Impact of bridging therapy on lisocabtagene maraleucel as second-line or later treatment of relapsed or refractory follicular lymphoma in the phase 2, open-label TRANSCEND FL study

Saurabh Dahiya, MD, MBBS,[1] Alexandre V. Hirayama, MD,[2] Stephen J. Schuster, MD,[3] Juan Luis Reguera Ortega, MD,[4] Franck Morschhauser, MD, PhD,[5] Alejandro Martin Garcia-Sancho, MD, PhD,[6] John Kuruvilla, MD, FRCPC,[7] Koji Izutsu, MD, PhD,[8] Anna Maria Barbui, MD,[9] Peter Borchmann, MD,[10] Stephan Mielke, MD,[11] Guillaume Cartron, MD, PhD,[12] Hervé Ghesquieres, MD, PhD,[13] Hideki Goto, MD, PhD,[14] Indumathy Varadarajan, MD, MBBS,[15] Manali Kamdar, MD,[16] Iris Isufi, MD,[17] Thalia Farazi, MD, PhD,[18] Grace Shih Hui Kao, MD,[19] Min Vedal, PhD,[20] Rashmi Bhatnagar, MSc,[21] Rina Nishii, PhD,[22] Jessica Papuga, PhD,[20] M. Lia Palomba, MD[23]

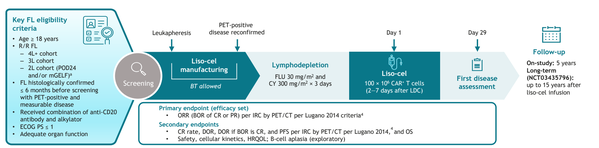
[1]Stanford University School of Medicine, Stanford, CA, USA; [2]Fred Hutchinson Cancer Center, Seattle, WA, USA; [3]Lymphoma Program, Abramson Cancer Center, Philadelphia, PA, USA; [4]Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS) / CSIC, Universidad de Sevilla, Seville, Spain; [5]Centre Hospitalier Universitaire de Lille, Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France; [6]Hospital Universitario de Salamanca, IBSAL, CIBERONC, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain; [7]Princess Margaret Cancer Centre, Toronto, ON, Canada; [8]National Cancer Center Hospital, Tokyo, Japan; [9]Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; [10]Universität zu Köln, Köln, Germany; [11]Karolinska Institutet and University Hospital; Karolinska Comprehensive Cancer Center, Karolinska ATMP Center, Stockholm, Sweden; [12]Montpellier University Hospital Center, UMR CNRS 5535, Montpellier, France; [13]Hôpital Lyon Sud, Lyon, France; [14]Hokkaido University Hospital, Sapporo, Japan; [15]University of Virginia, Charlottesville, VA, USA; [16]University of Colorado Cancer Center, Aurora, CO, USA; [17]Yale University School of Medicine, New Haven, CT, USA; [18]Bristol Myers Squibb, Brisbane, CA, USA; [19]Bristol Myers Squibb, Cambridge, MA, USA; [20]Bristol Myers Squibb, Boudry, Switzerland; [21]Syneos Health, Haryana, India; [22]Bristol Myers Squibb, Princeton, NJ, USA; [23]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Background

- Bridging therapy (BT) is often important for anticancer disease control during CAR T cell therapy manufacture for patients with R/R FL and high-risk disease/high tumor burden, but limited data exist on the impact of BT and outpatient administration on clinical outcomes
- Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, 4-1BB CAR T cell product
- In the primary analysis of the open-label, single-arm, global phase 2 TRANSCEND FL study (NCT04245839), liso-cel treatment in patients with second-line (2L) or later (2L+) R/R FL, including high-risk 2L FL, achieved high response rates and a safety profile consistent with the established safety profile of liso-cel in large B-cell lymphoma, with no new safety signals[1–3]
- Here, we present results from TRANSCEND FL in subgroups of patients with 2L+ R/R FL by BT status and for the subset of outpatients

Methods

Figure 1. TRANSCEND FL study design



ClinicalTrials.gov identifier: NCT04245839.
ªPOD24 was defined as progression within 24 months of diagnosis after treatment with an anti-CD20 antibody and an alkylating agent within the first 6 months of initial FL diagnosis. Patients who did not meet criteria of POD24 had to meet ≥ 1 criterion of the mGELF criteria: symptoms attributable to FL, threatened end-organ function, or cytopenia secondary to lymphoma or bulky disease [single mass > 7 cm, or 3 or more masses > 3 cm]; splenomegaly; or histologic progression over ≤ 6 months).
4L+, fourth line or later; BOR, best overall response; CY, cyclophosphamide; DOR, duration of response; FLU, fludarabine; HRQOL, health-related quality of life; IRC, independent review committee; LDC, lymphodepleting chemotherapy; mGELF, modified Groupe d'Etude des Lymphomes Folliculaires; POD24, progression of disease ≤ 24 months.

