Zamtocabtagene Autoleucel, a Tandem CD20-CD19 Directed CAR-T Cell Therapy in Relapsed/Refractory Large B-Cell Lymphoma: Crossover Analysis (Third-Line) from the Randomized, Pivotal DALY 2-EU Trial

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INTRODUCTION

- The efficacy of anti-cluster of differentiation (CD)19 chimeric antigen receptor (CAR)-T cell therapies as second-line (2L) treatment for relapsed/refractory (r/r) large B-cell lymphoma (LBCL) has been demonstrated in randomized studies with transplant-eligible patients.[1,2]
  - The level of evidence for CAR-T cell therapies should be strengthened for transplant-ineligible patients.[3-6]
- Zamtocabtagene autoleucel (zamto-cel) is an autologous, non-cryopreserved tandem CD20-CD19 directed CAR-T cell therapy with a fixed 12-day manufacturing window and an average vein-to-vein time of 15 days (range 14 to 16 days).[7]
- Zamto-cel was compared with standard of care (SoC; rituximab-gemcitabine-oxaliplatin [R-GemOx] or polatuzumab vedotin-bendamustine-rituximab [Pola-BR]) in transplant-ineligible patients with r/r LBCL in the randomized DALY 2-EU study (NCT04844866).[8]
  - Zamto-cel demonstrated superior event-free survival (EFS; median 6.2 vs 2.5 months) and improved best objective response (BOR; 72.0 vs 44.9%) and complete response (CR; 53.7 vs 14.1%) vs R-GemOx as assessed by an independent review committee (IRC).[7,9]
  - Zamto-cel had a manageable safety profile, with low rates of Grade ⩾3 immune effector cell-associated neurotoxicity syndrome (ICANS; 1.3%) and cytokine release syndrome (CRS; 5.3%).[7,9]

AIMS

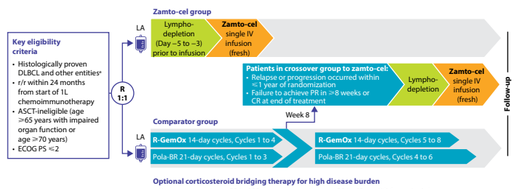
- To evaluate the efficacy and safety of zamto-cel for crossover patients from the SoC arm in DALY 2-EU.

METHODS

Study Design and Patient Population (Figure 1)

- DALY 2-EU is a multicenter, randomized, open-label, Phase II trial investigating the efficacy and safety of zamto-cel in patients with r/r LBCL vs SoC.
- Adult patients (aged ⩾18 years) were eligible for inclusion if they had r/r LBCL with Eastern Cooperative Oncology Group performance status ⩽2 and one transplant-ineligibility criterion.
- Patients were randomized 1:1 to zamto-cel or SoC (R-GemOx or Pola-BR).

Figure 1. DALY 2-EU Study Design (N=168)[8,9]



ASCT, autologous stem-cell transplant; BCL/BL, B-cell lymphoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HG, high-grade; IV, intravenous; L, line; LA, leukapheresis; NOS, not otherwise specified; Pola-BR, polatuzumab vedotin-bendamustine-rituximab; PR, partial response; QD, once daily; R, randomization; R-GemOx, rituximab-gemcitabine-oxaliplatin; r/r, relapsed/refractory; zamto-cel, zamtocabtagene autoleucel.

[a]As per the 4th World Health Organization classification (WHO 2016) the following entities could be included: DLBCL NOS, HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL/blastoid/intermediate histology or HGBL with *MYC* and *BCL2* and/or *BCL6* rearrangements (double-hit lymphoma/triple-hit lymphoma), high-grade BCL NOS, primary (thymic) large mediastinal BCL, disease transformed from an earlier diagnosis of low-grade lymphoma (e.g., an indolent pathology such as follicular lymphoma, marginal zone lymphoma) into DLBCL with DLBCL disease progression subsequent to DLBCL-directed systemic treatment, and follicular lymphoma Grade 3B.

Crossover Population

- A protocol amendment (February 2023) allowed one-sided crossover from SoC to zamto-cel as third-line (3L) treatment; no crossover occurred before the amendment.
- To be eligible, patients had to have relapsed or progressed ⩽1 year after randomization or failed to achieve partial response (PR) in ⩾8 weeks or CR at end of treatment, and the start of a new anti-lymphoma therapy was warranted.
- Leukapheresis product was collected after randomization (prior to SoC) or after the first cycle of SoC (recommended 14 days between SoC administration and leukapheresis) and cryopreserved.
- Crossover patients received an infusion of zamto-cel (target dose of 2.5×10^6 CAR-T cells/kg body weight).
- Bridging therapy was allowed prior to zamto-cel administration in the crossover setting.

Exploratory Endpoints in the Crossover Population

- Investigator-assessed BOR, EFS, progression-free survival (PFS), and overall survival (OS).
  - Although not reported in this presentation, these exploratory endpoints were also assessed via an IRC.
- Treatment-emergent adverse events (TEAEs), defined as any adverse event occurring from zamto-cel infusion to 90 days post-infusion and before new anti-lymphoma therapy.

