Lisocabtagene maraleucel in R/R MCL: primary analysis results from the MCL cohort of the single-arm, multicenter, phase 1 seamless design TRANSCEND NHL 001 study

MCL-096

M. Lia Palomba,[1] Tanya Siddiqi,[2] Leo I. Gordon,[3] Manali Kamdar,[4] Matthew Lunning,[5] Alexandre V. Hirayama,[6] Jeremy S. Abramson,[7] Jon Arnason,[8] Nilanjan Ghosh,[9] Amitkumar Mehta,[10] Charalambos Andreadis,[11] Scott R. Solomon,[12] Ana Kostic,[13] Christine Dehner,[13]* Ricardo Espinola,[14] Lily Peng,[13] Ken Ogasawara,[15] Amy Chattin,[13] Michael Wang[16]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]City of Hope National Medical Center, Duarte, CA, USA; [3]Northwestern University, Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; [4]University of Colorado Cancer Center, Aurora, CO, USA; [5]University of Nebraska Medical Center, Omaha, NE, USA; [6]Fred Hutchinson Cancer Center, Seattle, WA, USA; [7]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [8]Beth Israel Deaconess Medical Center, Boston, MA, USA; [9]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [10]University of Alabama at Birmingham, Birmingham, AL, USA; [11]University of California, San Francisco, San Francisco, CA, USA; [12]Northside Hospital Cancer Institute, Atlanta, GA, USA; [13]Bristol Myers Squibb, Seattle, WA, USA; [14]Bristol Myers Squibb, San Diego, CA, USA; [15]Bristol Myers Squibb, Princeton, NJ, USA; [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

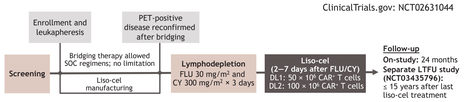
*Affiliation at the time the study was conducted

Introduction

- Patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) after ≥ 2 prior lines of therapy, including a Bruton tyrosine kinase inhibitor (BTKi), alkylator, and anti-CD20 monoclonal antibody, have a poor prognosis[1]
- 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 present the primary analysis results from the MCL cohort of the TRANSCEND NHL 001 (NCT02631044) study with a median (range) on-study follow-up of 16.1 months (0.4–60.5)

Methods

Figure 1. TRANSCEND NHL 001 study design: MCL cohort



Key eligibility criteria for MCL cohort

- Age ≥ 18 years
- PET-positive MCL with confirmed tissue diagnosis[a]
- ≥ 2 lines of therapy, including BTKi, alkylator, and CD20-targeted agent[b]
- ECOG PS 0–1[c]
- Secondary CNS lymphoma or prior autologous or allogeneic HSCT allowed
- Adequate bone marrow, organ, and cardiac function

Primary endpoint

- Safety
- ORR by IRC (Lugano 2014 criteria)

Secondary endpoints

- CR rate (key), DOR, PFS, OS
- Cellular kinetics
- Hospital resource utilization, HRQOL

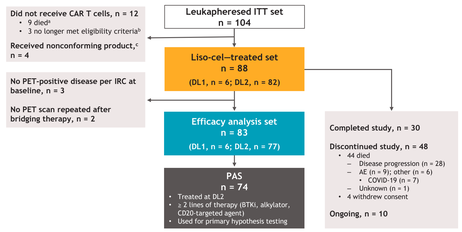
[a]Diagnosis confirmed with cyclin D1 expression or evidence of t(11;14) by cytogenetics, FISH, or PCR; [b]The original protocol eligibility criteria required ≥ 1 line of therapy, including a CD20-targeted agent, and was later amended to require ≥ 2 prior lines of therapy, including a BTKi, alkylating agent, and CD20-targeted agent; [c]The original protocol allowed enrollment of patients with an ECOG PS of 2 but was later amended to only allow enrollment of patients with an ECOG PS of 0–1.

CNS, central nervous system; CR, complete response; CY, cyclophosphamide; DL, dose level; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; FLU, fludarabine; HRQOL, health-related quality of life; HSCT, hematopoietic stem cell transplantation; IRC, independent review committee; LTFU, long-term follow-up; ORR, objective response rate; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival; SOC, standard of care.

