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Lisocabtagene maraleucel combined with ibrutinib in R/R CLL or SLL: primary results from TRANSCEND CLL 004

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Abstract:
Patients in the liso-cel plus ibrutinib cohort of the phase 1/2, open-label TRANSCEND CLL 004 study had relapsed/refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and received liso-cel (50×106 [dose level (DL)1] or 100×106 [DL2] chimeric antigen receptor–positive T cells) with concurrent ibrutinib from enrollment through 90 days after liso-cel infusion or longer per investigator discretion. Primary end point was complete response/remission (CR)/CR with incomplete marrow recovery (CRi) by investigator assessment. Among 56 patients who received ibrutinib plus liso-cel (DL1, n=5; DL2, n=51), median (range) age was 64.5 years (44–77), 98% had high-risk cytogenetics, 55% had progression on Bruton tyrosine kinase inhibitor and venetoclax failure, and median (range) number of prior therapies was 5 (1–13). Median (range) follow-up was 24.8 months (3.1–51.8). At DL2, CR/CRi rate was 45% (95% confidence interval [CI], 31–60) and overall response rate was 86% (95% CI, 74–94). Median (95% CI) duration of response was not reached (NR; 28.7–NR) for patients with CR/CRi and 41.4 months (23.3–NR) for all responders. Median (95% CI) progression-free survival was 31.4 months (20.1–NR). In DL1+DL2, most common grade ≥3 treatment-emergent adverse events (TEAE) were neutropenia (52%) and anemia (41%). Cytokine release syndrome was reported in 80% of patients (grade 3, 4%; no grade 4/5), and neurological events in 41% (grade 3/4, 11%; no grade 5). Ibrutinib-related TEAEs were reported in 68% of patients (grade 3/4, 43%; no grade 5). Liso-cel plus ibrutinib demonstrated notable efficacy in patients with relapsed/refractory CLL/SLL with predictable and manageable safety. Clinicaltrials.gov: NCT03331198; NCT03435796.

Conflict of interest: COI declared - see note

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Lisocabtagene maraleucel combined with ibrutinib in R/R CLL or SLL: primary results from TRANSCEND CLL 004

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DATA SHARING STATEMENT

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- Liso-cel plus ibrutinib showed substantial efficacy with deep remissions, supporting use of the combination in patients with R/R CLL/SLL (138/140 max)
- The safety profile was manageable with no new signals or added toxicity, supporting the potential of the combination in this population (137/140 max)

ABSTRACT (249/250 words)

Patients in the liso-cel plus ibrutinib cohort of the phase 1/2, open-label TRANSCEND CLL 004 study had relapsed/refractory chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and received liso-cel (50×10^6 [dose level (DL)1] or 100×10^6 [DL2] chimeric antigen receptor–positive T cells) with concurrent ibrutinib from enrollment through 90 days after liso-cel infusion or longer per investigator discretion. Primary end point was complete response/remission (CR)/CR with incomplete marrow recovery (CRi) by investigator assessment. Among 56 patients who received ibrutinib plus liso-cel (DL1, n=5; DL2, n=51), median (range) age was 64.5 years (44–77), 98% had high-risk cytogenetics, 55% had progression on Bruton tyrosine kinase inhibitor and venetoclax failure, and median (range) number of prior therapies was 5 (1–13). Median (range) follow-up was 24.8 months (3.1–51.8). At DL2, CR/CRi rate was 45% (95% confidence interval [CI], 31–60) and overall response rate was 86% (95% CI, 74–94). Median (95% CI) duration of response was not reached (NR; 28.7–NR) for patients with CR/CRi and 41.4 months (23.3–NR) for all responders. Median (95% CI) progression-free survival was 31.4 months (20.1–NR). In DL1+DL2, most common grade ≥3 treatment-emergent adverse events (TEAE) were neutropenia (52%) and anemia (41%). Cytokine release syndrome was reported in 80% of patients (grade 3, 4%; no grade 4/5), and neurological events in 41% (grade 3/4, 11%; no grade 5). Ibrutinib-related TEAEs were reported in 68% of patients (grade 3/4, 43%; no grade 5). Liso-cel plus ibrutinib demonstrated notable efficacy in patients with relapsed/refractory CLL/SLL with predictable and manageable safety. Clinicaltrials.gov: NCT03331198; NCT03435796.

INTRODUCTION

Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB chimeric antigen receptor (CAR) T-cell product that is approved for the treatment of multiple relapsed or refractory (R/R) B-cell malignancies, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).[1-7] In the TRANSCEND CLL 004 (NCT03331198) study, a single infusion of liso-cel as monotherapy resulted in durable complete responses/remissions (CR) or CR with incomplete marrow recovery (CRi) and manageable safety in patients with R/R CLL/SLL. In patients who previously experienced disease progression on a Bruton tyrosine kinase inhibitor (BTKi) and venetoclax failure, liso-cel at a target dose of 100×10^6 CAR^+ T cells achieved a CR/CRi rate of 18% (95% confidence interval [CI], 9–32; null hypothesis, ≤5%; *P* = .0006) per independent review committee assessment and median duration of response (DOR) of 35 months in the primary analysis[5]; the rate increased to 20% (95% CI, 10–34) in a subsequent analysis with longer follow-up.[8] Because T cells from patients with CLL/SLL are generally immunologically impaired, there is an opportunity to improve the efficacy of this treatment for patients with CLL/SLL.[9,10]

The effects of the BTKi, ibrutinib, including potential off-target activity on interleukin-2–inducible T-cell kinase (ITK) and TEC family kinases, can influence CAR T-cell biology directly by altering T-cell phenotype, function, and proliferation.[11-13] Preclinical data show that ibrutinib improves liso-cel activity directly, enhancing CAR T-cell efficiency through increased cytokine secretion and T-cell activation.[14] Both ibrutinib and the second-generation BTKi, acalabrutinib, extended survival in tumor-bearing mice combined with CAR T cells. Ibrutinib also has a broad off-target activity against ITK in T cells, including skewing T-cell development towards Th1 and memory phenotypes.[14] Based on these promising preclinical results, pilot and single-

center clinical studies of ibrutinib combined with other CAR T-cell therapies demonstrated the potential to improve in vivo CAR T-cell expansion and function and achieve high response rates in R/R CLL/SLL.[15,16] However, larger, multicenter studies were lacking.

Here, we report the results from the primary analysis of the cohort of patients with R/R CLL/SLL who received liso-cel plus ibrutinib in the multicenter, open-label, phase 1/2 TRANSCEND CLL 004 study.

METHODS

Study design and participants

TRANSCEND CLL 004 was a multicenter, open-label, phase 1/2 study conducted in the United States.[5] The study enrolled patients aged ≥18 years with a diagnosis of CLL or SLL with measurable disease and an indication for treatment based on investigator assessment, Eastern Cooperative Oncology Group performance status of ≤1, and adequate bone marrow (BM) and organ function. Additionally, patients must have met ≥1 of the following: 1) receiving a BTKi with progressive disease at the time of enrollment; 2) receiving a BTKi ≥6 months with a response less than CR and with high-risk cytogenetics (complex karyotype [≥3 chromosomal abnormalities], del(17p), *TP53* mutation, or unmutated immunoglobulin heavy-chain variable region gene); 3) have *BTK* or *PLCγ2* mutation per local laboratory assessment with or without progression on ibrutinib; and/or 4) previously received a BTKi with no contraindications to initiating or reinitiating ibrutinib. Additionally, starting on 16 February 2021 (after protocol amendment 5), patients must also have progressed on a BTKi and received prior venetoclax. The full eligibility criteria are provided in the **supplement**.

