Characteristics associated with response to lisocabtagene maraleucel in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: exploratory analyses from the phase 1/2 TRANSCEND CLL 004 study

CLL-184

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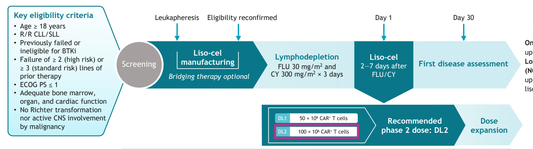
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Introduction

- In TRANSCEND CLL 004, at the primary analysis data cut (September 29, 2022; median follow-up, 21.1 months), a single infusion with lisocabtagene maraleucel (liso-cel) at dose level 2 (100×10^6 CAR$^+$ T cells) induced CR/CR with incomplete marrow recovery (CRi) and overall response (OR) with a manageable safety profile in patients with R/R CLL/SLL[1]
  - For the subgroup of patients whose disease previously progressed on a Bruton tyrosine kinase inhibitor (BTKi) and failed venetoclax (primary efficacy analysis set [PEAS]), CR rate was 18% (primary endpoint; $P = 0.0006$) and OR rate was 43%
- In a subsequent data cut (February 28, 2023; median follow-up, 23.5 months), the CR rate improved to 19% in the full efficacy-evaluable population and 20% in the PEAS; OR rate improved to 48% and 44%, respectively[2]
- Here, we assessed pretreatment characteristics associated with achieving CR or OR in TRANSCEND CLL 004 at the primary analysis data cut

Methods

Figure 1. TRANSCEND CLL 004 study design: phase 1/2, open-label, multicenter study



Primary analysis data cut: September 29, 2022	Full efficacy-evaluable set[b] at DL2 (n = 87)
CR/CRi rate	18% (95% CI, 11%–28%)
OR rate[c]	47% (95% CI, 36%–58%)
Median DOR	35.3 months (95% CI, 19.8–not reached)
Median PFS	18.0 months (95% CI, 9.4–30.1)
Median OS	43.2 months (95% CI, 26.9–not reached)

ClinicalTrials.gov: NCT03331198. Median on-study follow-up in full safety set: 21.1 months.
[a]Duration of follow-up was increased from 24 to 48 months in protocol amendment 5 (February 16, 2021). Patients still in ongoing lwCLL response after the 2-year follow-up were followed for safety, disease status, additional anticancer therapies, and survival for an additional 2 years or until progression, with additional assessments every 6 months; [b]Included patients who received liso-cel and had measurable disease before liso-cel infusion based on IRC assessment; [c]Includes responses of CR/CRi/PR/nPR.
CY, cyclophosphamide; DL, dose level; DOR, duration of response; FLU, fludarabine; IRC, independent review committee; lwCLL, International Workshop on Chronic Lymphocytic Leukemia; nPR, nodular partial response/remission.

Table 1. Comparison groups by endpoint

Endpoints	Comparisons (full efficacy-evaluable set, n = 87)
OR rate	OR group (CR/CRi/PR/nPR) versus NR group (SD/PD/nonevaluable)
CR rate	CR group (CR/CRi) versus non-CR group (PR/nPR/SD/PD/nonevaluable)
Any-grade safety	Any-grade CRS/NE versus no CRS/NE
High-grade safety	Grade ≥ 3 CRS/NE versus grade 0/1/2 CRS/NE

CRS, cytokine release syndrome; NE, neurological event; NR, nonresponder; SD, stable disease.

- Univariable analyses evaluated correlations between pretreatment variables, including demographic features, disease characteristics, and biomarker lab tests, with posttreatment response or safety endpoints (**Table 1**)
- Pretreatment variables were chosen based on their biological and clinical relevance, and data availability
  - Categorical variables were inspected using odds ratios and associated 95% CIs across categories
  - Continuous variables were inspected using means and 95% CIs across categories

Results

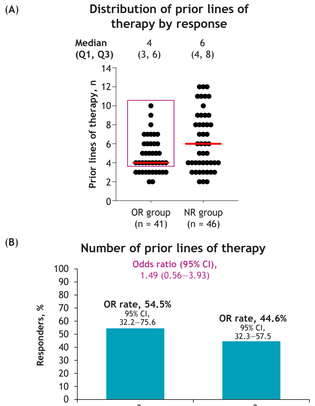
Table 2. Demographics and baseline disease characteristics