- In the MCL cohort (**Figure 1**), primary and key secondary efficacy hypotheses were tested hierarchically in the primary analysis set (PAS) in the following order: null hypothesis (H_0): ORR ≤ 40%, H_0: CR rate ≤ 18%, 1-sided *P* value

Results

Figure 2. Patient disposition and analysis sets

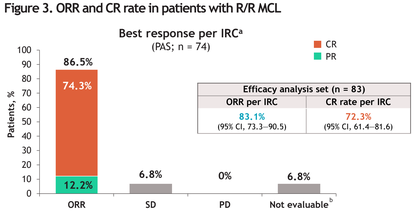


[a]Seven patients died because of disease progression, 1 because of an AE, and 1 because of other reasons (sepsis and pneumonia); [b]One patient was ineligible due to second primary malignancy before LDC and 2 patients remained in ongoing CR after receipt of bridging therapy; [c]Defined as any product wherein one of the CDR 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; LDC, lymphodepleting chemotherapy; PET, positron emission tomography.

Liso-cel treatment resulted in high, durable ORR and CR rate and was well tolerated with low rates of grade ≥ 3 cytokine release syndrome (CRS) and neurological events (NE), thus representing a potential new treatment option for patients with high-risk, aggressive R/R MCL

Figure 3. ORR and CR rate in patients with R/R MCL



[a]Best disease response per IRC by Lugano 2014 criteria from the time of liso-cel infusion until disease progression, end of study, start of another anticancer therapy, or HSCT; [b]No postbaseline scans were submitted to IRC for evaluation.

CI, confidence interval.

Figure 4. ORR per IRC by prespecified subgroups (efficacy analysis set)

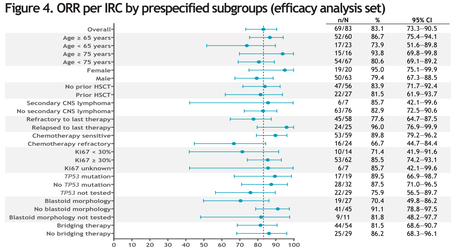
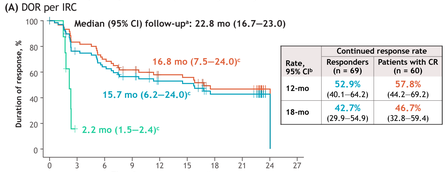


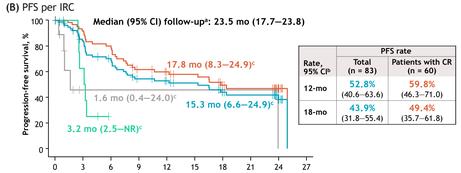
Figure 5. DOR, PFS, and OS (efficacy analysis set)

(A) DOR per IRC



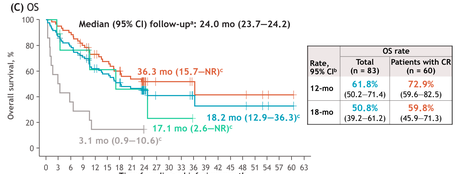
Rate, 95% CI[b]	Continued response rate	
	Responders (n = 69)	Patients with CR (n = 60)
12-mo	52.9% (40.1–64.2)	57.8% (44.2–69.2)
18-mo	42.7% (29.9–54.9)	46.7% (32.8–59.4)

(B) PFS per IRC



Rate, 95% CI[b]	PFS rate	
	Total (n = 83)	Patients with CR (n = 60)
12-mo	52.8% (40.6–63.6)	59.8% (46.3–71.0)
18-mo	43.9% (31.8–55.4)	49.4% (35.7–61.8)

(C) OS



Rate, 95% CI[b]	OS rate	
	Total (n = 83)	Patients with CR (n = 60)
12-mo	61.8% (50.2–71.4)	72.9% (59.6–82.5)
18-mo	50.8% (39.2–61.2)	59.8% (45.9–71.3)

[a]Reverse Kaplan-Meier method was used to obtain median follow-up and its 95% CI; [b]Kaplan-Meier method was used to obtain 2-sided 95% CI intervals; [c]Values represent median (95% CI). NR, not reached.

Table 2. Incidence of CRS and NEs

Patients with CRS and NEs	Liso-cel—treated set (n = 88)
CRS,[a] n (%)	
Any grade	54 (61)
Grade 1/2	53 (60)
Grade 3	0
Grade 4	1 (1)
Grade 5	0
Median (range) time to onset, days	4.0 (1–10)
Median (range) time to resolution, days	4.0 (1–14)
NEs,[b] n (%)	
Any grade	27 (31)
Grade 1/2	19 (22)
Grade 3	7 (8)
Grade 4	1 (1)
Grade 5	0
Median (range) time to onset, days	8.0 (1–25)
Median (range) time to resolution, days	5.0 (1–45)

[a]CRS was graded based on the Lee 2014 criteria; [b]NEs were defined as investigator-identified neurological AEs related to liso-cel.