- Eligible patients had R/R FL, including 2L patients who all had POD24 from diagnosis (ie, progressed ≤ 24 months of diagnosis and were treated with anti-CD20 antibody and alkylator within 6 months of initial FL diagnosis) and/or met mGELF criteria (**Figure 1**)
- Optional BT was allowed per investigator discretion during liso-cel manufacturing, including systemic therapy, radiation therapy, or both
- To be efficacy evaluable, reconfirmation of PET-positive FL after BT was required before LDC
- PET/CT-based response assessments were performed at baseline (after end of BT and ≤ 7–14 days before LDC), from Day 29 after liso-cel infusion, and continued for up to 60 months after liso-cel infusion

Results

Patients

Table 1. Analysis sets (2L+ FL)

	BT	No BT	Total, N
Leukapheresed set, n (%)	54 (39)	85 (61)	139
Liso-cel–treated set (safety set), n (%)	49 (38)	81 (62)	130
Efficacy-evaluable set (efficacy set), n (%)	45 (36)	79 (64)	124

- For each analysis set, percentages were calculated based on the total sample size for the respective set (**Table 1**)
- BT was used in 49 (38%; 3L+, n = 44 [90%]; 2L, n = 5 [10%]) liso-cel–treated patients
- Nine leukapheresed patients were not treated with liso-cel (BT, n = 5; No BT, n = 4)
  - Five patients received nonconforming product (BT, n = 4; No BT, n = 1)
  - Three patients no longer met eligibility criteria
    - One patient in the BT subgroup achieved CR after BT per investigator assessment and was not infused
    - One patient in the No BT subgroup had history of transformed FL and 1 patient had PET-negative disease at pretreatment assessment
  - One patient had an AE of acute respiratory failure hypoxic (No BT subgroup)
- Six liso-cel–treated patients were not efficacy evaluable (BT, n = 4; No BT, n = 2)
  - Four patients did not have confirmed PET-positive disease at baseline per IRC (BT, n = 2; No BT, n = 2) and 2 had no repeated PET after BT
- Median on-study follow-up was 18.9 months (range, 0.3–28.2)

Table 2. Patient demographics and baseline characteristics (2L+ FL; leukapheresed set)

	BT (n = 54)	No BT (n = 85)
Median (range) age, y	62.0 (23–78)	59.0 (34–80)
Male, n (%)	38 (70)	52 (61)
FL grade at screening, n (%)		
1 or 2	38 (70)	66 (78)
3a	16 (30)	18 (21)
Ann Arbor stage at screening, n (%)		
Stage I/II	3 (6)	15 (18)
Stage III/IV	51 (94)	70 (82)
FL International Prognostic Index at screening, n (%)		
Low risk (0–1) / intermediate risk (2)	4 (7) / 8 (15)	21 (25) / 32 (38)
High risk (3–5)	42 (78)	32 (38)
SPD ≥ 50 cm² at screening per investigator, n (%)	22 (41)	10 (12)ª
SPD ≥ 50 cm² before LDC per IRC, n (%)	14 (26)	12 (14)
LDH > ULN before LDC, n (%)	28 (52)	30 (35)
Met mGELF criteria at most recent relapse, n (%)	39 (72)	41 (48)
Symptoms attributable to FL	9 (17)	13 (15)
Threatened end-organ function/cytopenia secondary to lymphoma/bulky disease	18 (33)	15 (18)
Splenomegaly	4 (7)	1 (1)
Steady progression over ≥ 6 months	8 (15)	12 (14)
Prior lines of therapy, n (%)		
1	5 (9)	18 (21)
2	17 (31)	32 (38)
3	14 (26)	16 (19)
≥ 4	18 (33)	19 (22)
Refractory to last systemic therapy,ª n (%)	42 (78)	48 (56)
Double refractory (anti-CD20 and alkylator),ª n (%)	42 (78)	44 (52)
POD24 from diagnosis, n (%)	29 (54)	36 (42)
POD24 from initial immunochemotherapy, n (%)	35 (65)	44 (52)

ªDenominator is N – (N: 1 patient did not have SPD data at screening; 1 Defined as progression while on the last line of therapy or ≤ 6 months of completing the last line of therapy; 1Patients whose disease did not respond or progressed during or up to 6 months after completion of the following: 1) combination treatment with anti-CD20 antibody and alkylating agent; or 2) anti-CD20 maintenance therapy.
SPD, sum of the product of perpendicular diameters.

