TRANSCEND FL: Phase 2 study results of lisocabtagene maraleucel in patients with relapsed or refractory follicular lymphoma

IBCL-098

Oral presentation in Session IX: Indolent B-cell Lymphoma
Friday, Sept. 8, 2023, 11:22AM—11:32AM

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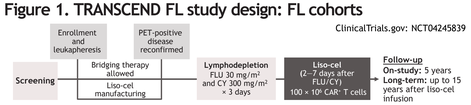
Introduction

- There is an unmet need for effective treatments for patients with relapsed or refractory (R/R) follicular lymphoma (FL) who received ≥ 2 prior lines of systemic therapy or who received 1 prior line of systemic therapy and have high-risk features, due to lack of a definitive standard of care[1,2]
- Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB chimeric antigen receptor (CAR) T cell product
- TRANSCEND FL is a global, open-label, single-arm, multicohort, phase 2, pivotal study to assess efficacy and safety of liso-cel in R/R indolent non-Hodgkin lymphoma
- Here, we report the primary analysis for patients with R/R FL, including efficacy in patients having received ≥ 2 prior therapies (third line or later [3L+]) and safety across all R/R FL cohorts (second line or later [2L+])[3]

Methods

Figure 1. TRANSCEND FL study design: FL cohorts

ClinicalTrials.gov: NCT04245839



Key patient eligibility criteria
- Age ≥ 18 years
- R/R FL
  - 4L+ cohort
  - 3L cohort
  - 2L cohort (POD24 and/or GELF)
- FL histologically confirmed ≤ 6 months before screening with PET-positive and measurable disease
- Received combination of anti-CD20 antibody and alkylator
- ECOG PS ≤ 1
- Adequate bone marrow, kidney, liver, and cardiac function

Primary endpoint
- ORR (BOR of CR or PR) per IRC by PET/CT using Lugano 2014 criteria[4] in the efficacy set

Secondary endpoints
- CR rate, DOR, DOR if BOR is CR, and PFS per IRC by PET/CT using Lugano 2014 criteria[4] in the efficacy set
- OS
- Safety, cellular kinetics, and HRQOL

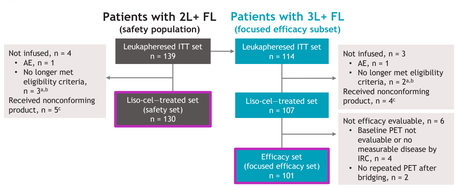
Exploratory endpoint
- B-cell aplasia

2L, second line; 3L, third line; 4L+, fourth line or later; BOR, best overall response; CR, complete response; CT, computed tomography; CY, cyclophosphamide; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FLU, fludarabine; GELF, Groupe d'Etude des Lymphomes Folliculaires; HRQOL, health-related quality of life; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; POD24 (per protocol), disease progression within 24 months of diagnosis and treated with combination systemic therapy with an anti-CD20 antibody and alkylator within 6 months of initial FL diagnosis[5]; PR, partial response.

- ORR and CR rate were tested hierarchically with null hypotheses in the following order at 1-sided α = 0.025 significance: 3L+ FL (ORR ≤ 60%), 4L+ FL (ORR ≤ 50%), 3L+ FL (CR rate ≤ 30%), and 4L+ FL (CR rate ≤20%). 2L+ data were descriptive with no predefined testing hypothesis

Results

Figure 2. Patient disposition and analysis groups

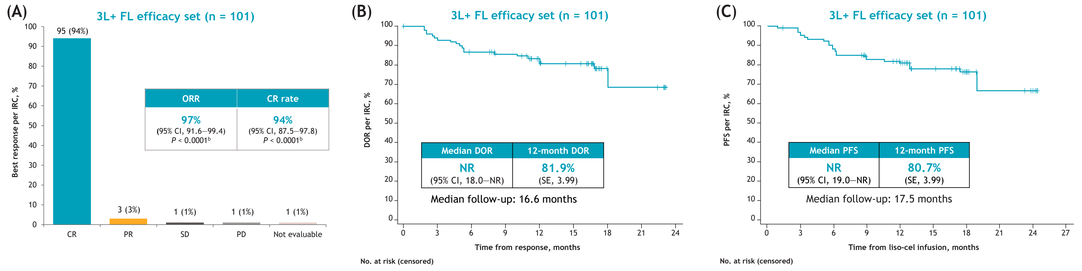


[a]History of transformed FL (n = 1); [b]PET-negative at pretreatment assessment (2L+, n = 2; 3L+, n = 1); [c]Nonconforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered appropriate for infusion. AE, adverse event; ITT, intention to treat.