Table 1. Demographics and baseline characteristics

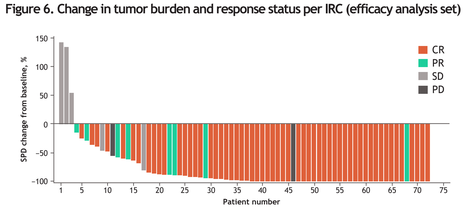
	Liso-cel—treated set (n = 88)
Median (range) age, y	68.5 (36–86)
≥ 65 y, n (%)	64 (73)
≥ 75 y, n (%)	18 (20)
Median (range) prior lines of systemic therapy	3 (1–11)
≥ 5 prior lines of systemic therapy, n (%)	26 (30)
Prior autologous or allogeneic HSCT, n (%)	29 (33)
Prior BTKi, n (%)	83 (94)
Prior ibrutinib	65 (74)
Refractory disease, n (%)[a]	61 (69)
Refractory to BTKi, n (%)[b]	47 (53)
Ki67 proliferation fraction ≥ 30%, n (%)	66 (75)
TP53 mutation, n (%)	20 (23)
Blastoid morphology, n (%)	27 (31)
LDH before LDC ≥ 500 U/L, n (%)	10 (11)
SPD before LDC ≥ 50 cm^2, n (%)[c]	7 (9)
Secondary CNS lymphoma at liso-cel infusion, n (%)	7 (8)
Received bridging therapy, n (%)	58 (66)

[a]Best response of PR, SD, or PD to last systemic treatment with curative intent or HSCT; [b]Any response to BTKi less than PR; [c]Percentages are based on number of patients with nonmissing results.

LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease; SPD, sum of the product of perpendicular diameters; TP53, tumor protein 53.

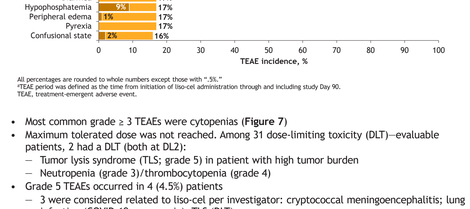
- Among the 88 liso-cel—treated patients (**Figure 2**), many had high-risk disease features, including 75% with Ki67 proliferation fraction ≥ 30%, 23% with *TP53* mutation, 31% with blastoid morphology, and 8% with secondary CNS lymphoma (**Table 1**)
- Primary (ORR) and key secondary (CR rate) efficacy endpoints were met based on the PAS (n = 74) (**Figure 3**)
  - ORR: 86.5% (95% CI, 76.5–93.3); CR rate: 74.3% (95% CI, 62.8–83.8); *P* < 0.0001 for both
- Consistently high ORR and CR rate were observed in the efficacy analysis set (n = 83)
  - Median (range) time to first CR or PR was 0.95 months (0.7–3.0)
- ORR was consistent among prespecified subgroups of patients in the efficacy analysis set, including patients with high-risk disease features (**Figure 4**)
- Responses were durable (**Figure 5**)
- As most patients were enrolled during the COVID-19 pandemic, DOR, PFS, and OS were also analyzed censoring for the 6 patients in ongoing CR who died because of COVID-19
  - Median DOR was 17.5 months (95% CI, 7.6–24.0), median PFS was 17.8 months (95% CI, 7.6–24.9), and median OS was 24.8 months (95% CI, 15.7–NR) when patients in ongoing response who died because of COVID-19 were censored
- Most patients experienced a reduction in lymphadenopathy (**Figure 6**)

Figure 6. Change in tumor burden and response status per IRC (efficacy analysis set)



Lymphadenopathy was measured by the maximum change from baseline in SPD per IRC assessment for all patients in the efficacy analysis set with baseline and ≥ 1 postbaseline target lesion measurement. Eleven patients were excluded due to lack of measurable target lesions at baseline (n = 5), or missing scans postbaseline (n = 6).

Figure 7. Treatment-emergent adverse events[a]



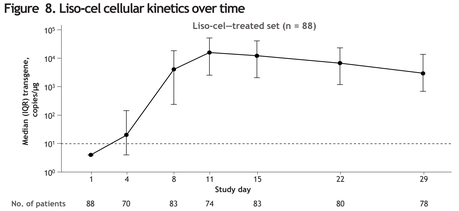
All percentages are rounded to whole numbers except those with ".5%."