Procedures

The ibrutinib combination cohort was evaluated in phase 1 dose-escalation and dose-expansion portions of the study. Results of the dose-escalation portion of the study were reported.[17] At enrollment, patients started or continued ibrutinib at 420 mg daily (or less if previously reduced to manage toxicity) through leukapheresis and for up to 90 days after liso-cel administration (or longer per investigator discretion), unless toxicity required dose reductions or discontinuation. Patients who previously

discontinued ibrutinib restarted treatment as soon as possible after confirming eligibility, before leukapheresis. Bridging therapy in addition to ibrutinib during liso-cel manufacturing was allowed at the investigator's discretion (**supplement**) with measurable disease reconfirmed before lymphodepletion (30 mg/m^2 fludarabine and 300 mg/m^2 cyclophosphamide intravenously daily for 3 days). Patients received liso-cel infusion at a target dose of 50 × 10^6 (dose level [DL]1) or 100 × 10^6 (DL2) CAR$^+$ T cells 2–7 days after lymphodepletion. DL2 was selected as the recommended dose for expansion based on dose-escalation results.[17]

End Points and Assessments

The primary end point of the dose-expansion portion of the study was CR/CRi rate per investigator using 2018 International Workshop on CLL criteria at the recommended dose (end point definitions are in **supplemental Table 1**).[18] Secondary end points included safety (type, frequency, and severity of adverse events [AE] and laboratory abnormalities), overall response rate (ORR), undetectable minimal residual disease at 10^{-4} sensitivity (uMRD4) rate in peripheral blood (PB; in all patients and those with best response of CR/CRi), DOR, DOR in patients with CR/CRi, time to response, time to CR/CRi, progression-free survival (PFS), and overall survival (OS). Exploratory end points included cellular kinetics, liso-cel transgene persistence, rates of B-cell aplasia (defined as <3% CD19$^+$ B cells in PB lymphocytes as assessed by flow cytometry) and gene expression. Assessment of uMRD4 rate in BM was conducted post hoc. Assessment details are in the **supplemental Methods** and **supplemental Table 2**.

Post hoc analyses of gene signatures indicative of T-cell exhaustion/dysfunction were performed on cells from patients in the liso-cel plus ibrutinib and liso-cel monotherapy cohorts from TRANSCEND CLL 004. T-cell exhaustion analyses are

described in the **supplement**.

Liso-cel–treated patients who completed or withdrew from TRANSCEND CLL 004 could enroll in a separate long-term follow-up (LTFU) study (NCT03435796) for safety and OS for up to 15 years after liso-cel. Data from LTFU were included for study duration, OS, and death analyses.

Statistical analysis

The study planned to enroll approximately 20 patients evaluable for dose-limiting toxicities in the dose-escalation portion; those patients not evaluable were replaced. After enrollment of the dose-escalation portion, the cohort was expanded to treat an additional ~20–50 patients at the recommended dose to further evaluate safety and efficacy. Analyses were performed on the combined population of patients from the dose-escalation and dose-expansion portions.

Post hoc propensity score matching and weighting analyses were performed to compare efficacy and safety outcomes between the liso-cel plus ibrutinib and liso-cel monotherapy cohorts (conducted in parallel [nonrandomized]) from TRANSCEND CLL 004. The methodology and end points assessed are detailed in the **supplement**.

There was no efficacy hypothesis testing; all analyses were descriptive except for the propensity score matching and weighting analyses. Analysis sets are defined in **supplemental Table 3**.

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and

applicable regulatory requirements. Institutional review boards at participating institutions approved the study protocol and amendments. All patients provided written informed consent before any study-related procedures.

DATA SHARING STATEMENT

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

RESULTS

Patients

Between 16 August 2018 and 23 November 2021, 65 patients were enrolled in the liso-cel plus ibrutinib cohort and underwent leukapheresis. Of those, CAR T-cell product was successfully manufactured for 63 (97%) patients (liso-cel, n = 62; nonconforming product, n = 1; **supplemental Table 4**). Fifty-six (86%) patients received liso-cel (DL1, n = 5; DL2, n = 51) plus ibrutinib (**supplemental Table 5**); reasons for not receiving combination treatment are in **Figure 1**. All 56 patients were efficacy evaluable. In the combination-treated set, 55 (98%) patients had high-risk cytogenetics (del[17p], mutated *TP53*, unmutated immunoglobulin heavy-chain variable region, or ≥3 chromosomal aberrations), and median (range) sum of the product of perpendicular diameters was 27.3 cm^2 (1.4–217.7) (**Table 1**). Patients had a median (range) of 5 (1–13) prior lines of systemic therapy, including 13 (23%) who received ≤2 prior therapies, and 55% experienced progression on prior BTKi and discontinued venetoclax due to progression, intolerability, or lack of response. Sixteen (29%) patients received bridging therapy for disease control in addition to concurrent ibrutinib during liso-cel manufacturing (**supplemental Table 6**).

Median (range) time from leukapheresis to liso-cel availability was 25 days (17–79) and from leukapheresis to liso-cel infusion was 35 days (28–179). Median (range) time of ibrutinib exposure was 34 days (15–188) from leukapheresis to liso-cel infusion and 95 days (6–1517) after liso-cel infusion (**supplemental Table 7**); 12 (21%) patients required ibrutinib dose adjustment and 31 (55%) discontinued ibrutinib due to AEs or other reasons (**supplemental Table 8**). At data cutoff (12 January 2024), 28 (50%) of 56 patients discontinued the study, 11 (20%) completed the study, and 17 (30%) were ongoing; 5 (18%) of 28 eligible patients enrolled in LTFU

(**Figure 1**). Median (range) on-study follow-up (including LTFU) was 24.8 months (3.1–51.8).

