Lisocabtagene Maraleucel Versus Standard of Care for Second-Line Relapsed or Refractory Large B-Cell Lymphoma: First Results from Long-term Follow-up of TRANSFORM

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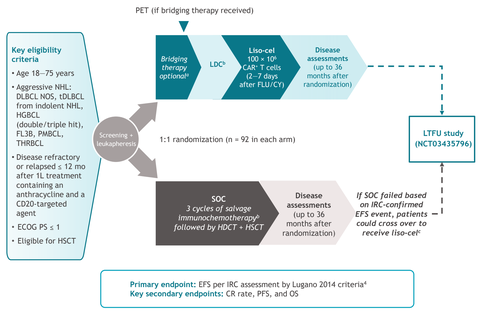
Introduction

- Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB CAR T cell product
- TRANSFORM (NCT03575351) is a global, randomized, open-label, phase 3 study of liso-cel versus standard of care (SOC) as second-line (2L) therapy in adults with R/R large B-cell lymphoma (LBCL)
- In the TRANSFORM study, liso-cel showed superior, more durable efficacy versus SOC, with a potential long-term survival benefit and a favorable safety profile, highlighting the curative potential of liso-cel for 2L R/R LBCL[1–3]
- Upon completion of TRANSFORM, liso-cel—treated patients could enroll into a separate, long-term follow-up (LTFU) study (NCT03435796)
- Here, we report results after approximately 4 years of follow-up in patients from TRANSFORM who consented to the LTFU study

Methods

Figure 1. TRANSFORM study design

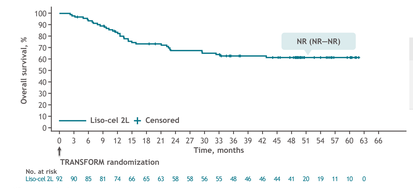


ClinicalTrials.gov identifier: NCT03575351.
[a]One of the protocol-defined SOC therapies; [b]FLU 30 mg/m² and CY 300 mg/m² × 3 days; [c]SOC crossover patients were assessed up to 12 months after liso-cel infusion.
1L, first line; CY, cyclophosphamide; EFS, event-free survival; FL3B, follicular lymphoma grade 3B; FLU, fludarabine; HDCT, high-dose chemotherapy; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PMBCL, primary mediastinal B-cell lymphoma; tDLBCL, transformed diffuse large B-cell lymphoma; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

- The LTFU study includes patients who:
  - had received liso-cel as 2L therapy, and either discontinued early or completed the TRANSFORM study
  - crossed over to receive liso-cel as third-line (3L) therapy if SOC failed
- No liso-cel was administered during the LTFU as part of the protocol; subsequent therapies were provided at the investigator's discretion
- In the LTFU-alone analyses, OS was calculated from the date of consent to participate in the LTFU study to the event or censoring
  - Patients who received liso-cel as 2L therapy (liso-cel arm) were followed for up to 36 months after randomization in TRANSFORM before enrolling in the LTFU
  - Patients from the SOC arm who crossed over to receive liso-cel as 3L therapy were followed for up to 12 months after infusion in TRANSFORM before enrolling in the LTFU
- Selected AEs considered related to liso-cel and OS were assessed for up to 15 years after liso-cel infusion, or until study withdrawal or death, whichever occurred first
  - Selected AEs included malignancies, neurologic, hematologic, or rheumatologic/autoimmune disorders
  - AEs and OS were assessed at Month 3 after infusion, then every 6 months from years 1 to 5, and annually thereafter

In the combined TRANSFORM + LTFU cohort, 48-month rates for liso-cel were 61.5% for OS and 52.2% for PFS, supporting liso-cel as an effective 2L treatment with curative potential for R/R LBCL

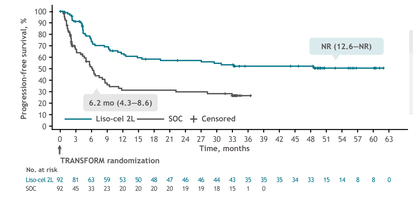
Figure 3. OS in the combined TRANSFORM + LTFU cohort



	Liso-cel 2L (n = 92)
48-month rate (95% CI)	61.5% (51.2–71.7)
Median (95% CI) follow-up	49.5 months (48.9–50.6)

NR, not reached.

