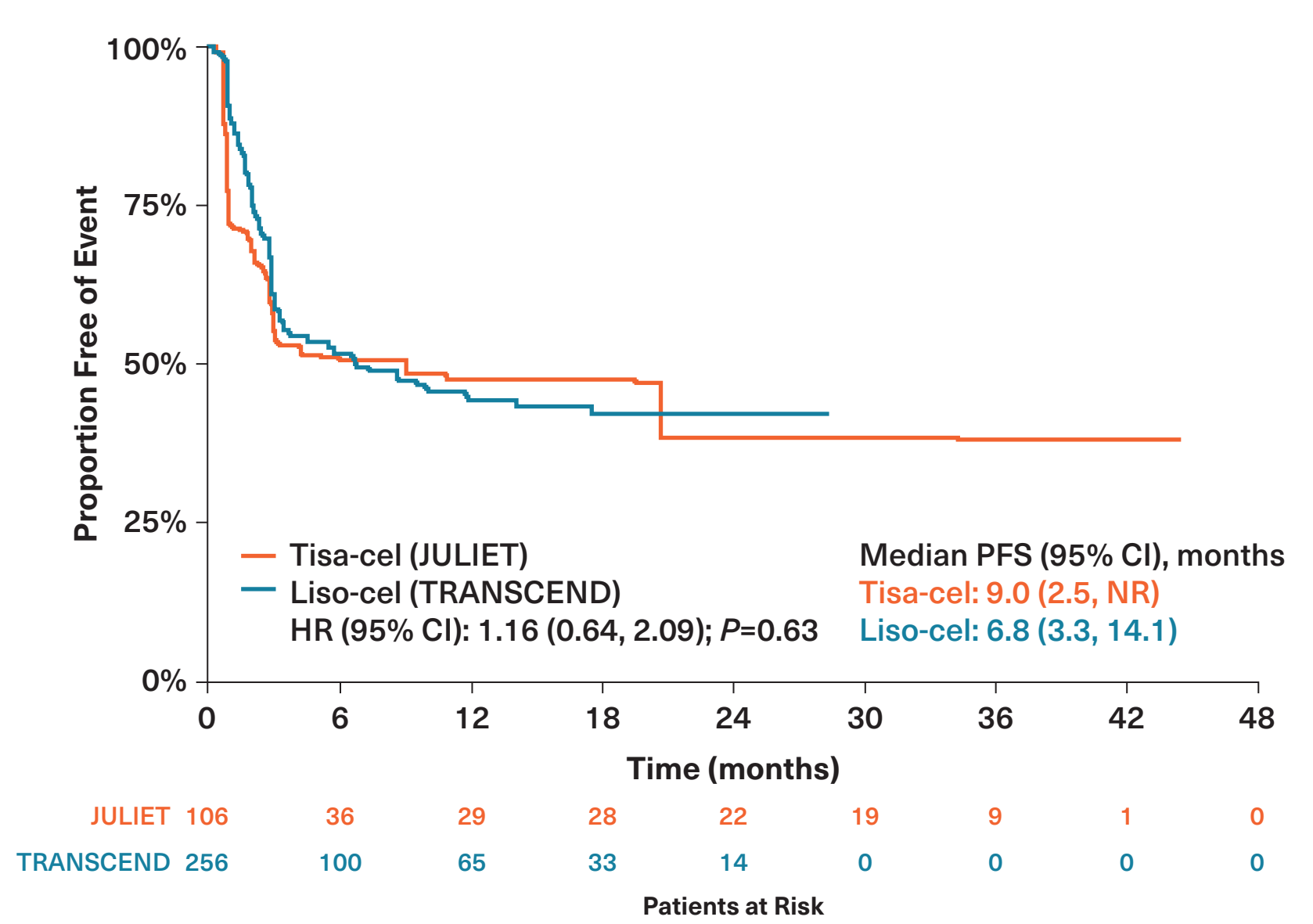
| OS Rate, % (95% CI) | JULIET               | TRANSCEND            |
|---------------------|----------------------|----------------------|
| Month 6             | 65.3% (53.1%, 80.4%) | 74.7% (68.9%, 79.6%) |
| Month 12            | 55.1% (42.5%, 71.4%) | 57.9% (51.3%, 63.8%) |
| Month 24            | 45.6% (33.2%, 62.6%) | 43.8% (35.2%, 52.1%) |

CI, confidence interval; EES, efficacy-evaluable set; HR, hazard ratio; NR, not reached; OS, overall survival.