Efficacy

Efficacy results are reported in patients in the combination-treated efficacy set who received liso-cel at DL2 (n = 51). The primary end point of investigator-assessed CR/CRi rate was 45% (n = 23; 95% CI, 31–60; CR, n = 21; CRi, n = 2), and the secondary end point of ORR was 86% (n = 44; 95% CI, 74–94) (**Table 2**). CR/CRi rate and ORR were generally consistent across patient subgroups, including those with high-risk cytogenetics and BTKi progression/venetoclax failure (**supplemental Figure 1**). All 51 patients were MRD-evaluable in PB and 49 were evaluable in BM. The uMRD4 rate based on all patients in the efficacy set was 86% (n = 44; 95% CI, 74–94) in PB and 84% (n = 43; 95% CI, 71–93) in BM. In patients who achieved CR/CRi (n = 23), uMRD4 rate was 96% (n = 22; 95% CI, 78–100) in both PB and BM (**supplemental Table 9**). For most responders, CLL cell clearance in both PB and BM occurred by day 30 (**supplemental Table 10**). Median (range) time to first response (CR/CRi/partial response/remission [PR]/nodular PR [nPR]) and first CR/CRi was 1.0 month (0.9–6.0) and 3.1 months (0.9–12.1), respectively. Of the 23 patients with a best response of CR/CRi, 11 had CR/CRi as their first response; the remaining 12 had a first response of PR/nPR, which deepened to CR/CRi. Median (95% CI) PFS and OS were 31.4 months (20.1–NR) (**Figure 2A**) and NR (27.5–NR) (**Figure 2B**), respectively, with a 24-month PFS and OS rate of 62% (95% CI, 46–74) and 80% (95% CI, 65–88), respectively. All 16 patients who were ongoing (ie, in follow-up at data cutoff) were responders (12 patients had a best response of CR/CRi and 4 had a best response of PR/nPR). Median (95% CI) DOR was 41.4 months (23.3–not reached [NR]) (**Figure 2C**) with a 24-month probability of continued

response of 65% (95% CI, 47–79) and the median (95% CI) DOR in patients with CR/CRi was NR (28.7–NR) with a 24-month probability of continued CR/CRi of 85% (95% CI, 60–95).

In post hoc analyses of the 44 patients in the combination-treated efficacy set at DL2 with uMRD4 in PB, the median (95% CI) PFS was 31.4 months (20.1–NR) (**Table 2**); for the 22 patients who achieved CR/CRi, median (95% CI) PFS was NR (29.6–NR) and for the 19 patients who achieved PR/nPR, median (95% CI) PFS was 16.6 months (11.9–31.4) (**Figure 2D**).

Safety

In the combination-treated set, 48 (86%) patients experienced grade ≥3 treatment-emergent AEs (TEAE; defined as AEs that occurred within 90 days of liso-cel administration or within 30 days of ibrutinib completion, whichever ended later; **Table 3** and **supplemental Table 11**), most commonly neutropenia (52%) and anemia (41%). There were no grade 5 TEAEs, including no grade 5 TEAEs related to liso-cel or ibrutinib. Grade ≥3 TEAEs considered related to liso-cel by investigator assessment occurred in 32 (57%) patients (**supplemental Table 12**) and grade ≥3 TEAEs considered related to ibrutinib by investigator assessment occurred in 24 (43%) patients (**supplemental Table 13**), including cardiovascular events of hypertension (7%) and atrial fibrillation (2%). There were a total of 5 hemorrhage events reported on study as follows: 2 low-grade hemorrhage events considered related to ibrutinib by investigator assessment (grade 2 post-procedural hematuria, n = 1; grade 1 catheter site hemorrhage, n = 1) and 3 additional low-grade hemorrhage events not considered related to treatment (grade 1 oral blood blister, n = 1; grade 1 hemoptysis, n = 1; grade 1 hematuria, n = 1). None led to ibrutinib

discontinuation. Four of the 5 patients with hemorrhage events were receiving anticoagulant or antiplatelet therapy at the time of event.

A total of 18 deaths occurred on study (**supplemental Table 14**), including 2 between leukapheresis and lymphodepletion (intraparenchymal hemorrhage, n = 1 [this patient was on ibrutinib when the event started, which eventually led to its discontinuation]; unknown, n = 1) and 16 >90 days after CAR T-cell infusion. The primary causes of death were disease progression (n = 6), unknown (n = 6, including 3 patients who had withdrawn consent), COVID-19 infection (n = 3), and mixed septic/cardiogenic shock (n = 1).

Any-grade cytokine release syndrome (CRS) was reported in 45 (80%) patients in the combination-treated set (**Table 3** and **supplemental Table 15**) with 2 (4%) patients experiencing grade 3 CRS and no grade 4 or 5 events reported. Any-grade neurological events (NE) were reported in 23 (41%) patients with 5 (9%) patients experiencing grade 3 NEs, 1 (2%) with a grade 4 NE, and no grade 5 events reported. The most common grade ≥3 nervous system TEAEs regardless of attribution were aphasia and encephalopathy in 3 (5%) patients each (**supplemental Table 16**). Thirty-three (59%) patients received tocilizumab and/or corticosteroids for the treatment of CRS and/or NEs, including 9 (16%) who received tocilizumab only, 5 (9%) who received corticosteroids only, and 19 (34%) who received both tocilizumab and corticosteroids; 1 (2%) patient received a vasopressor. Grade 3 infections were reported in 8 (14%) patients, with no grade 4 or 5 infections reported. Prolonged cytopenias (grade ≥3 at the day 30 visit) were reported in 25 (45%) patients; of patients with prolonged cytopenia and laboratory results after day 30, 3 (100%) of 3 patients with anemia, 14 (70%) of 20 patients with neutropenia, and 14 (100%) of 14 patients with thrombocytopenia recovered to grade ≤2 levels by day 90

(**supplemental Table 17**). Five (9%) patients had second primary malignancies; none were T-cell malignancies. Macrophage activation syndrome and tumor lysis syndrome (both grade 3 events) were reported in 1 (2%) patient each.

Cellular kinetics

In the cellular kinetic set (n = 54), liso-cel showed rapid expansion with a median (interquartile range [IQR]) time to maximum expansion (t_{max}) of 10 days (IQR, 9–14) (**Figure 3A** and **supplemental Table 18**); median (IQR) maximum transgene level (C_{max}) was 127,350 copies/µg (47,091–228,924) and area under the curve for transgene levels from 0 to 28 days after infusion ($AUC_{(0–28d)}$) was 833,643 days × copies/µg (446,493–1,671,085) with no apparent differences in cellular kinetics between DLs (**supplemental Table 18**). For context, while TRANSCEND CLL 004 was not designed to compare cohorts, in the monotherapy cohort, median (IQR) t_{max} was 14 days (10–15), C_{max} was 76,662 copies/µg (29,568–182,265), and $AUC_{(0–28d)}$ was 663,910 days × copies/µg (204,380–1,714,815).[5] Persistence of the liso-cel transgene was detected up to 24 months after liso-cel infusion in 7 of 20 evaluable patients (**Figure 3B**). B-cell aplasia rates over time are in **supplemental Figure 2**.

Propensity score matching and weighting analyses

Post hoc propensity score matching and weighting analyses were conducted to adjust for any differences in key characteristics between the liso-cel monotherapy and liso-cel plus ibrutinib combination cohorts. Patient characteristics before and after balancing are shown in **supplemental Table 19**. The odds of CR/CRi and overall response were higher with combination treatment (statistically significant) by most comparison methods (**supplemental Table 20**). Hazard ratios for PFS and OS and odds ratios for grade ≥3 CRS/NE were numerically lower with combination

326 treatment vs monotherapy, though not statistically significant for most comparison
327 methods.