Liso-cel demonstrated similar efficacy and safety with low rates of severe CRS, NE, and infections in patients with R/R FL regardless of BT status

Figure 2. ORR and CR rates per IRC by BT status (2L+ FL; efficacy set)

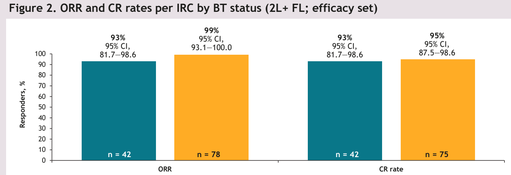
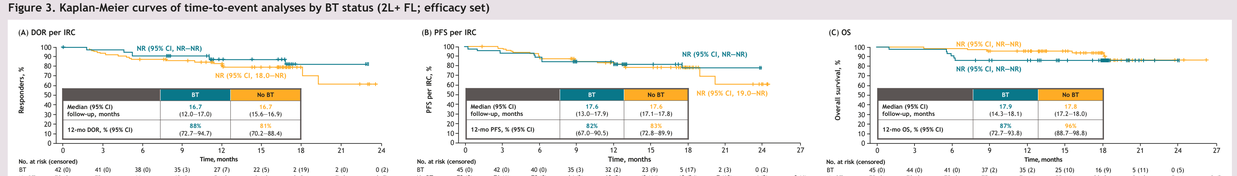


Figure 3. Kaplan-Meier curves of time-to-event analyses by BT status (2L+ FL; efficacy set)



NA, not available; NR, not reached.

- Patients in the BT subgroup had higher disease burden and a higher proportion of patients with high-risk clinical characteristics at baseline compared with the No BT subgroup (**Table 2**; purple boxes)

Table 3. Types of BT (2L+ FL)

	Liso-cel–treated set (N = 130)
Received any BT,ª n (%)	49 (38)
Systemic BT regimens used,[b] n (%)	44 (34)
Anti-CD20 antibody-containing regimens[c]	25 (53)
Regimens without anti-CD20 antibody[d]	19 (40)
Anti-CD20 antibody (single regimen)	0
Corticosteroid-containing regimens[e]	19 (43)
PI3Ki-containing regimens[f]	7 (14)
Bendamustine-containing regimens	4 (9)
Radiation therapy,[g] n (%)	5 (4)

ªCould have included systemic therapy, radiation therapy, or both; [b]Data are reported among the 44 liso-cel–treated patients who received systemic therapy using 47 different regimens; 3 liso-cel–treated patients had received 2 different combination therapies during the bridging period, accounting for the greater relative number of regimens to recipients; [c]R-GemOx (n = 6); B + R, R + len, and R-CVP (n = 3 each); R-CHOP (n = 2); B + O, O-CHPni, O-CHOP, PI3Ki + O, B-DHAOx, R-EPOH, R-GDP, R-GemOx (n = 1 each); [d]B, CVP, cyclophosphamide + P, and VDC (n = 2 each); B + P, carboplatin + doxorubicin, CHOP, DHAOx, D-GemOx, GDP, GemOx, len, len + GemOx, P-ETIx, and Pol-CH (n = 1); [e]No patients received corticosteroids alone as BT; [f]four (8%) patients received PI3Ki as a single regimen, 2 (4%) received PI3Ki plus anti-CD20 antibody, and 1 (2%) received PI3Ki plus chemotherapy; [g]Data are reported for liso-cel–treated patients who received only radiation as BT. No liso-cel–treated patients received both radiation and chemotherapy as BT.
B, bendamustine; BTKi, Bruton tyrosine kinase inhibitor; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHPni, cyclophosphamide, doxorubicin, and polatuzumab; CVP, cyclophosphamide, vincristine, and prednisone; D, dexamethasone; DHAOx, dexamethasone, cytarabine, and oxaliplatin; EPOH, etoposide, prednisone, vincristine, and doxorubicin; GDP, gemcitabine, dexamethasone, and cisplatin; GemOx, gemcitabine and oxaliplatin; len, lenalidomide; O, obinutuzumab; P, prednisone; PI3Ki, phosphoinositide 3-kinase inhibitor; Pol-CH, polatuzumab, cyclophosphamide, and doxorubicin; R, rituximab; VDC, vincristine, doxorubicin, and cyclophosphamide.