	Full efficacy-evaluable set (n = 87)
Demographics at screening	
Median (Q1, Q3) age, y	65 (59, 69)
Prior therapy	
Median (Q1, Q3) prior lines of systemic therapy	5 (4, 7)
Prior chemoimmunotherapy, n (%)	79 (91)
Prior small molecule inhibitor exposure, n (%)	
BTKi and venetoclax	69 (79)
BTKi only	18 (21)
Disease stage/burden at screening	
Rai stage at screening, n (%)[a]	
0–II / III–IV	37 (43) / 44 (51)
Bulky lymph nodes at pre-LDC (n = 79), n (%)[a,b]	41 (47)
Median (Q1, Q3) SPD at pre-LDC (n = 79), cm²[a]	34.9 (17.0, 91.6)
Median (Q1, Q3) LDH (n = 85), U/L[a]	240 (201, 319)
Risk factors at screening	
Unmutated IGHV (n = 60), n (%)[a]	41 (47)
Del(17p) (n = 85), n (%)[a]	34 (39)
TP53 mutation (n = 86), n (%)[a]	36 (41)
Complex karyotype (n = 86), n (%)[a,c]	52 (60)

[a]For the remaining patients (to total n = 87), the variable was unknown or missing; [b]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [c]Defined as the presence of ≥ 3 chromosomal aberrations.
IGHV, immunoglobulin heavy-chain variable region; LDC, lymphodepleting chemotherapy; Q, quartile; SPD, sum of the product of perpendicular diameters.

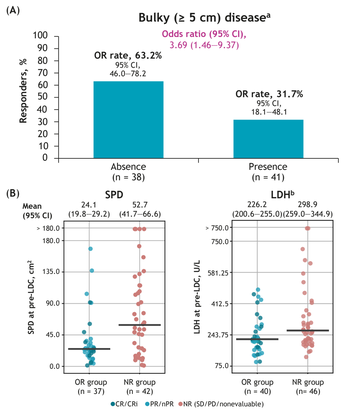
Lower baseline tumor burden and fewer lines of prior systemic therapy may be associated with achieving overall and complete response to liso-cel in patients with R/R CLL/SLL

Figure 2. Number of prior lines of systemic therapy and overall response



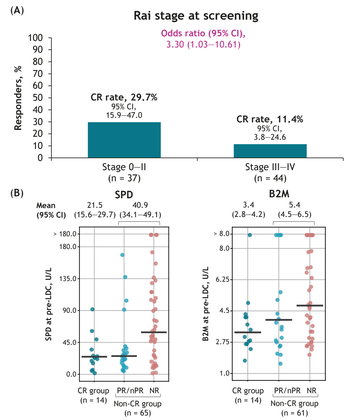
Red lines indicate the median number of prior lines of therapy for each group.

Figure 3. Tumor burden correlation with overall response



All characteristics were collected at the prelymphodepletion study visit unless otherwise specified.
[a]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [b]LDH was also associated with OR when treated as a discrete variable ≤ ULN.

Figure 4. Tumor burden correlation with complete response



All characteristics were collected at the prelymphodepletion study visit unless otherwise specified.
B2M, beta-2 microglobulin.

- Patients had a median of 5 prior lines of systemic therapy; 91% of patients had previously received chemoimmunotherapy, and 79% had previously received both a BTKi and venetoclax (**Table 2**)
- Nearly half (47%) of patients had bulky lymph nodes before LDC, defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm, and 51% had Rai stage III–IV at screening
- Forty-seven percent of patients had unmutated IGHV, 39% had del(17p), 41% had *TP53* mutation, and 60% had complex karyotype, defined as the presence of ≥ 3 chromosomal aberrations

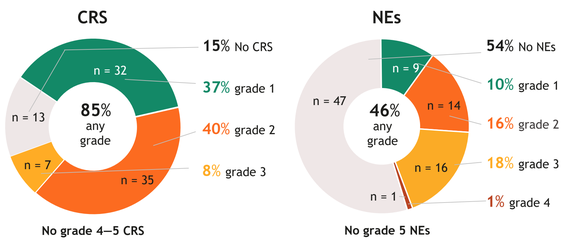
Table 3. Response in patients with high-risk genomic features