328 **T-cell exhaustion gene signature score**

329 In pooled gene signature score analyses using cells from patients who received
330 liso-cel plus ibrutinib and liso-cel monotherapy, reduced T-cell exhaustion gene
331 signature score[19,20] in sorted CAR-positive T cells at C_{max} was associated with a
332 trend toward improved PFS (**Figure 4A**). Furthermore, a significantly lower T-cell
333 exhaustion score at C_{max} was observed in CAR-positive T cells from patients who
334 achieved uMRD4 in BM compared with those who were MRD detectable; however,
335 no significant differences were observed in CAR-negative T cells or by MRD status in
336 PB (**Figure 4B**). In analyses comparing gene signature scores in cells from patients
337 who received liso-cel plus ibrutinib vs liso-cel monotherapy, significantly lower T-cell
338 exhaustion score at C_{max} was observed in patients who received combination
339 treatment vs monotherapy (**Figure 4C**). No difference was observed in exhaustion
340 scores in CAR-negative T cells between treatment groups.

DISCUSSION

In this primary analysis of the combination cohort from TRANSCEND CLL 004, liso-cel plus ibrutinib treatment demonstrated substantial efficacy with deep remissions in patients with R/R CLL/SLL. The safety profile was manageable, with low rates of severe CRS and NEs and no new safety signals or added toxicity, supporting the potential of the combination in this population.

Liso-cel is an effective treatment for patients with R/R CLL/SLL, including those with disease that has failed targeted therapies. However, the efficacy of CAR T-cell therapies in CLL has historically been limited by acquired T-cell dysfunction, characterized by impaired proliferative capacity, exhausted phenotype, and diminished T-cell cytotoxicity.[19,21,22] Ibrutinib- and other BTKi-mediated effects on CAR T-cell functionality may improve CAR T-cell performance.[14] Additionally, in preliminary analyses of CAR^+ T cells from patients treated with liso-cel plus ibrutinib compared with liso-cel alone, ibrutinib decreased the expression of pathways associated with inflammatory signaling and reduced serum interleukin-6, and these changes were associated with enhanced CAR T-cell function and efficacy.[23] Overall, these studies suggested that adding ibrutinib could enhance both efficacy and safety of CAR T-cell treatment in B-cell malignancies.

The feasibility of ibrutinib plus CAR T-cell combination treatment in patients with R/R CLL was originally explored by smaller, single-center studies.[15,16] A phase 1/2 feasibility study of 19 patients with R/R CLL and high-risk disease features treated with CD19-directed CAR T-cell therapy with or without concomitant ibrutinib was conducted at the Fred Hutchinson Cancer Center/University of Washington (NCT01865617).[15] Patients treated with combined therapy achieved an ORR of 83%, CR rate of 22%, and BM uMRD4 rate of 72%.[15] Similarly, in a single-center, phase 2

study of 19 patients with CLL treated with CD19-directed CAR T cells and ibrutinib at the University of Pennsylvania (NCT02640209), the CR rate was 44% and BM uMRD at 10^{-5} sensitivity rate was 72% in evaluable patients.[16]

In TRANSCEND CLL 004, high ORR and uMRD4 rates were also observed with combined therapy. Among the 51 liso-cel plus ibrutinib-treated patients who received liso-cel at DL2, CR/CRi rate was 45%, ORR was 86%, and PB uMRD4 rate was 86% (BM uMRD4 rate, 84%). In patients treated at DL2 who achieved CR/CRi, uMRD4 rate was 96% in both PB and BM. Grade ≥3 CRS (4%) and NEs (11%) were low in all combination-treated patients. The heterogeneity in ibrutinib treatment duration after liso-cel infusion in TRANSCEND CLL 004 limits understanding of the optimal duration of ibrutinib in this combination therapy.

Previous reports suggested that increased T-cell exhaustion markers and late differentiation of CAR T cells derived from patients with CLL were associated with lack of favorable responses.[19,23] Our exploratory gene expression analysis extends previous work by demonstrating a significant reduction in CAR T-cell exhaustion at the time of maximal CAR T-cell expansion in patients treated with liso-cel and ibrutinib compared with patients treated with liso-cel alone. These data suggest that ibrutinib treatment may reduce exhaustion in CAR T cells after infusion and are among the first data demonstrating that combination treatment can directly improve CAR T-cell function in patients, translating into improved responses. BTKi therapy holds promise in mitigating intrinsic factors that could otherwise diminish CAR T-cell function over time during antigen exposure, either through BTK-dependent or -independent mechanisms, such as ITK inhibition.[12] Preclinical data indicate that acalabrutinib exhibits limited impact on ITK activity, while ibrutinib induces broader gene expression changes, consistent with preclinical studies.[14] Zanubrutinib has also

demonstrated ITK inhibition preclinically,[24] but its effects and the effects of noncovalent BTKis on CAR T-cell therapy remain to be explored.[25-27] Therefore, a class-wide (covalent or noncovalent) BTKi benefit in combination with CAR T-cell therapy cannot be ruled out, as BTKis differ in off-target profiles and T-cell modulation mechanisms. This distinction, not explored in this study, warrants further investigation.

Results of the current study also compare favorably with the efficacy and safety of ibrutinib monotherapy in patients with R/R CLL/SLL, though comparisons should be made with caution due to differences in study designs, patient characteristics, and treatment history. While reported ORRs with ibrutinib monotherapy in patients with R/R CLL were generally similar to the ORR observed in this study, CRs are rarely achieved with ibrutinib alone, with reported CR rates of 0–10%.[28-31] In contrast, the combination of liso-cel plus ibrutinib in this heavily pretreated population resulted in high CR and uMRD rates. Although ibrutinib monotherapy has been associated with a risk of severe hemorrhage and cardiovascular AEs,[28,30,31] the combination therapy did not appear to increase the risk; in fact, no such events were observed in this study.

In the primary analysis of the monotherapy cohort from the TRANSCEND CLL 004 study, a single administration of liso-cel achieved an independent review committee–assessed CR/CRi rate of 18% and ORR of 43% in efficacy-evaluable patients with R/R CLL/SLL and previous BTKi progression/venetoclax failure who received liso-cel at a target dose of 100×10^6 CAR^+ T cells.[5] Median DOR, PFS, and OS were 35.3 months, 11.9 months, and 30.3 months, respectively. The safety profile was manageable in all liso-cel–treated patients, with grade 3 CRS reported in 10 (9%)

patients with no grade 4 or 5 events and grade 3 NEs in 21 (18%) patients, grade 4 NE in 1 (1%) patient, and no grade 5 NEs.

The differences in study design and patient populations (due to differences in inclusion criteria) between the liso-cel plus ibrutinib combination and liso-cel monotherapy cohorts in the TRANSCEND CLL 004 study preclude any direct comparisons between cohorts. In the absence of a comparator arm in the current study, post hoc propensity score–balancing analyses were performed to allow efficacy and safety to be compared between the liso-cel plus ibrutinib and liso-cel monotherapy cohorts from TRANSCEND CLL 004. In the analyses, liso-cel plus ibrutinib demonstrated a trend for better efficacy and safety compared with monotherapy, with statistically significant differences in CR rates and ORR and numerically lower rates of grade ≥3 CRS/NEs. No differences in PFS or OS were observed. Of note, the combination cohort of the current study was not designed or powered for hypothesis testing.

