Measurable Residual Disease by Circulating Tumor DNA in Patients With Third-Line or Later Relapsed or Refractory Follicular Lymphoma Treated With Lisocabtagene Maraleucel in TRANSCEND FL

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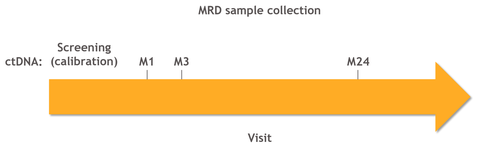
Background

- Lisocabtagene maraleucel (liso-cel), an autologous, CD19-directed CAR T cell product, demonstrated meaningful and durable clinical benefit (ORR, 97%; CR rate, 94%; 36-month PFS, 68%) in patients with third-line or later (3L+) R/R FL in TRANSCEND FL (NCT04245839)[1]
- Circulating tumor DNA (ctDNA) is a minimally invasive method for detecting MRD; MRD negativity (MRD^{neg}) has been associated with durable disease control and longer PFS across various malignancies, including in large B-cell lymphoma after liso-cel treatment[2–5]
- There is limited evidence to date assessing the prognostic value of MRD after CAR T cell therapy in R/R FL[2,6,7]
- We report the prognostic value of ctDNA-based MRD in patients with 3L+ R/R FL treated with liso-cel in TRANSCEND FL, including its association with PFS and its complementarity with PET response

Methods

- The global, phase 2, open-label, single-arm, multicenter TRANSCEND FL study evaluated the efficacy and safety of liso-cel in patients ≥ 18 years of age with histologically confirmed FL[1]
- Tumor-derived phased variants were primarily identified from screening (baseline) plasma or tumor tissue when plasma was insufficient, using the CLARITY assay based on PhasED-Seq technology (Natera, formerly Foresight Diagnostics)[8]
- Posttreatment ctDNA-MRD was assessed at Month (M)1 and M3 after infusion for all patients, and at M24 for ongoing responders (**Figure 1**)
- Of 103 efficacy-evaluable patients with 3L+ FL, 89 (86%) had ctDNA samples, of whom 90% (80/89) had evaluable ctDNA and efficacy data after liso-cel infusion
- MRD positivity (MRD^{pos}) was defined as ctDNA detected at levels above the assay threshold (lower limit of detection of 0.7 parts per million, with sample-specific sensitivity dependent on DNA input)[9]
- Responses, including CR, were assessed by PET

Figure 1. Study design

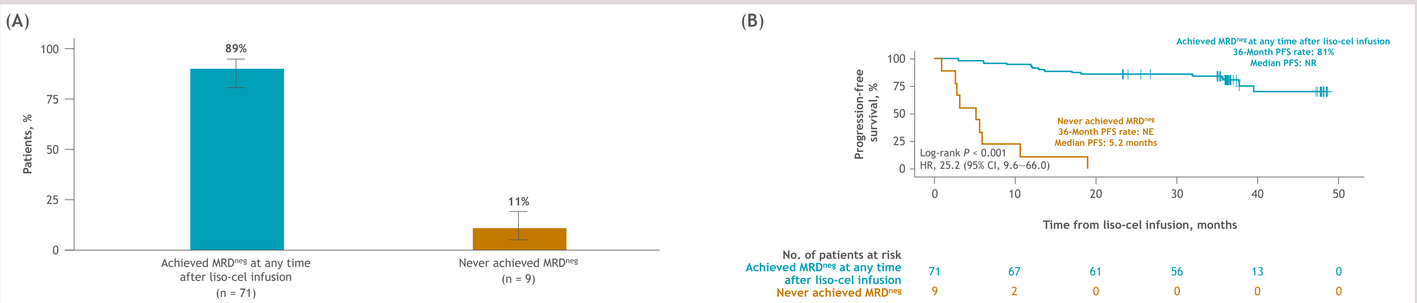


3L+ FL plasma ctDNA samples	N	% of total
Patients with samples tested at ≥ 1 time point[a]	89	100%
Patients with nonevaluable[b] MRD data at screening	9	10%
Patients with evaluable MRD[c] at screening and evaluable efficacy data after infusion	80	90%

[a]All ctDNA patient samples from the efficacy analysis set were tested if patient consent was provided and samples were available; [b]Nonevaluable MRD data: patients with samples that failed calibration using screening plasma ctDNA and/or tumor tissue; [c]MRD evaluable definition: successful calibration of phased variants at screening.

Liso-cel induced deep molecular responses in patients with 3L+ R/R FL, with 89% of patients achieving ctDNA-based MRD^{neg} after treatment (Figure 2A). Achieving MRD^{neg} after liso-cel infusion was significantly associated with longer PFS (Figure 2B)

Figure 2. MRD^{neg} status (A) and PFS by MRD status (B)



NE, not estimable; NR, not reached.

- The majority of patients achieved MRD^{neg}, consistent with deep responses achieved with liso-cel (**Figure 2A**)
  - 89% (71/80) of patients were MRD^{neg} for ≥ 1 time point
  - 11% (9/80) of patients never achieved MRD^{neg}
  - Among patients with a best overall response of CR, 93% (71/76) achieved MRD^{neg} at any time after liso-cel
- Achieving MRD^{neg} at any time after treatment was significantly associated with longer PFS compared with MRD^{pos} (**Figure 2B**)

Results

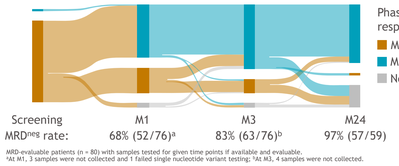
Table 1. Baseline characteristics of the TRANSCEND FL efficacy analysis set and MRD-evaluable patients