Characteristic	OR rate	CR rate
Unmutated IGHV at screening		
Yes (n = 41) vs No (n = 19), %	41.5 vs 63.2	22.0 vs 21.1
Odds ratio (95% CI)	0.41 (0.13–1.27)	1.05 (0.28–3.98)
Del(17p) status at screening		
Yes (n = 34) vs No (n = 51), %	47.1 vs 45.1	26.5 vs 13.7
Odds ratio (95% CI)	1.08 (0.45–2.58)	2.26 (0.75–6.82)
***TP53* mutation at screening**		
Yes (n = 36) vs No (n = 50), %	41.7 vs 50.0	22.2 vs 16.0
Odds ratio (95% CI)	0.71 (0.30–1.69)	1.50 (0.50–4.46)
Del(17p) AND *TP53* mutation at screening		
Yes (n = 25) vs No (n = 60), %	44.0 vs 46.7	28.0 vs 15.0
Odds ratio (95% CI)	0.90 (0.35–2.30)	2.20 (0.72–6.78)
Complex karyotype at screening[a]		
Yes (n = 52) vs No (n = 34), %	44.2 vs 52.9	19.2 vs 17.6
Odds ratio (95% CI)	0.70 (0.30–1.68)	1.11 (0.36–3.40)

[a]Defined as the presence of ≥ 3 chromosomal aberrations.

- Patients had consistent overall and complete response rates regardless of the absence/presence of high-risk genomic features (**Table 3**)
- Age was also not correlated with response
- Patients in TRANSCEND CLL 004 had heavily pretreated disease, and responses were observed in patients with multiple prior treatments (**Figure 2A**)
- OR rate was numerically higher in patients who received ≤ 3 versus > 3 prior lines of therapy (**Figure 2B**)
- Lower tumor burden was correlated with overall response (**Figure 3**) and complete response (**Figure 4**)

Figure 5. Cytokine release syndrome and neurological events in efficacy-evaluable patients (n = 87)



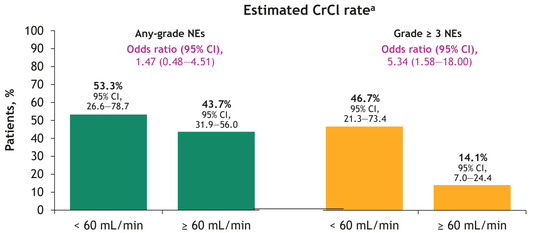
- Any-grade CRS occurred in 85% of patients (grade ≥ 3, 8%) and any-grade NEs in 46% (grade ≥ 3, 20%) (**Figure 5**)
- Due to the small number of patients with no CRS events, CRS associations are inconclusive; only NE data associations are presented

Table 4. Baseline inflammation and SPD correlation with neurological events

Characteristic, mean (95% CI)	Any NE	No NE	Grade ≥ 3 NE	No grade ≥ 3 NE
SPD, cm²	49.1 (40.7–59.2) n = 38	27.7 (21.6–35.7) n = 41	45.4 (33.4–61.7) n = 17	34.4 (28.4–41.6) n = 62
CRP, mg/L	16.6 (9.6–28.5) n = 38	5.1 (3.5–7.5) n = 47	22.5 (9.4–53.6) n = 16	6.9 (4.8–9.9) n = 69
Ferritin, pmol/L	457.0 (293.9–710.6) n = 38	275.5 (186.1–407.7) n = 47	278.5 (226.4–342.6) n = 16	258.8 (231.3–289.5) n = 69

All characteristics were collected at the prelymphodepletion study visit unless otherwise specified.
CRP, C-reactive protein.

Figure 6. Baseline renal insufficiency correlation with neurological events



All characteristics were collected at the prelymphodepletion study visit unless otherwise specified.
[a]Calculated using Cockcroft-Gault equation; inclusion in the TRANSCEND CLL 004 study required serum creatinine ≤ 1.5 × age-adjusted ULN or calculated CrCl rate > 30 mL/min.

- Inflammatory markers, bulky disease, and lower estimated CrCl rate may be associated with an increased risk of NEs (**Table 4** and **Figure 6**)

Conclusions

- Post hoc exploratory univariable analyses from TRANSCEND CLL 004 indicate that responses to liso-cel are consistent in patients with R/R CLL/SLL regardless of high-risk disease features, including unmutated IGHV, del(17p), *TP53* mutation, and complex karyotype
- Lower baseline tumor burden and fewer lines of prior systemic therapy may be associated with achieving response
  - Additional analyses are required to understand other factors associated with long-term outcomes, including on-treatment variables
- Higher baseline levels of inflammation markers (including CRP and ferritin) and renal insufficiency, in addition to high tumor burden, may be associated with an increased risk of NEs
- Collectively, these data suggest that patients may have better responses with liso-cel when treated in earlier lines of therapy and when tumor burden is lower, warranting further investigation of the role of debulking bridging therapy

References

1. Siddiqi T, et al. *Lancet* 2023;402:641–654.
2. Siddiqi T, et al. *Blood* 2023;142(suppl 1):330.

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