### Comparison of PFS

- PFS was comparable between tisa-cel and liso-cel (**Figure 3**)
  - Before MAIC: HR of tisa-cel vs liso-cel (95% CI) = 1.34 (0.99, 1.81),  $P=0.06$
  - After MAIC: HR of tisa-cel vs liso-cel (95% CI) = 1.16 (0.64, 2.09),  $P=0.63$

Figure 3. PFS Curves for JULIET Patients and the TRANSCEND EES, After Matching



| PFS Rate, % (95% CI) | JULIET              | TRANSCEND           |
|----------------------|---------------------|---------------------|
| Month 6              | 50.6% (37.6, 68.1%) | 51.4% (44.6, 57.7%) |
| Month 12             | 47.4% (34.4, 65.3%) | 44.1% (37.3, 50.7%) |
| Month 24             | 38.2% (25.7, 56.8%) | 42.1% (35.0, 48.9%) |

CI, confidence interval; EES, efficacy-evaluable set; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

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Table 1. Baseline Prognostic Factors Adjusted in the MAIC

| Category                       | Parameter                                                                                                                                                                                                                                                            |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patient characteristics        | Age<br>Sex                                                                                                                                                                                                                                                           |
| Disease characteristics        | Disease histology (high-grade B-cell lymphoma [HGBCL], DLBCL)<br>Eastern Cooperative Oncology Group performance status (ECOG PS)<br>Left-ventricular ejection fraction (LVEF)<br>Sum of product diameter (SPD)<br>Lactate dehydrogenase (LDH)                        |
| Treatment and response history | Use of bridging chemotherapy<br>Prior stem cell transplant (SCT)<br>Number of prior lines of therapy<br>Refractory status (refractory to the last treatment or relapsed <12 months after autologous SCT)<br>Never achieved complete response (CR) with prior therapy |

- In the scenario analysis, JULIET patients were compared to the TRANSCEND primary analysis set (PAS; N=133), a subset of the TRANSCEND efficacy-evaluable set (EES)<sup>7</sup>
  - The TRANSCEND PAS included patients from the EES who were treated at dose level 2 (100×10<sup>6</sup> CAR-T cells), a subset of liso-cel approved label dose, and excluded patients with ECOG PS of 2, prior allogeneic SCT, primary mediastinal large B-cell lymphoma, follicular lymphoma (FL) grade 3B, or transformation from indolent lymphoma other than FL
  - Because baseline data were not reported for the TRANSCEND PAS in Abramson et al,<sup>7</sup> baseline summary data were assumed to be the same as those for the TRANSCEND dose level 2 population (N=177)

### Comparison of OR and CR Rates

- After MAIC, the TRANSCEND EES had numerically higher OR (rate difference: −9.7%,  $P=0.07$ ) and CR (−5.4%,  $P=0.29$ ) than JULIET; the differences were not statistically significant (**Table 3**)

Table 3. Comparison of OR and CR Rates Between JULIET Main Cohort\* (N=91) Patients and the TRANSCEND EES (N=256), Before and After Matching

|    | Before Matching |               |                                    | After Matching |               |                                    |
|----|-----------------|---------------|------------------------------------|----------------|---------------|------------------------------------|
|    | JULIET [A]      | TRANSCEND [B] | Rate Difference (95% CI) [A] - [B] | JULIET [C]     | TRANSCEND [D] | Rate Difference (95% CI) [C] - [D] |
| OR | 57.1%           | 72.7%         | −15.5% (−27.1%, −3.9%)             | 62.9%          | 72.7%         | −9.7% (−20.0%, 0.6%)               |
| CR | 42.9%           | 53.1%         | −10.3% (−22.2%, 1.6%)              | 47.7%          | 53.1%         | −5.4% (−15.5%, 4.7%)               |

\* $P<0.05$ .  
\*OR and CR rates were assessed only in the JULIET main cohort to be consistent with the main analyses per JULIET trial protocol, which only included patients treated with tisa-cel from the United States manufacturing facility in Morris Plains, NJ. CI, confidence interval; CR, complete response; EES, efficacy-evaluable set; OR, overall response.

### Sensitivity and Scenario Analyses

- The findings in the sensitivity and scenario analyses were consistent with the findings from the primary analysis, with no significant differences observed, except in the scenario analysis, the OR rate was significantly higher in the TRANSCEND PAS compared with JULIET (**Table 4**)

Table 4. Comparison of OR, CR, PFS, and OS From the Sensitivity and Scenario Analyses, After Matching

|                                          | Sensitivity Analysis              |                                 | Scenario Analysis                  |
|------------------------------------------|-----------------------------------|---------------------------------|------------------------------------|
|                                          | Sensitivity Analysis I            | Sensitivity Analysis II         | JULIET vs TRANSCEND PAS*           |
| HR of OS (tisa-cel vs liso-cel), 95% CI  | 1.16 (0.67, 2.04)<br>$P=0.59$     | 0.80 (0.47, 1.38)<br>$P=0.42$   | —                                  |
| HR of PFS (tisa-cel vs liso-cel), 95% CI | 1.13 (0.65, 1.98)<br>$P=0.67$     | 0.73 (0.43, 1.25)<br>$P=0.26$   | —                                  |
| OR rate difference, 95% CI               | −11.6% (−25.1%, 1.8%)<br>$P=0.09$ | 3.8% (−4.9%, 12.4%)<br>$P=0.40$ | −13.5% (−25.6%, −1.5%)<br>$P<0.05$ |
| CR rate difference, 95% CI               | −3.0% (−17.1%, 11.1%)<br>$P=0.67$ | 2.9% (−9.1%, 14.9%)<br>$P=0.64$ | −7.7% (−20.1%, 4.8%)<br>$P=0.23$   |

\*As there was no KM curves for OS and PFS reported for the TRANSCEND PAS, HR was not estimated. CI, confidence interval; CR, complete response; HR, hazard ratio; OR, overall response; OS, overall survival; PAS, primary analysis set; PFS, progression-free survival.

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