Lisocabtagene maraleucel in relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: primary analysis of the phase 1/2, single-arm, multicenter TRANSCEND CLL 004 study

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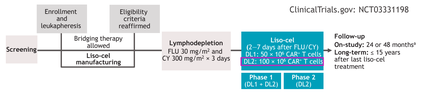
Introduction

- Outcomes remain poor for patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who have relapsed after prior Bruton tyrosine kinase inhibitor (BTKi) and venetoclax failure, with low complete response/remission (CR)/CR with incomplete marrow recovery (CRi) rates of 0%–5% and short median overall survival (OS)[1–6]
- Real-world evidence indicates progressively worse outcomes as treatment options become exhausted[7]
- Median time from dual discontinuation of BTKi and venetoclax to subsequent treatment failure or death was 5.6 months
- Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB chimeric antigen receptor (CAR) T cell product administered at equal target doses of $CD8^+$ and $CD4^+$ CAR$^+$ T cells
- Here we report the primary analysis of the liso-cel monotherapy portion of TRANSCEND CLL 004 (NCT03331198), with a median on-study follow-up of 21.1 months

Methods

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



Key patient eligibility criteria
- Age ≥ 18 years
- R/R CLL/SLL with an indication for treatment
- Previously failed or ineligible for BTKi therapy
- Failure of ≥ 2 (high risk) or ≥ 3 (standard risk) lines of prior therapy
- ECOG PS ≤ 1
- Adequate bone marrow, organ, and cardiac function
- No Richter transformation nor active CNS involvement by malignancy

Primary endpoint (PEAS at DL2)
- CR/CRi rate per iwCLL 2018 by IRC assessment

Key secondary endpoints (PEAS at DL2)
- ORR, uMRD rate in blood

Other secondary endpoints
- DOR, DOCR, PFS, TTR, TTCR per IRC assessment, OS, uMRD CR rate in blood, and safety

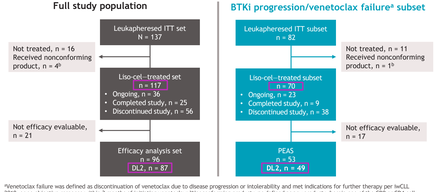
[a]Duration of follow-up was increased to 48 months in protocol amendment 5 (February 16, 2021). Patients still in ongoing response per iwCLL 2018 criteria after the 2-year follow-up were followed for safety, disease status, additional anticancer therapies, and survival for an additional 2 years or until progression.

CY, cyclophosphamide; CNS, central nervous system; DL, dose level; DOCR, duration of complete response/remission; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FLU, fludarabine; IRC, independent review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; OS, overall survival; PEAS, primary efficacy analysis set; PFS, progression-free survival; TTCR, time to complete response/remission; TTR, time to response; uMRD, undetectable minimal residual disease.

- Primary and key secondary endpoints were tested in a prespecified subset of patients with BTKi progression and venetoclax failure (PEAS) at DL2 by the following hierarchy: CR/CRi rate (null hypothesis [H_0] ≤ 5%), ORR (H_0 ≤ 40%), and uMRD rate in blood (H_0 ≤ 5%) (**Figure 1**)

Results

Figure 2. CONSORT diagram



[a]Venetoclax failure was defined as discontinuation of venetoclax due to disease progression or intolerability and met indications for further therapy per iwCLL 2018, or no objective response within 3 months of initiating venetoclax; [b]nonconforming product was 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 was considered appropriate for infusion.

ITT, intention to treat.

- Of 137 leukapheresed patients, liso-cel was successfully manufactured for 131 patients and infused into 117 patients (**Figure 2**)
- Safety results are presented for the full study population of 117 patients who were infused with liso-cel, known as the liso-cel–treated set
- Efficacy results are presented for the 87 patients in the full study population and 49 patients in the PEAS who were treated at DL2

TRANSCEND CLL 004 met its primary endpoint, with a CR/CRi rate of 18% in patients with R/R CLL/SLL after BTKi progression/venetoclax failure, and demonstrated rapid, deep, and durable responses

- All minimal residual disease (MRD)—evaluable responders were uMRD in blood and marrow; 12 of 20 MRD-evaluable patients with SD were uMRD in blood; a majority of patients achieved uMRD by Day 30 (**Table 2**)
- In patients with CR/CRi, median DOR, PFS, and OS were not reached (**Figures 3—5**)