Cellular kinetics were not considered in the propensity score analyses; however, in comparisons with primary analysis results from the liso-cel monotherapy cohort, median t_{max} was shorter (10 vs 14 days) in the combination cohort vs the monotherapy cohort with no other apparent differences in expansion.[5] Of note, unmatched comparisons between cohorts should be made with caution due to differences in study design and patient characteristics.

In conclusion, the combination of liso-cel plus ibrutinib treatment was efficacious and feasible in this cohort of patients with R/R CLL/SLL and induced deep and durable responses. The safety profile was manageable and predictable, with no new signals detected with combination treatment.

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661 **Table 1. Demographics and baseline characteristics (combination-treated set)**

Characteristic	DL2* (n = 51)†	Total (n = 56)†
Age, median (range), y	65.0 (44–77)	64.5 (44–77)
Male, n (%)	34 (67)	37 (66)
Race, n (%)		
White	42 (82)	46 (82)
Black or African American	6 (12)	7 (12.5)
Unknown	3 (6)	3 (5)
Ethnicity, n (%)		
Hispanic or Latino	2 (4)	2 (4)
Not Hispanic or Latino	45 (88)	49 (87.5)
Unknown	4 (8)	5 (9)
ECOG PS at screening, n (%)		
0	23 (45)	23 (41)
1	28 (55)	33 (59)
Bulky disease per investigator ≥5 cm before LDC, n (%)		
Yes	18 (35)	18 (32)
No	29 (57)	33 (59)
Unknown	4 (8)	5 (9)
SPD per investigator before LDC, cm^2		
No.	47	51
Median (range)	28.5 (1.4–217.7)	27.3 (1.4–217.7)
LDH before LDC, U/L		
Median (range)	208.0 (2.1–679.0)	205.0 (2.1–679.0)
≥ ULN, n (%)	22 (43)	24 (43)
Rai disease stage at screening, n (%)		
0–II	26 (51)	29 (52)
III or IV	23 (45)	25 (45)
Unknown or missing	2 (4)	2 (4)
Binet disease stage at screening, n (%)		
A or B	27 (53)	30 (54)
C	21 (41)	23 (41)

Unknown or missing	3 (6)	3 (5)
High-risk cytogenetics, n (%)		
Any	50 (98)	55 (98)
del(17p)	23 (45)	25 (45)
Mutated *TP53*	23 (45)	24 (43)
Unmutated IGHV	37 (73)	39 (70)
At least 3 chromosomal aberrations	25 (49)	29 (52)
Previous lines of systemic therapy, median (range)	5 (1–13)	5 (1–13)
1	3 (6)	4 (7)
2	9 (18)	9 (16)
3	7 (14)	7 (12.5)
4	6 (12)	7 (12.5)
≥5	26 (51)	29 (52)
Previous therapy, n (%)		
Previous BTKi	51 (100)	56 (100)
BTKi refractory‡	49 (96)	54 (96)
BTKi relapsed§	0	0
BTKi intolerant only	0	0
Previous venetoclax	39 (76)	42 (75)
Venetoclax refractory‡	32 (63)	33 (59)
Venetoclax relapsed§	5 (10)	5 (9)
Venetoclax intolerant only	1 (2)	3 (5)
Previous BTKi and venetoclax	39 (76)	42 (75)
BTKi progression and venetoclax failure‖	28 (55)	31 (55)
Previous chemoimmunotherapy	37 (73)	42 (75)
Previous HSCT	3 (6)	3 (5)
Previous PI3K inhibitor	10 (20)	11 (20)
Received bridging therapy,¶ n (%)	13 (25)	16 (29)
Time from diagnosis to liso-cel infusion, months, median (range)	114 (14–281)	114 (14–281)

All percentages are rounded to whole numbers except those with ".5%."

BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response/remission; CRi, complete response/remission with incomplete marrow recovery; DL, dose level; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplantation; IGHV, immunoglobulin heavy-chain variable region; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; LDC, lymphodepleting chemotherapy; LDH, lactate dehydrogenase; liso-cel, lisocabtagene maraleucel; nPR, nodular partial response/remission; PI3K, phosphoinositide 3-kinase; PR, partial response/remission; SPD, sum of the product of perpendicular diameters; *TP53*, tumor protein 53; ULN, upper limit of normal.

*Target dose of 100×10^6 CAR^+ T cells.

†Includes 2 patients diagnosed with small lymphocytic lymphoma.

‡Defined as treatment failure (nonresponse) or as progression within 6 months from last dose of therapy.

§Defined as disease progression in a patient who has previously reached CR/CRi or PR/nPR for a period of at least 6 months.

‖Includes patients who progressed on a BTKi and met one of the following criteria: 1) discontinued venetoclax due to disease progression or intolerability and the patient's disease met indications for further treatment per iwCLL 2018 criteria or 2) failed to achieve an objective response within 3 months of initiating therapy.

¶Bridging therapy included other anticancer therapies in addition to concurrent ibrutinib treatment given for disease control during liso-cel manufacturing.

685 **Table 2. Efficacy outcomes (combination-treated efficacy set)**

	DL1* (n = 5)	DL2† (n = 51)	Total (n = 56)
Investigator-assessed CR/CRi rate, n (%) [95% CI]‡ – primary end point	3 (60) [15–95]	23 (45) [31–60]	26 (46) [33–60]
Investigator-assessed ORR, n (%) [95% CI]‡	4 (80) [(28–100]	44 (86) [74–94]	48 (86) [74–94]
Best overall response, n (%)			
CR/CRi	3 (60)	23 (45)	26 (46)
CR	3 (60)	21 (41)	24 (43)
CRi	0	2 (4)	2 (4)
PR/nPR	1 (20)	21 (41)	22 (39)
Stable disease	1 (20)	3 (6)	4 (7)
Progressive disease	0	4 (8)	4 (7)
uMRD4 in PB, n (%) [95% CI]‡,§	4 (80) [28–100]	44 (86) [74–94]	48 (86) [74–94]
MRD-evaluable patients, n (%)‖	5 (100)	51 (100)	56 (100)
uMRD4 in BM, n (%) [95% CI]‡,§	4 (80) [28–100]	43 (84) [71–93]	47 (84) [72–92]
MRD-evaluable patients, n (%)‖	5 (100)	49 (96)	54 (96)
uMRD4 in PB in patients with CR/CRi, n (%) [95% CI]‡,§	3 (100) [29–100]	22 (96) [78–100]	25 (96) [80–100]
MRD-evaluable patients, n (%)‖	3 (100)	23 (100)	26 (100)
uMRD4 in BM in patients with CR/CRi, n (%) [95% CI]‡,§	3 (100) [29–100]	22 (96) [78–100]	25 (96) [80–100]
MRD-evaluable patients, n (%)‖	3 (100)	22 (96)	25 (96)