- Among liso-cel–treated patients who received systemic therapy for bridging (n = 44), most received anti-CD20 antibody-containing regimens (25 [53%]), primarily rituximab plus gemcitabine and oxaliplatin (6 [14%]) (**Table 3**)

Table 4. Manufacturing summary (2L+ FL; leukapheresed set)

Median (IQR) time to event, days	BT (n = 54)	No BT (n = 85)
Leukapheresis to liso-cel availability[a]	30 (26–32)	29 (25–31)
Liso-cel availability[a] to infusion	20 (14–30)	20 (14–26)
Leukapheresis to the start of BT	6 (2–15)	—
Leukapheresis to the end of BT	17.5 (10–31)	—
Manufacturing failure, n (%)[b]	4 (7)	2 (2)

[a]Availability is defined as the date the manufacturer determined the product was ready (occurs before shipping to clinical sites); [b]Manufacturing failure rate was defined as (number of patients for whom liso-cel product [confirming at time of release] could not be manufactured) divided by (number of patients who had leukapheresis and manufacturing information available) multiplied by 100. Rejected lots were excluded from the calculation.

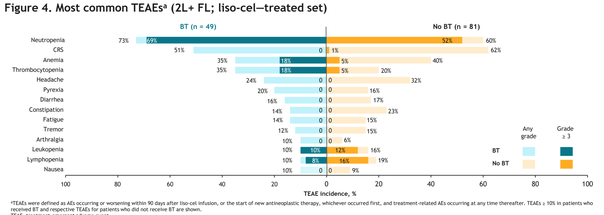
- There were no differences in BT rates across study regions (Europe, 39%; United States/Canada, 37%; Japan, 42%)
- In the total population, BT versus No BT had no impact on time to liso-cel infusion after product availability (20 days across groups) (**Table 4**)
  - Median (IQR) duration of BT based on start/end dates of individual agents was 8 (22) days
  - Median (IQR) time from BT to liso-cel infusion was 34.5 (19) days

Efficacy

- ORR and CR rates were high and consistent across subgroups, with all responders in the BT subgroup achieving CR (**Figure 2**)
- Among 49 liso-cel–treated patients in the BT subgroup, all 5 patients who received radiation therapy alone as BT (ie, no systemic therapy) were efficacy evaluable and achieved CR with ongoing response at the data cutoff
- Median DOR, PFS, and OS were NR in both subgroups (**Figure 3**)
- Twelve-month DOR and PFS rates were similar between subgroups, but 12-month OS was numerically higher in the No BT subgroup, which could be due to the higher disease burden in the BT subgroup

Safety

Figure 4. Most common TEAEsª (2L+ FL; liso-cel–treated set)



ªTEAEs were defined as AEs occurring or worsening within 90 days after liso-cel infusion, or the start of new antineoplastic therapy, whichever occurred first, and treatment-related AEs occurring at any time thereafter. TEAEs ≥ 10% in patients who received BT and respective TEAEs for patients who did not receive BT are shown.
TEAE, treatment-emergent adverse event.

- Incidence of any-grade and grade ≥ 3 TEAEs was consistent with primary analysis and generally similar across subgroups, but with numerically higher neutropenia, anemia, and thrombocytopenia in the BT subgroup (**Figure 4**)
- No grade 4–5 CRS in either subgroup; no grade 3 CRS in the BT subgroup and 1 grade 3 CRS in the No BT subgroup (**Figure 5**)
- No grade 4–5 NEs in either subgroup; 3 (6.1%) grade 3 NEs in the BT subgroup that resolved, and no grade ≥ 3 NEs in the No BT subgroup
- Median times to onset and resolution of CRS and NEs were similar between subgroups

Figure 6. Treatment for CRS and NEs (2L+ FL; liso-cel–treated set)

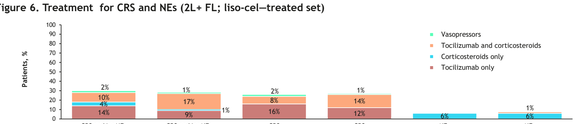
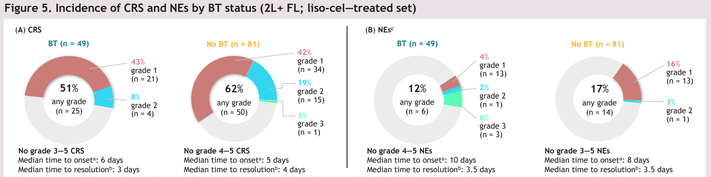


Figure 5. Incidence of CRS and NEs by BT status (2L+ FL; liso-cel–treated set)



ªTime to onset was calculated from liso-cel infusion to the first onset of a CRS event or NE; ᵇTime to resolution of CRS was defined when the last CRS event or NE of the first episode ends; ᶜNEs were defined as investigator-identified neurological AEs related to liso-cel and graded per the NCI CTCAE, version 5.0.
CRS, cytokine release syndrome; NE, neurological event.