- In total, 139 patients across all FL cohorts received leukapheresis, 130 received liso-cel, and 5 received nonconforming product (**Figure 2**)
- Safety results are presented in the 2L+ FL population, comprised of patients across all FL cohorts who received liso-cel
- Focused efficacy results are presented for efficacy-evaluable patients with 3L+ FL

Liso-cel achieved deep and durable remissions, with an ORR of 97% and CR in all but 3 responders, and had a favorable safety profile after single infusion in patients with 3L+ R/R FL, including those with high-risk features

Figure 3. (A) Primary endpoint: ORR per IRC by best overall response, (B) DOR per IRC, (C) PFS per IRC, and (D) most common TEAEs[a] (≥ 10%)



[a]TEAE period was defined as the time from initiation of liso-cel administration through and including study Day 90; [b]One-sided *P* value (H_0 of ORR ≤ 60%; H_0 of CR rate ≤ 30%).
CRS, cytokine release syndrome; H_0, null hypothesis; NR, not reached; PD, progressive disease; SD, stable disease; SE, standard error; TEAE, treatment-emergent adverse event.

Table 1. Patient demographics and baseline characteristics

	Liso-cel—treated set[a]	
	2L+ FL (n = 130)	3L+ FL (n = 107)
Median (range) age, y	60 (23—80)	62 (23—80)
Male, n (%)	83 (64)	66 (62)
FL subtype/grade at screening, n(%)		
Grade 1/2	15 (12)/83 (64)	9 (8)/72 (67)
Grade 3A	31 (24)	25 (23)
Unknown	1 (1)	1 (1)
Ann Arbor stage at screening, n (%)		
Stage I/II	2 (2)/16 (12)	1 (1)/11 (10)
Stage III/IV	45 (35)/67 (52)	39 (36)/56 (52)
FL International Prognostic Index at screening, n (%)		
Low risk (0—1)	23 (18)	12 (11)
Intermediate risk (2)	38 (29)	34 (32)
High risk (3—5)	69 (53)	61 (57)
Lactate dehydrogenase > ULN, n (%)	53 (41)	47 (44)
Met modified GELF criteria at most recent relapse, n (%)	73 (56)	57 (53)
Prior lines of systemic therapy, median (range)	2 (1—10)	3 (2—10)
Prior HSCT,[b] n (%)	33 (25)	33 (31)
Received prior rituximab and lenalidomide, n (%)	23 (18)	23 (21)
Refractory to last systemic therapy,[c] n (%)	86 (66)	72 (67)
Double refractory (anti-CD20 and alkylator), n (%)	80 (62)	69 (64)
POD24,[d] n (%)	73 (56)	58 (54)
Received bridging therapy, n (%)	49 (38)	44 (41)

[a]Percentages may not add up to 100% due to rounding; [b]All prior HSCT was autologous HSCT; [c]Defined as progression or stable disease while on last line of therapy or within 6 months of completing the last line of therapy; [d]Defined as progression within 24 months from initiation of chemoimmunotherapy.
HSCT, hematopoietic stem cell transplantation; ULN, upper limit of normal.

Table 2. Adverse events of special interest (AESI)

Patients with CRS and NEs	2L+ FL liso-cel—treated set (n = 130)
CRS,[a] n (%)	
Any grade	75 (58)
Grade 1	55 (42)
Grade 2	19 (15)
Grade 3	1 (1)
Grade 4/5	0
Median (range) time to onset, days	6 (1—17)
Median (range) time to resolution, days	3 (1—10)
NE,[b] n (%)	
Any grade	20 (15)
Grade 1	15 (12)
Grade 2	2 (2)
Grade 3	3 (2)
Grade 4/5	0
Median (range) time to onset, days	8.5 (4—16)
Median (range) time to resolution, days	3.5 (1—17)
Treatment for CRS and/or NEs, n (%)	
Tocilizumab only	14 (11)
Corticosteroids only	3 (2)
Tocilizumab and corticosteroids	19 (15)
Other AESIs, n (%)	
Prolonged cytopenia (grade ≥ 3 at Day 29)[c]	29 (22)
Recovery to grade ≤ 2 neutropenia at Day 90,[c] n/N (%)	18/20 (90)
Recovery to grade ≤ 2 anemia at Day 90,[c] n/N (%)	5/6 (83)
Recovery to grade ≤ 2 thrombocytopenia at Day 90,[c] n/N (%)	11/19 (58)
Grade ≥ 3 infection[a]	7 (5)
MAS/HLH	1 (1)
Tumor lysis syndrome	0
Hypogammaglobulinemia[d]	6 (5)
SPM (2 AML, 1 rectal cancer, 1 colon adenocarcinoma)[d]	4 (3)

[a]Graded according to the Lee 2014 criteria; [b]Defined as investigator-identified neurological AEs related to liso-cel and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03; [c]Grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia on Day 29; [d]Recovery data are presented for patients with prolonged cytopenia who had laboratory results after Day 29; [e]Within the 90-day treatment-emergent period: bacterial urinary tract infection (n = 1), bronchitis (n = 1), COVID-19 and COVID-19 pneumonia (n = 1), device-related bacteremia (n = 1), Escherichia sepsis and pyelonephritis (n = 1), perforated appendicitis (n =1), and pneumonia (n =1); [f]Could occur within or beyond the 90-day treatment-emergent period.
AML, acute myeloid leukemia; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; NE, neurological event; SPM, second primary malignancy.