Time to first response, median (range), months	1.0 (1.0–1.0)	1.0 (0.9–6.0)	1.0 (0.9–6.0)
Time to first CR/CRi, median (range), months	1.0 (1.0–1.0)	3.1 (0.9–12.1)	2.1 (0.9–12.1)
DOR			
Median (95% CI), months¶	NR (4.4–NR)	41.4 (23.3–NR)	41.4 (23.3–NR)
Probability of continued response at 24 months, % (95% CI)¶	NE	65 (47–79)	66 (48.5–79)
Probability of continued response at 30 months, % (95% CI)¶	NE	61 (41.5–75)	61 (42.5–76)
Median follow-up, months (range)#	22.6 (4.4–23.3+)	23.4 (2.3–47.2)	23.3 (2.3–47.2)
DOR in patients with CR/CRi			
Median, months (95% CI)¶	NR	NR (28.7–NR)	NR (28.7–NR)
Median follow-up, months, median (range)#	22.6 (21.7–23.3+)	23.4 (8.6–47.2)	23.1 (8.6–47.2)
PFS			
No. of events	2	22	24
Median, months (95% CI)¶	NR (5.4–NR)	31.4 (20.1–NR)	31.4 (20.1–NR)
PFS rate at 24 months, % (95% CI)¶	60 (13–88)	62 (46–74)	62 (47–73.5)
PFS rate at 30 months, % (95% CI)¶	NE	54 (36.5–68)	54 (37–68)
Median follow-up, months (range)#	23.6 (5.4–24.2+)	24.25 (0.8–48.2)	24.05 (0.8–48.2)
PFS in patients with CR/CRi			
No. of events	0	4	4
Median, months (95% CI)¶	NR	NR (29.6–NR)	NR (29.6–NR)
PFS rate at 24 months, % (95% CI)¶	100 (NR–NR)	85 (60–95)	87 (65–96)
PFS rate at 30 months, % (95% CI)¶	NE	76 (45–91)	77 (47–92)

Median follow-up, months (range)#	23.6 (22.7–24.2+)	24.25 (9.5–48.2)	24.05 (9.5–48.2)
PFS in patients with uMRD4 in PB			
No. of patients with uMRD4 in PB	4	44	48
No. of events	1 (25)	18 (41)	19 (40)
Median (95% CI), months¶	NR (5.4–NR)	31.4 (20.1–NR)	31.4 (21.2–NR)
PFS rate at 24 months, % (95% CI)¶	75 (13–96)	63 (46–76)	64 (48–76)
PFS rate at 30 months, % (95% CI)¶	NR	53 (34–69)	54 (35–70)
Median (95% CI) follow-up, months#	23.6 (5.4–24.2+)	24.1 (2.8–48.2)	24.0 (2.8–48.2)
PFS in patients with uMRD4 in PB who achieved CR/CRi			
No. of patients with uMRD4 in PB who achieved CR/CRi	3	22	25
No. of events, %	0	4 (18)	4 (16)
Median (95% CI), months¶	NR	NR (29.6–NR)	NR (29.6–NR)
PFS rate at 24 months, % (95% CI)¶	100 (NR–NR)	84 (58–95)	86 (63–95)
PFS rate at 30 months, % (95% CI)¶	NR	74 (41–90)	76 (43–91)
Median (range) follow-up, months#	23.6 (22.7–24.2+)	24.1 (9.5–48.2)	24.1 (9.5–48.2)
PFS in patients with uMRD4 in PB who achieved PR/nPR			
No. of patients with uMRD4 in PB who achieved PR/nPR	1	19	20
No. of events, %	1 (100)	11 (58)	12 (60)
Median (95% CI), months¶	5.4 (NR–NR)	16.6 (11.9–31.4)	16.6 (8.6–31.4)
PFS rate at 24 months, % (95% CI)¶	0 (NR–NR)	47 (23–68)	45 (21–66)
PFS rate at 30 months, % (95% CI)¶	0 (NR–NR)	35 (12–61)	34 (11–58)

Median (range) follow-up, months#	NR (5.4–5.4)	23.9 (3.4–36.8+)	23.9 (3.4–36.8+)
OS			
No. of events	1	15	16
Median (95% CI), months¶	NR (15.5–NR)	NR (27.5–NR)	NR (31.4–NR)
OS rate at 24 months, % (95% CI)¶	80 (20–97)	79.5 (65–88)	79.5 (66–88)
OS rate at 30 months, % (95% CI)¶	80 (20–97)	68 (50–81)	69 (52–81)
Median (range) follow-up, months#	33.5 (15.5–49.3+)	26.8 (3.6–49.8)	26.8 (3.6–49.8)

+, ongoing; BM, bone marrow; CAR, chimeric antigen receptor; CI, confidence interval; CR, complete response/remission; CRi, complete response/remission with incomplete marrow recovery; DL, dose level; DOR, duration of response; NE, not estimable; nPR, nodular partial response/remission; NR, not reached; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PR, partial response/remission; uMRD4, undetectable minimal residual disease, 10^{-4} sensitivity.

*Target dose of 50 × 10^6 CAR^+ T cells.

†Target dose of 100 × 10^6 CAR^+ T cells.

‡Two-sided 95% exact Clopper-Pearson CI.

§Rates are calculated out of the total number of patients.

‖Patients with baseline and ≥1 postbaseline MRD result.

¶Kaplan-Meier method was used to obtain 2-sided 95% CIs.

#Reverse Kaplan-Meier method was used to obtain the median follow-up.

698 **Table 3. Treatment-emergent adverse events and adverse events of special**

699 **interest (combination-treated set)**

Treatment-emergent adverse events		
	Total (n = 56)	
	Any grade	**Grade ≥3**
Any TEAE,* n (%)	56 (100)	48 (86)
Most common TEAEs (≥20%), n (%)		
CRS	45 (80)	2 (4)
Neutropenia†	30 (54)	29 (52)
Anemia	29 (52)	23 (41)
Fatigue	22 (39)	1 (2)
Headache	22 (39)	0
Diarrhea	21 (37.5)	0
Nausea	18 (32)	0
Hypokalemia	15 (27)	0
Pyrexia	15 (27)	0
Thrombocytopenia	15 (27)	10 (18)
Decreased appetite	14 (25)	0
Confusional state	13 (23)	2 (4)
Febrile neutropenia	13 (23)	12 (21)
Neutrophil count decreased†	13 (23)	12 (21)
Peripheral edema	13 (23)	0
Chills	12 (21)	0
Constipation	12 (21)	0
Hypophosphatemia	12 (21)	3 (5)
Treatment-emergent adverse events of special interest		
	Total (n = 56)	
CRS‡		
Any grade, n (%)	45 (80)	
Grade 1, n (%)	20 (36)	

Grade 2, n (%)	23 (41)
Grade 3, n (%)	2 (4)
Grade 4, n (%)	0
Grade 5, n (%)	0
Time to onset, median (range), days	7 (1–14)
Time to resolution, median (range), days	5 (2–18)
NEs§	
Any grade, n (%)	23 (41)
Grade 1, n (%)	8 (14)
Grade 2, n (%)	9 (16)
Grade 3, n (%)	5 (9)
Grade 4, n (%)	1 (2)
Grade 5, n (%)	0
Time to onset, median (range), days	8 (1–15)
Time to resolution, median (range), days	8 (1–362)
Tocilizumab and/or corticosteroid use for CRS and/or NEs‖	
Tocilizumab and/or corticosteroids, n (%)	33 (59)
Tocilizumab only, n (%)	9 (16)
Corticosteroids only, n (%)	5 (9)
Both tocilizumab and corticosteroids, n (%)	19 (34)
Doses of tocilizumab, median (range)	2 (1–4); n=28
Other AESIs, n (%)	
Prolonged cytopenia¶	25 (45)
Grade ≥3 infections	8 (14)
Second primary malignancy#,**	5 (9)
Tumor lysis syndrome	1 (2)
Macrophage activation syndrome	1 (2)
Infusion-related reaction	0
Autoimmune disorders#	0

All percentages are rounded to whole numbers except those with ".5%."