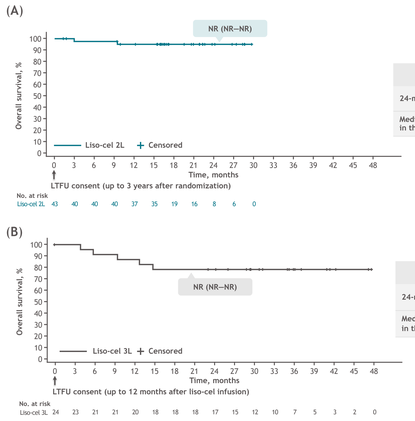
Figure 4. PFS in liso-cel 2L (TRANSFORM + LTFU) and SOC (TRANSFORM only)



	Liso-cel 2L (n = 92)	SOC (n = 92)
48-month rate (95% CI)	52.2% (41.5–62.8)	NA (NA–NA)
Median (95% CI) follow-up	49.4 months (48.7–50.3)	33.2 months (32.9–33.6)

NA, not available.

Figure 5. OS in liso-cel 2L (A) and liso-cel 3L (B) patients in the LTFU



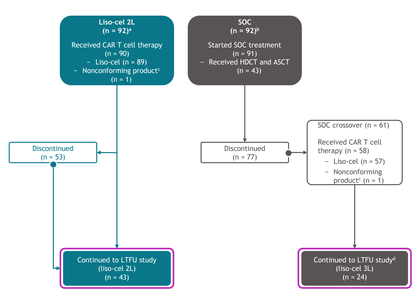
	Liso-cel 2L (liso-cel arm; n = 43)
24-month rate (95% CI)	95.1% (88.4–100.0)
Median (95% CI) follow-up in the LTFU	17.1 months (16.1–21.9)

	Liso-cel 3L (SOC crossover; n = 24)
24-month rate (95% CI)	78.3% (61.4–95.1)
Median (95% CI) follow-up in the LTFU	35.0 months (28.8–37.1)

- For the combined TRANSFORM and LTFU studies:
  - OS was defined as the time from randomization to death from any cause
  - PFS was defined as the time from randomization to disease progression or death from any cause; PFS from TRANSFORM was assessed per IRC and from LTFU per investigators
  - Censoring rules for OS were applied per TRANSFORM and LTFU statistical analysis plans and adapted for PFS
  - Patients in the liso-cel arm and SOC crossover who enrolled in LTFU and who did not have an event were censored for PFS at the start date of subsequent therapy or the last known alive date in LTFU (whichever occurred first) and for OS at the last known alive date in LTFU
- All results are reported descriptively

Results

Figure 2. Patient disposition



[a]Bridging therapy was allowed per protocol; [b]Patients received 3 cycles of SOC platinum-based immunochemotherapy followed by HDCT and ASCT; [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 could be considered appropriate for infusion; [d]Patients in the SOC crossover subgroup received CAR T cell therapy in the 3L setting.

Table 1. Demographics and baseline disease characteristics

	Liso-cel 2L		SOC	
	TRANSFORM (ITT) (n = 92)	LTFU[a] (n = 43)	TRANSFORM (ITT) (n = 92)	LTFU[a] (SOC crossover) (n = 24)
Male, n (%)	44 (48)	19 (44)	61 (66)	13 (54)
Age, y				
Median (range)	60 (20–74)	57 (20–74)	58 (26–75)	58.5 (29–70)
≥ 65, n (%)	36 (39)	13 (30)	25 (27)	7 (29)
Histology, n (%)				
DLBCL NOS	53 (58)	24 (56)	50 (54)	12 (50)
HGBCL with rearrangements in *MYC* and *BCL2*, *BCL6*, or both	22 (24)	5 (12)	21 (23)	5 (21)
PMBCL	8 (9)	6 (14)	9 (10)	4 (17)
tDLBCL from any indolent lymphoma	7 (8)	6 (14)	8 (9)	3 (12.5)
THRBCL	1 (1)	1 (2)	4 (4)	0
FL3B	1 (1)	1 (2)	0	0
LBCL subtype based on cell of origin, n (%)				
GCB	45 (49)	18 (42)	40 (43)	11 (46)
ABC, non-GCB	21 (23)	10 (23)	29 (32)	8 (33)
ECOG PS at screening, n (%)				
0	48 (52)	28 (65)	57 (62)	17 (71)
1	44 (48)	15 (35)	35 (38)	7 (29)
sAAIPI, n (%)				
0 or 1	56 (61)	29 (67)	55 (60)	17 (71)
2 or 3	36 (39)	14 (33)	37 (40)	7 (29)
Prior response status, n (%)				
Refractory[b]	67 (73)	28 (65)	70 (76)	17 (71)
Relapsed[c]	25 (27)	15 (35)	22 (24)	7 (29)