	3L+ FL efficacy analysis set (n = 103)[a]	3L+ FL with MRD evaluable (n = 80)[b]
Median (range) age, y	62 (23—80)	62 (23—80)
POD24 after initial immunochemotherapy, n (%)	44 (43)	33 (41)
Met mGELF criteria at most recent relapse, n (%)	54 (52)	40 (50)
Bulky disease, n (%)	31 (30)	23 (29)
FLIPI, n (%)		
Low risk (0—1)/intermediate risk (2)	11 (11)/34 (33)	8 (10)/24 (30)
High risk (3—5)	58 (56)	48 (60)
Ann Arbor stage, n (%)		
Stage I/II	12 (12)	7 (9)
Stage III/IV	38 (37)/53 (52)	30 (38)/43 (54)
FL grade, n (%)		
Grade 1/2	10 (10)/68 (66)	9 (11)/51 (64)
Grade 3A	24 (23)	20 (25)
Unknown	1 (1)	0
Median (range) no. of prior lines of systemic therapy	3 (2—10)	3 (2—10)
Prior treatment, n (%)		
HSCT	31 (30)	25 (31)
Rituximab and lenalidomide	20 (19)	15 (19)
Bendamustine	61 (59)	47 (59)
Double refractory (anti-CD20 and alkylator), n (%)	57 (55)	42 (52.5)
Received bridging therapy, n (%)	41 (40)	32 (40)

All percentages are rounded to whole numbers except those with ".5%".
[a]All patients in the FL cohort of TRANSCEND FL who received liso-cel and had positive disease present before liso-cel administration; [b]Including patients with successful calibration of phased variants at screening.
FLIPI, Follicular Lymphoma International Prognostic Index; HSCT, hematopoietic stem cell transplantation; mGELF, modified Groupe d'Etude des Lymphomes Folliculaires; POD24, progression of disease ≤ 24 months.

- Baseline demographic and disease characteristics for patients in this analysis set were consistent with the overall population in TRANSCEND FL (**Table 1**)
- Baseline ctDNA levels were significantly correlated with FLIPI (P = 0.018), Ann Arbor stage (P = 0.027), and FL grade indices (P = 0.043) in patients with 3L+ FL
- No association was found between POD24 and baseline ctDNA levels (with vs without POD24, P = 0.72)

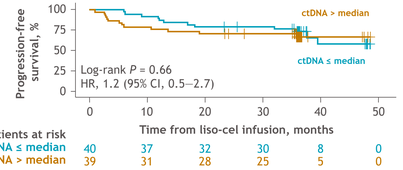
Figure 3. Sankey diagram showing MRD status over time



MRD-evaluable patients (n = 80) with samples tested for given time points if available and evaluable.
[a]At M1, 3 samples were not collected and 1 failed single nucleotide variant testing; [b]At M3, 4 samples were not collected.

- Most patients achieved MRD^{neg} at M1 (similar to the majority of patients achieving a response at M1)
- Approximately half of the patients with MRD^{pos} CR at M1 converted to MRD^{neg} CR at M3 (11/20)
- Patients with partial response, stable disease (SD), or PD (n = 4) never achieved MRD^{neg}
- At M24, 97% (57/59) of patients in ongoing response remained MRD^{neg} (**Figure 3**)

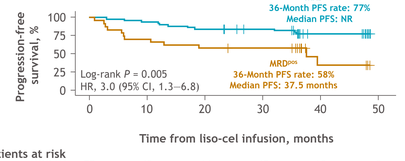
Figure 4. PFS by baseline ctDNA level



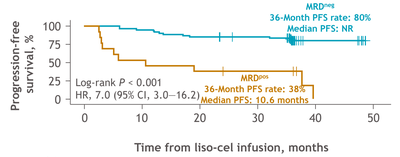
- Patients derived comparable PFS benefit from liso-cel regardless of whether ctDNA levels were below or above the median (**Figure 4**)
  - Further separating the baseline ctDNA in quartiles did not show any significant association with PFS (data not shown)

Figure 5. Achieving MRD^{neg} at (A) M1 or (B) M3 was associated with longer PFS

(A) PFS by MRD status at M1 after liso-cel infusion

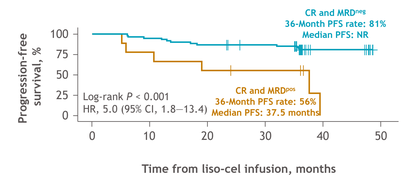


(B) PFS by MRD status at M3 after liso-cel infusion



- MRD status at M3 showed a stronger correlation with PFS than at M1, with M36 PFS rates of 80% for MRD^{neg} at M3 (n = 63) versus 38% for MRD^{pos} at M3 (n = 13) (**Figure 5**)

Figure 6. PFS in patients with CR at M3 by MRD status



- PFS was longer for patients with both CR and MRD^{neg} at M3 (n = 62) compared with patients who achieved CR and were MRD^{pos} (n = 9), with M36 PFS rates of 81% versus 56%, respectively, suggesting that adding MRD to PET at M3 may provide additional prognostic information for long-term outcomes (**Figure 6**)

Conclusions

- Liso-cel induced deep molecular responses in 3L+ R/R FL, with most patients (89%) achieving MRD^{neg} after infusion
- PFS benefits were comparable regardless of whether ctDNA levels were below or above the median at the time of treatment, highlighting the therapeutic benefit of liso-cel
- MRD^{neg} after infusion was strongly associated with longer PFS; 80% of patients who were MRD^{neg} at M3 were still in response at M36
- These findings support ctDNA-based MRD as a potential prognostic biomarker in FL and further underscore liso-cel as an effective treatment option that delivers durable clinical benefits with deep molecular responses in patients with 3L+ R/R FL

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