AE, adverse event; AESI, adverse event of special interest; CRS, cytokine release syndrome; liso-cel, lisocabtagene maraleucel; NE, neurological event; TEAE, treatment-emergent adverse event.

*AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 26.0. CRS was graded per Lee 2014 criteria.[32] All other AEs were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. TEAEs were defined as AEs that occurred within 90 days of liso-cel administration or within 30 days of ibrutinib completion, whichever ended later. AEs occurring after the initiation of a subsequent therapy or liso-cel retreatment were not considered TEAEs.

†Neutropenia and neutrophil count decreased were coded using MedDRA version 26.0, where neutropenia is under the System Organ Class of Blood and Lymphatic System Disorders and neutrophil count decreased is under the System Organ Class of Investigations.

‡CRS was graded based on Lee 2014 grading criteria.[32]

§NEs were defined as investigator-identified neurological AEs related to liso-cel.

‖One (2%) patient received vasopressors for management of CRS and/or NEs.

¶Prolonged cytopenias were defined as grade ≥3 laboratory result of anemia, neutropenia, or thrombocytopenia not resolved at the day 29 study visit.

#Includes AEs from the long-term follow-up study if any were reported.

**Included events of malignant papillary urothelial carcinoma (n = 1), squamous cell carcinoma of the tonsil (n = 1), squamous cell carcinoma and myelodysplastic syndrome (n = 1), squamous cell carcinoma, skin (n = 1), and basal cell carcinoma (n = 1).

FIGURE LEGENDS

Figure 1. Patient disposition (CONSORT). *Defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but could be considered appropriate for infusion; the patient who received nonconforming product was not included in efficacy or safety analyses. †All combination-treated patients were efficacy evaluable, defined as all patients who received liso-cel and at least 1 dose of ibrutinib who also met the following baseline criteria: 1) had measurable disease present before liso-cel administration based on investigator assessment; 2) did not develop Richter transformation or mantle cell lymphoma before liso-cel infusion; and 3) for those receiving bridging therapy in addition to ibrutinib, patients had baseline disease assessments completed and had measurable disease present on baseline disease assessment after bridging therapy and before liso-cel administration. ‡Includes 3 patients who completed TRANSCEND CLL 004 and 2 patients who had discontinued the study. AE, adverse event; DL, dose level; ITT, intent to treat; liso-cel, lisocabtagene maraleucel; LTFU, long-term follow-up; PD, progressive disease.

Figure 2. Time-to-event outcomes. Kaplan-Meier curves of (A) PFS (B) OS, (C) DOR, and (D) PFS in patients with uMRD4 in PB by best overall response (combination-treated efficacy set). Reverse Kaplan-Meier method was used to obtain median follow-up. PFS was defined as the time from liso-cel infusion to progressive disease or death; OS was defined as the time from liso-cel infusion to death; DOR was defined as the time from first response to progressive disease or death. CI, confidence interval; CR, complete response/remission; CRi, complete response/remission with incomplete marrow recovery; DL, dose level; DOR, duration of response; liso-cel, lisocabtagene maraleucel; MRD, minimal residual disease;

nPR, nodular partial response/remission; NR, not reached; OS, overall survival; PB, peripheral blood; PD, progressive disease; PFS, progression-free survival; PR, partial response/remission; SD, stable disease; uMRD4, undetectable minimal residual disease at 10^{-4} sensitivity.

Figure 3. Liso-cel cellular kinetics and persistence. Liso-cel transgene (A) expansion profile and (B) persistence (cellular kinetic set). Data are number of patients with liso-cel persistence/number of patients with an available sample at the specific time point. Persistence was defined as a transgene count greater than or equal to the lower limit of detection (5 copies/reaction). Concentration values after the initiation of retreatment of liso-cel (including lymphodepletion) or after another anticancer treatment were excluded. DL, dose level; IQR, interquartile range; liso-cel, lisocabtagene maraleucel.

Figure 4. T-cell exhaustion gene signature score analysis. T-cell exhaustion gene signature score analyses in sorted CAR T cells at C_{max} association with (A) PFS, (B) MRD status, and (C) treatment. Panels A and B include pooled samples from patients treated with liso-cel as monotherapy or in combination with ibrutinib. In panel A, comparisons of survival outcomes between patients with high and low T-cell exhaustion score in sorted CAR-positive T cells were performed using log-rank *P* values. Boxplots were used to present the median and quartiles of T-cell exhaustion score between patients based on MRD status in bone marrow and peripheral blood (panel B) and between patients treated with monotherapy and combination therapy (panel C) in both sorted CAR-negative and CAR-positive T cells. CAR, chimeric antigen receptor; C_{max}, maximum transgene level; MRD, minimal residual disease; PFS, progression-free survival.

Figure 1

FIG 1. Patient disposition (CONSORT)

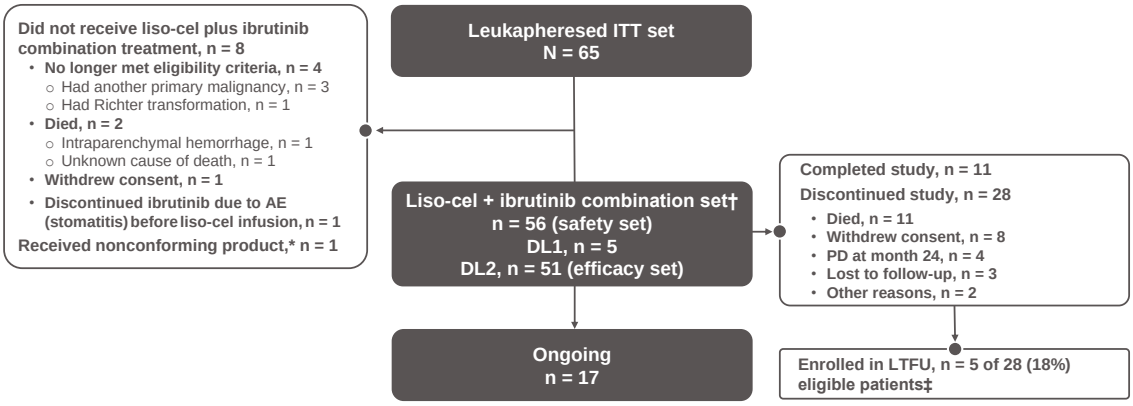


FIGURE 2.