Table 2. Efficacy outcomes

Efficacy	Full efficacy analysis population at DL2 (n = 87)	BTKi progression/venetoclax failure subset at DL2 (n = 49)
Primary endpoint: IRC-assessed CR/CRi rate (95% CI) per iwCLL 2018, %	18 (11–28)	**18 (9–32); P = 0.0006[a]**
Key secondary endpoints		
IRC-assessed ORR (95% CI), %	47 (36–58)	43 (29–58); P = 0.3931[a]
uMRD rate in blood (95% CI), %	64 (53–74)	63 (48–77)[b]
Exploratory endpoint: uMRD rate in marrow (95% CI), %	59 (48–69)	59 (44–73)
Other secondary endpoints		
Best overall response, n (%)		
CR/CRi	16 (18)	9 (18)
PR/nPR	25 (29)	12 (24)
SD	34 (39)	21 (43)
PD	6 (7)	4 (8)
Not evaluable	6 (7)	3 (6)
Median (range) time to first response, months	1.5 (0.8–17.4)	1.2 (0.8–17.4)
Median (range) time to first CR/CRi, months	4.4 (1.1–17.9)	3.0 (1.1–6.1)

[a]One-sided P value from binomial exact test (H_0 of CR/CRi ≤ 5%; H_0 of ORR ≤ 40%); [b]P value not presented for uMRD rate in blood (H_0 ≤ 5%) because the ORR hypothesis was not rejected at 1-sided 2.5% significance level.

CI, confidence interval; PD, progressive disease; SD, stable disease.

Figure 3. Duration of response by best overall response

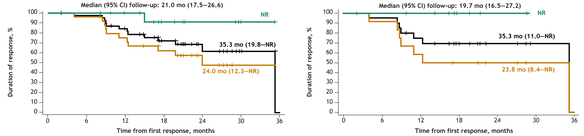


Figure 4. Progression-free survival by best overall response

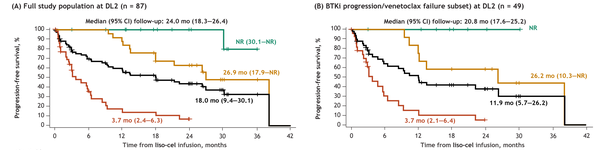
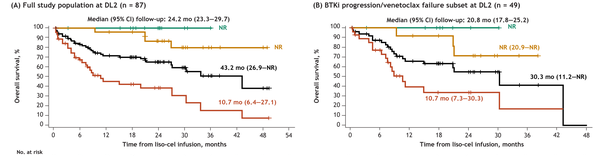


Figure 5. Overall survival by best overall response



Data on Kaplan-Meier curves are expressed as median (95% CI, if available). NR, not reached.

Table 1. Demographics and baseline characteristics

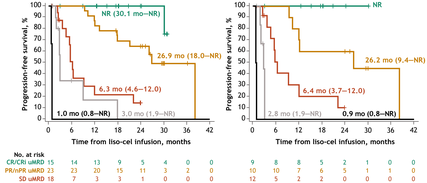
Characteristic	Full study population (n = 117)	BTKi progression/venetoclax failure subset (n = 70)
Median (range) age, y	65.0 (49–82)	66.0 (49–78)
Median (range) prior lines of systemic therapy	5 (2–12)	5 (2–12)
Bulky lymph nodes,[a] n (%)		
Yes	52 (44)	32 (46)
Unknown	9 (8)	8 (11)
High-risk cytogenetics, n (%)	97 (83)	60 (86)
Prior BTKi, n (%)	117 (100)	70 (100)
BTKi refractory[b]	103 (88)	70 (100)
BTKi relapsed[c]	2 (2)	0
BTKi intolerant only	12 (10)	0
Prior venetoclax, n (%)	94 (80)	70 (100)
Venetoclax refractory[b]	89 (76)	67 (96)
Venetoclax relapsed[c]	0	0
Venetoclax intolerant only	4 (3)	3 (4)
Prior BTKi and venetoclax, n (%)	94 (80)	70 (100)
BTKi progression/venetoclax failure,[d] n (%)	70 (60)	70 (100)
Received bridging therapy, n (%)	89 (76)	55 (79)

[a]Defined as ≥ 1 lesion with the longest diameter of ≥ 5 cm; [b]Defined as no response or progression ≤ 6 months from last dose of therapy; [c]Defined as disease progression in a patient who previously had CR/CRi or PR/nPR for ≥ 6 months; [d]Including patients who progressed on a BTKi and met one of the following: (1) discontinued venetoclax due to disease progression or intolerability and patient's disease met indications for further therapy per iwCLL 2018, or (2) failed to achieve an objective response ≥ 3 months of initiating therapy.

nPR, nodular partial response/remission; PR, partial response/remission.

- In the full study population of 117 patients, median age was 65 years, 44% of patients had bulky lymph nodes, and 83% had high-risk cytogenetics (**Table 1**)
- Patients had a median of 5 prior lines of therapy, including BTKi in 100%
- Eighty-eight percent of patients were refractory to BTKi, 76% were refractory to venetoclax, and 60% had BTKi progression and venetoclax failure
- Seventy-six percent received bridging therapy during liso-cel manufacturing; presence of measurable disease was reconfirmed before receiving liso-cel

Figure 6. Progression-free survival by BOR and MRD status in blood by next-generation sequencing at 10^{-4} sensitivity



Data on Kaplan-Meier curves are expressed as median (95% CI, if available). Patients with unknown MRD status are excluded.