Table 3. Summary of total deaths (ITT set)

Events, n	Leukapheresed ITT set (N = 139)	Considered related to liso-cel per investigator
Total deaths before liso-cel infusion (n = 1)		
Respiratory failure	1	No
Total deaths after liso-cel infusion (n = 12)		
Disease progression	4	No
Grade 5 TEAE[a] (MAS/HLH)	1	Yes
AE, after 90-day TE period (PML)	1	Yes
New malignancy, after 90-day TE period (AML)	2	No
Other, after 90-day TE period	–	–
Cardiac event (heart failure)	1	No
COVID-19	2	No
Erythema multiforme	1	No

[a]TEAE period was defined as the time from initiation of liso-cel administration through and including study Day 90.
PML, progressive multifocal leukoencephalopathy; TE, treatment emergent.

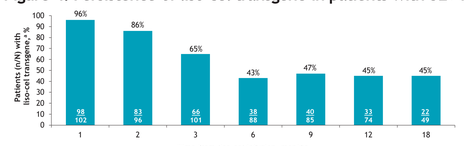
- Serious TEAEs were reported in 32 (25%) patients
- There were 13 deaths on study, 1 before liso-cel infusion in a patient with acute respiratory infection and 12 after liso-cel infusion (**Table 3**)
  - 1 patient had a grade 5 TEAE of MAS/HLH, which occurred in the context of disease progression per IRC

Table 4. Liso-cel cellular kinetic parameters by PCR[a]

Liso-cel transgene by PCR, median (IQR)	3L+ FL liso-cel—treated set (n = 105)[b]
C_{max}, copies/µg	30,530 (12,412—96,795)
t_{max}, days	10 (8—11)
AUC_{0-28d}, days × copies/µg	253,400 (105,912—622,704)

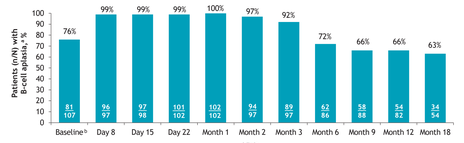
[a]Assessed in 3L+ FL liso-cel—treated set with evaluable cellular kinetic parameters.
AUC_{0-28d}, area under the curve for transgene levels from 0 to 28 days after infusion; C_{max}, maximum transgene levels; IQR, interquartile range; PCR, polymerase chain reaction; t_{max}, time to maximum transgene levels.

Figure 4. Persistence of liso-cel transgene in patients with 3L+ FL



[a]Data in 3L+ FL liso-cel—treated set: 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 ≥ LLOD (40 copies/µg). Values after another anticancer treatment were excluded. LLOD, lower limit of detection.

Figure 5. B-cell aplasia in patients with 3L+ FL



[a]Data in 3L+ FL liso-cel—treated set: number of patients with B-cell aplasia/number of patients with an available sample at the specific time point. B-cell aplasia was defined as < 3% CD19⁺ B cells in peripheral blood lymphocytes as assessed by flow cytometry; [b]Defined as the last measurement before liso-cel infusion.

- Persistence of liso-cel was observed up to 18 months after infusion (22 of 49 evaluable patients), with follow-up ongoing (**Figure 4**)
- Majority of patients (76%) had B-cell aplasia at baseline (**Figure 5**)
- Proportion of patients with B-cell aplasia increased after liso-cel infusion, was maintained above 90% through Month 3, then decreased at Month 6, but remained relatively constant through Month 18

Conclusions

- Single liso-cel infusion in patients with 3L+ R/R FL, including those with high-risk features, achieved deep and durable remissions
  - Primary and key secondary endpoints were met: ORR, 97% and CR rate, 94%
  - After median follow-up of 16.6 mo, median DOR was NR and 12-mo DOR was 82%
  - After median follow-up of 17.5 mo, median PFS was NR and 12-mo PFS was 81%
- Liso-cel had a favorable and manageable safety profile in patients with R/R FL, and no new safety signals were identified
  - 58% of patients had CRS, with only 1% grade 3 event and no grade 4 or 5 events
  - 15% of patients had NEs, with only 2% grade 3 events and no grade 4 or 5 events
- Liso-cel demonstrated clinically meaningful benefit in patients with R/R FL, supporting liso-cel as a potential new treatment option for these patients

References

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Acknowledgments

- The patients and families who are making the study possible
- The clinical study teams who participated
- Study supported by Celgene (Bristol-Myers Squibb Company)
- All authors contributed to and approved the presentation
- Writing and editorial assistance were provided by Amy Agbonbhase, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb

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