All percentages are rounded to whole numbers except those with ".5%".
[a]At time of randomization to TRANSFORM; [b]Defined as stable disease, PD, PR, or CR with relapse < 3 months after 1L therapy; [c]Defined as CR with relapse on or after 3 months within 12 months after 1L therapy.
ABC, activated B cell; GCB, germinal center B cell; sAAIPI, secondary age-adjusted International Prognostic Index.

- In total, 184 patients were randomized in TRANSFORM (92 per arm; **Figure 2**); key demographics and characteristics at baseline in TRANSFORM are reported in **Table 1**
- The LTFU study enrolled 67 patients who received liso-cel (liso-cel 2L, n = 43; liso-cel 3L [SOC crossover], n = 24)
- For the LTFU study, the median (range) follow-up was 16.9 months (1.3–29.7) for the liso-cel arm and 30.1 months (0–47.6) for the SOC crossover patients; when combined with TRANSFORM, median (range) follow-up was 40.1 months (2.2–61.9) for the liso-cel arm and 33.4 months (0.9–65.0) for the SOC arm (including crossover patients)

Table 2. AEs occurring during LTFU

	Liso-cel 2L (n = 43)	Liso-cel 3L (SOC crossover) (n = 24)
Any AE, n (%)	2 (5)	3 (12.5)
COVID-19	0	1 (4)
Invasive ductal breast carcinoma	0	1 (4)
Cognitive disorder	0	1 (4)
Hypogammaglobulinemia	1 (2)	0
Dyspnea	1 (2)	0
Grade 3/4 AE, n (%)	1 (2)	1 (4)
COVID-19	0	1 (4)
Dyspnea	1 (2)	0
Serious AEs,[a] n (%)	1 (2)	1 (4)
AE leading to death, n (%)	0	0

All percentages are rounded to whole numbers except those with ".5%".
[a]Dyspnea in the liso-cel arm and COVID-19 in the SOC crossover subgroup (n = 1 each).

Table 3. Deaths occurring during LTFU

	Liso-cel 2L (n = 43)	Liso-cel 3L (SOC crossover) (n = 24)
Overall deaths, n (%)	2 (5)	5 (21)
Cause of death, n (%)		
B-cell lymphoma progression[a]	0	4 (17)
Cardiac arrest	0	1 (4)
Mucormycosis	1 (2)	0
SARS-CoV-2 infection	1 (2)	0
Cause of death category, n (%)		
Death from malignant disease under study, or complication due to malignant disease under study	0	5 (21)
Other	2 (5)	0

[a]Includes B-cell lymphoma, lymphoma, and NHL progression.

- Safety results from the LTFU study in the liso-cel arm showed no new signals compared with previous reports from TRANSFORM[1–3] (**Table 2**)
  - AEs of any grade occurred in 2 patients (hypogammaglobulinemia and dyspnea; n = 1 each)
  - No second primary malignancies or serious infections were reported
  - AEs of grade 3 or 4 occurred in 1 patient (dyspnea)
  - No AEs led to death
- Overall, 7 deaths occurred during the LTFU as follows: 2 (5%) in the liso-cel 2L arm and 5 (21%) in the liso-cel 3L (SOC crossover) patients (**Table 3**)

Conclusions

- After a median follow-up of approximately 4 years combining data from the TRANSFORM and LTFU studies, liso-cel continued to demonstrate curative potential with high PFS and OS rates in patients with 2L R/R LBCL
  - Median OS and median PFS were not reached for liso-cel after 4-year follow-up
- The safety profile of liso-cel continued to be manageable with no new safety signals observed during LTFU[1–3,5–8]

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