[a]TEAE period was defined as the time from initiation of liso-cel administration through and including study Day 90.

TEAE, treatment-emergent adverse event.

- Most common grade ≥ 3 TEAEs were cytopenias (**Figure 7**)
- Maximum tolerated dose was not reached. Among 31 dose-limiting toxicity (DLT)–evaluable patients, 2 had a DLT (both at DL2):
  - Tumor lysis syndrome (TLS; grade 5) in patient with high tumor burden
  - Neutropenia (grade 3)/thrombocytopenia (grade 4)
- Grade 5 TEAEs occurred in 4 (4.5%) patients
  - 3 were considered related to liso-cel per investigator: cryptococcal meningoencephalitis; lung infection (COVID-19 pneumonia); TLS (DLT)
  - 1 was considered unrelated to liso-cel per investigator: cardiopulmonary arrest
- Most CRS and NEs were of low grade, with grade 3–4 events of 1% and 9%, respectively, and no grade 5 events reported (**Table 2**)
- Overall, 7% of patients received corticosteroids only, 12.5% received tocilizumab only, and 14% received tocilizumab and corticosteroids to manage CRS and/or NEs
- Forty percent of patients had prolonged cytopenias (grade ≥ 3 laboratory abnormalities of neutropenia, anemia, or thrombocytopenia at Day 29 after liso-cel infusion), 15% had grade ≥ 3 infections (system organ class of infections and infestations), and 7% had hypogammaglobulinemia

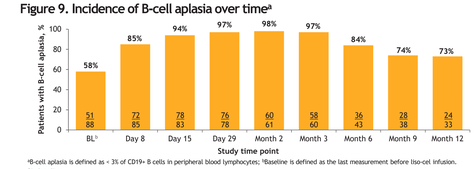
Figure 8. Liso-cel cellular kinetics over time



IQR, interquartile range.

- Median (IQR) time to maximum transgene levels (t_{max}) was 10 days (9–14) (**Figure 8**), maximum transgene levels (C_{max}) was 29,335 copies/µg (9255–136,684), and area under the curve for transgene levels from 0 to 28 days after infusion ($AUC_{(0-28d)}$) was 288,557 days × copies/µg (91,759–900,208)
- Persistence of the liso-cel transgene (transgene count ≥ lower limit of detection of 5 copies per reaction) was detected at Month 12 in 23/33 (70%) patients and at Month 24 in 6/17 (35%) patients

Figure 9. Incidence of B-cell aplasia over time[a]



[a]B-cell aplasia is defined as < 3% of CD19+ B cells in peripheral blood lymphocytes; [b]Baseline is defined as the last measurement before liso-cel infusion.

BL, baseline.

- After liso-cel infusion, the frequency of B-cell aplasia increased to 98% by Month 2, then decreased to 73% by Month 12 (**Figure 9**)

Conclusions

- Treatment with liso-cel resulted in a rapid, high rate of durable CR with a manageable safety profile in patients with heavily pretreated R/R MCL
  - Primary and key secondary endpoints were met with an ORR of 86.5% and CR rate of 74.3% in the PAS
- Clinically meaningful activity was observed across all prespecified subgroups, including patients with high-risk features (high Ki67 proliferation index, *TP53* mutation, secondary CNS lymphoma)
- Responses were durable, with a median DOR of 15.7 months and a median PFS of 15.3 months
  - Results were potentially impacted by the COVID-19 pandemic, as the COVID-19 sensitivity analysis showed a median DOR of 17.5 months, median PFS of 17.8 months, and median OS of 24.8 months
- Liso-cel was well tolerated, with low rates of grade ≥ 3 CRS (1%), NEs (9%), and infections (15%), and no new safety signals were identified
- Overall, these results support liso-cel as a potential new treatment option for R/R MCL

References

1. Kumar A, et al. *Blood Cancer J* 2019;9:50.

Acknowledgments

- We would like to thank the patients, caregivers, investigators, and study personnel
- This study was funded by Juno Therapeutics, a Bristol-Myers Squibb Company
- All authors contributed to and approved the presentation; writing and editorial assistance were provided by Allison Green, PhD, CMPP, and Nikola Vojtov, PhD, of The Lockwood Group (Stamford, CT, USA), funded by Bristol Myers Squibb

Scientific Content on Demand

To request a copy of this poster:

Scan QR code via a barcode reader application

QR codes are valid for 90 days after the congress presentation date

Copies of this poster obtained through QR (Quick Response) and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.