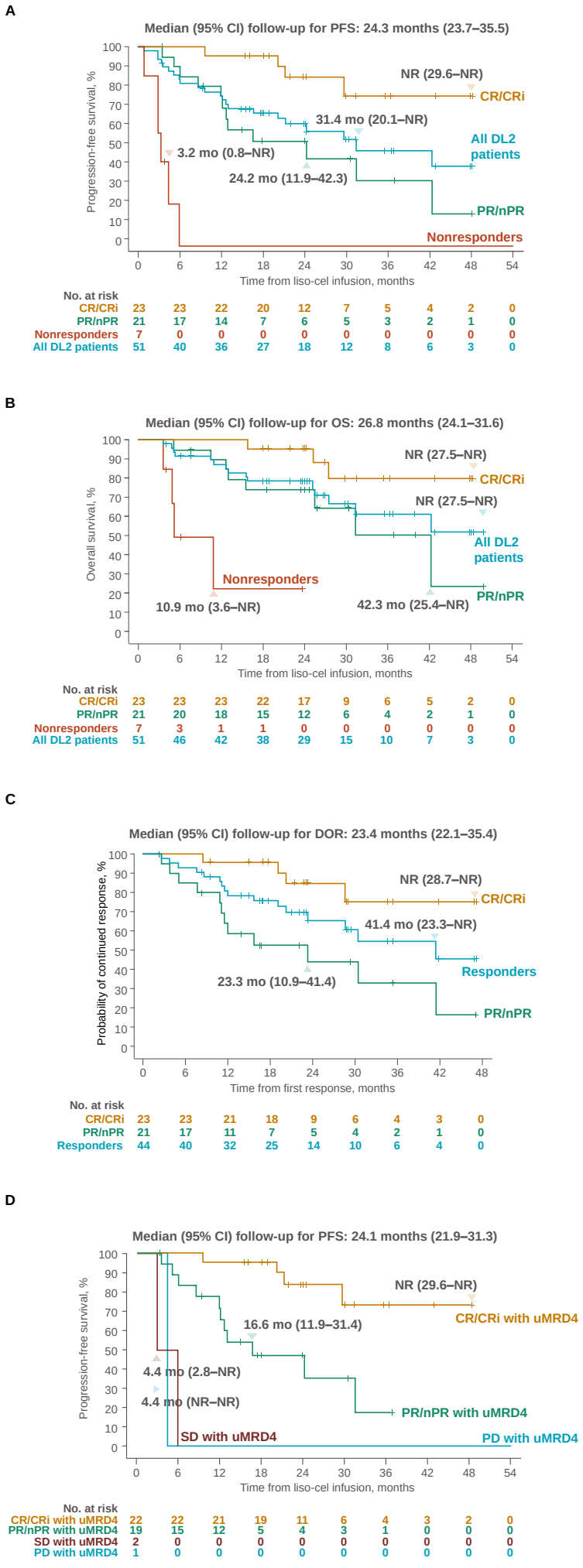
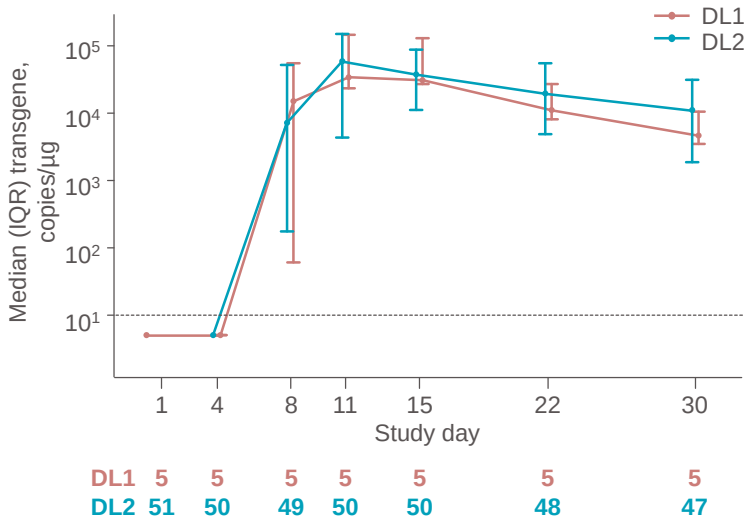


FIGURE 3.

A



B

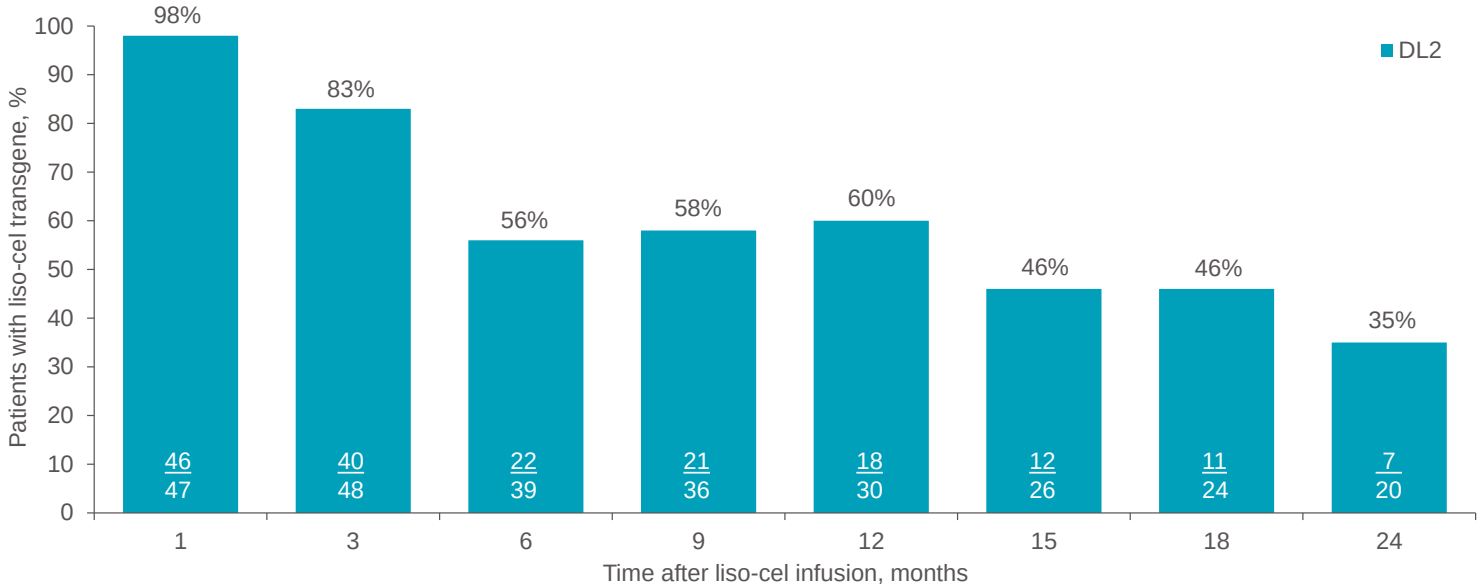


FIGURE 4.