BOR, best overall response.

- In exploratory analyses of PFS by uMRD in blood, median PFS was around 26—27 months in patients with uMRD and < 3 months in those with detectable MRD in both population sets (**Figure 6**)
- The most common grade ≥ 3 TEAEs (≥ 40%) were neutropenia (61%), anemia (52%), and thrombocytopenia (41%)

Table 3. Adverse events of special interest

Patients with CRS and NEs	Full study population (n = 117)
CRS,[a] n (%)	99 (85)
Grade 1/2	43 (37)/46 (39)
Grade 3	10 (9)
Grade 4/5	0
Median (range) time to onset/resolution, days	4.0 (1–18)/6.0 (2–37)
NE,[b] n (%)	53 (45)
Grade 1/2	13 (11)/18 (15)
Grade 3	21 (18)
Grade 4	1 (1)
Grade 5	0
Median (range) time to onset/resolution, days	7.0 (1–21)/7.0 (1–83)
Other AESIs, n (%)	
Prolonged cytopenia[c]	63 (54)
Grade ≥ 3 infections[d]	20 (17)
Hypogammaglobulinemia[e]	18 (15)
Tumor lysis syndrome	13 (11)
Second primary malignancy[e]	11 (9)
Macrophage activation syndrome	4 (3)

[a]CRS was graded based on the Lee 2014 criteria; [b]NEs were defined as investigator-identified neurological AEs related to liso-cel; [c]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, and/or thrombocytopenia at Day 30 after liso-cel infusion; [d]Includes grade ≥ 3 TEAEs from the Infections and Infestations (System Organ Class) by AE high-level group term; [e]AEs from the 90-day treatment-emergent period, postmarketing-emergent period, and long-term follow-up were included.

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

- CRS was reported in 85% of patients (grade 3, 9%; no grade 4 or 5 events) and NEs were reported in 45% of patients (grade 3, 18%; grade 4, 1%; no grade 5 events; **Table 3**)
- A total of 81 (69%) patients received tocilizumab and/or corticosteroids for management of CRS and/or NEs
- Five deaths due to TEAEs were reported
  - 4 considered unrelated to liso-cel by investigators (respiratory failure, sepsis, *Escherichia coli* infection, and invasive aspergillosis)
  - 1 considered related to liso-cel by investigators (macrophage activation syndrome)

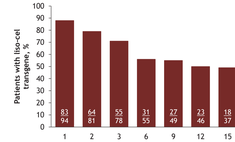
Table 4. Liso-cel cellular kinetics by qPCR at DL2

	Cellular kinetic set at DL2 (n = 89)
Median (IQR) C_{max}, copies/µg	79,338.0 (29,895.0–184,172.0)
Median (IQR) t_{max}, days	14.0 (10.0–14.0)
Median (IQR) $AUC_{0–28d}$, day*copies/µg	693,864.1 (221,422.7–1,765,580.9)

$AUC_{0–28d}$, area under the curve from 0 to 28 days after infusion; C_{max}, maximum expansion; IQR, interquartile range; qPCR, quantitative polymerase chain reaction; t_{max}, time to maximum expansion.

- Liso-cel exhibited rapid expansion with a median time to maximum expansion of 14 days after liso-cel (**Table 4**)

Figure 7. Persistence of liso-cel in blood by qPCR at DL2[a]



[a]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 ≥ 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.

- Persistence of the liso-cel transgene was detected up to 36 months after liso-cel infusion in 1 of 4 evaluable patients (**Figure 7**)

Conclusions

- A single administration of liso-cel demonstrated rapid, deep, and durable responses in patients with R/R CLL/SLL
- The study met its primary endpoint, with a CR/CRi rate of 18% in patients with R/R CLL/SLL after BTKi progression/venetoclax failure, which compares favorably with historical CR/CRi rates of 0%—5%[1–7]
- Liso-cel achieved high uMRD rates in both blood (63%) and marrow (59%)
- Efficacy outcomes were similar in the full study population (R/R CLL/SLL after prior BTKi), demonstrating a clinical benefit of liso-cel in this broader population
- Functional CAR T cells were successfully manufactured and demonstrated expansion and persistence in most patients
  - Higher liso-cel expansion was observed in responders and patients with uMRD
- The safety profile was manageable, with low rates of grade ≥ 3 CRS and NEs
- Overall, these results support liso-cel as a potential new treatment option for R/R CLL/SLL

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