- Use of tocilizumab and/or corticosteroids to treat CRS/NEs was low and similar between subgroups (**Figure 6**)

Table 5. Prolonged cytopenia and other AESIs (2L+ FL; liso-cel–treated set)

	BT (n = 49)	No BT (n = 81)
Prolonged cytopenia (grade ≥ 3 at Day 29), n (%)	18 (37)	11 (14)
Recovery to grade ≤ 2 neutropenia at Day 90, n/Nª (%)	10/12 (83)	8/8 (100)
Recovery to grade ≤ 2 anemia at Day 90, n/Nª (%)	5/6 (83)	NAᵇ
Recovery to grade ≤ 2 thrombocytopenia at Day 90, n/Nª (%)	10/15 (67)	1/4 (25)
Other AESIs, n (%)		
Grade ≥ 3 infections	1 (2)	6 (7)
Macrophage activation syndrome	1 (2)	0
Second primary malignancyᶜ	1 (2)	3 (4)

ªn/N represents number of patients with cytopenia recovered to grade ≤ 2 by Day 90 divided by number of patients with cytopenia results at the Day 29 visit; ᵇThere were no patients with anemia at the Day 29 visit; ᶜCould occur within or beyond the 90-day treatment-emergent period.
AESI, adverse event of special interest.

- Prolonged cytopenia (grade ≥ 3 cytopenias based on laboratory values at Day 29) was numerically higher in the BT subgroup compared with the No BT subgroup; most patients in both subgroups recovered to grade ≤ 2 by Day 90 (**Table 5**)

Cellular kinetics and persistence

Table 6. Liso-cel cellular kinetics by PCR

Median (IQR) liso-cel cellular kinetic parameters by PCR	BT (n = 49)ª	No BT (n = 79)ª
C_{max}, copies/µg	39,125 (11,529–121,758)	44,655 (15,808–100,239)
t_{max}, days	10.0 (9.0–12.0)	10.0 (7.0–10.0)
$AUC_{0–28d}$, days × copies/µg	265,209 (82,991–963,229)	260,274 (107,888–638,586)

ªAssessed in BT and No BT 2L+ FL liso-cel–treated sets with evaluable cellular kinetic parameters. Any quantifiable values obtained before liso-cel infusion were excluded.
$AUC_{0–28d}$, area under the curve for liso-cel transgene levels from 0 to 28 days after infusion; C_{max}, maximum transgene levels; LLOQ, lower limit of detection; t_{max}, time from liso-cel infusion to maximum transgene levels.

- Liso-cel peak transgene levels and time to peak expansion were similar between subgroups (**Table 6**)

Table 7. AESIs and hospitalizations in outpatients

	Outpatients (n = 15)
CRS	
Any grade, n (%)	6 (40)
Grade ≥ 3, n (%)	0
Median (range) time to onset, days	4 (3–6)
Median (range) time to resolution, days	4.5 (1–8)
NE	
Any grade, n (%)	2 (13)
Grade ≥ 3, n (%)	0
Median (range) time to onset, days	7 (6–8)
Median (range) time to resolution, days	3 (2–4)
Patients hospitalized, n (%)	7 (47)
Median (range) time to initial hospitalization in outpatients, days	7 (4–16)
Hospitalization within 4 days of infusion, n (%)	2 (29)
Median (range) duration of initial hospitalization, days	5 (3–8)

- Of 15 outpatients, 6 experienced CRS and 2 experienced NEs that were grade 1/2 events only (**Table 7**)
  - Seven outpatients were hospitalized, but none were admitted to the ICU

Conclusions

- Liso-cel treatment showed similar efficacy and safety in the BT and No BT subgroups in patients with 2L+ R/R FL
- Clinically meaningful activity was achieved in both subgroups and was generally consistent with the previously presented data in the overall population[1,2]
- The safety profile was consistent with the established liso-cel safety profile, irrespective of BT status
- Cellular kinetic parameters were similar between subgroups
- Results suggest BT may mitigate potential negative impacts of high-risk disease characteristics, including worse outcomes and increased risk of CAR T cell–associated AEs, allowing patients with high tumor burden and poor prognostic markers to achieve optimal benefit from liso-cel treatment
- Safety in the outpatient setting was consistent with the overall population and with liso-cel in OUTREACH (NCT03744676; large B-cell lymphoma outpatient setting), with no new safety signals

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