Crossover Analysis Populations

- **Full analysis population:** patients who were approved for crossover.
- **Efficacy population:** patients who were approved for crossover and received zamto-cel.
- **Safety population:** patients who were approved for crossover and started lymphodepletion.

RESULTS

Patient Population

- Between October 2021 and July 2024, 168 patients were randomized to zamto-cel (n=82) or SoC (n=86).
- Of the 54 patients who received SoC and provided informed consent following the protocol amendment, 31 were eligible for crossover and 29 received zamto-cel.
  - Crossover criteria: relapsed/progressed ⩽1 year after randomization or failed to achieve PR in ⩾8 weeks or CR at end of treatment, and the start of a new anti-lymphoma therapy was warranted.
  - One patient withdrew informed consent, and one died due to progressive disease.
  - Crossover patient baseline characteristics are shown in **Table 1**.
  - Four patients received a cryopreserved product.
- In total, 16 (53%) patients received bridging therapies; those used are shown in **Figure 2**.
  - Median time from last SoC infusion to crossover bridging therapy was 26 days (range 14 to 92 days).

Efficacy at Data Cut-off (15 January 2025)

- Median follow-up of 7.9 months (range 1.5 to 8.3 months).
- In the crossover population, BOR (CR + PR) was 79.3% (**Figure 3A**).
- 6-month EFS, PFS, and OS rates are shown in **Figure 3B**.

Safety

- Neutropenia was the most common hematologic TEAE (16 [55.2%] patients) (**Table 2**).
- TEAEs leading to death occurred in 4 (13.8%) patients.
  - Malignant neoplasm progression (lymphoma progression; n=2), bronchitis, and septic shock (both n=1).
- Reported rates of any grade CRS and ICANS were 48.3% and 17.2%, respectively (**Figure 4**).
  - No Grade 5 CRS or ICANS were observed.

Table 1. Patient Characteristics for the Overall and Crossover Populations

Characteristic, n (%)	Overall population (2L)[a]		Crossover population (3L)[b]
	Zamto-cel (n=82)	R-GemOx (n=78)	Zamto-cel (n=30)
Median age, years (range)	74.5 (19-87)	74.0 (55-86)	74.0 (55-82)[c]
Age, ⩾75 years	41 (50)	33 (42)	12 (41)[c]
Sex, male	52 (63)	48 (62)	17 (59)[c]
ECOG PS at baseline[d]			
0	24 (29)	31 (40)	11 (37)
1	33 (40)	31 (40)	13 (43)
2	25 (31)	16 (21)	5 (17)
3	-	-	1 (3)
Histologic diagnosis by investigator assessment[e]			
DLBCL (NOS)	62 (76)	48 (62)	20 (67)
HGBCL	5 (6)	9 (12)	2 (7)
Other[f]	15 (18)	20 (26)	8 (27)
Missing/not confirmed	0	1 (1)	-
Status after 1L therapy			
Relapsed	41 (50)	32 (41)	14 (47)
Relapsed after ⩽12 months	21 (26)	19 (24)	10 (71)
Refractory	42 (51)	47 (60)	16 (53)
Modified Ann Arbor Stage III and IV at screening	55 (67)	52 (67)	20 (67)
IPI score between 3 and 5 at screening	47 (57)	45 (58)	15 (50)
LDH			
⩽2x ULN	68 (83)	64 (82)	22 (73)
>2x ULN	11 (13)	10 (13)	4 (13)
Missing	3 (4)	4 (5)	4 (13)

DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; L, line; LDH, lactate dehydrogenase; NOS, not otherwise specified; R-GemOx, rituximab-gemcitabine-oxaliplatin; ULN, upper limit of normal; zamto-cel, zamtocabtagene autoleucel.

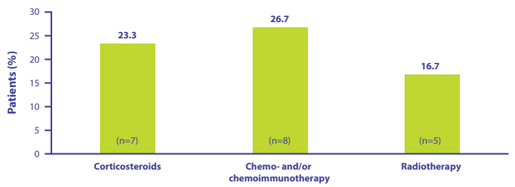
[a]Full analysis population; [b]Crossover full analysis population unless otherwise stated; [c]Crossover efficacy population; [d]At crossover baseline for patients within the crossover population; [e]As per WHO 2016 classification; [f]Other included HGBCL NOS and disease transformed from an earlier diagnosis of low-grade lymphoma into DLBCL with disease progression after systemic treatment.

Table 2. Summary of AEs and Clinically Relevant Hematologic TEAEs in the Crossover Population (Crossover Safety Population)

TEAEs, n (%)	Zamto-cel crossover population (n=29)	
Patients experiencing any TEAE	26 (89.7)	
Patients experiencing any Grade ⩽3 TEAE	18 (62.1)	
TEAEs related to zamto-cel	24 (82.8)	
AEs related to lymphodepletion	25 (86.2)	
Serious AE	15 (51.7)	
TEAE leading to death	4 (13.8)	
Malignant neoplasm progression (lymphoma progression)	2 (6.9)	
Bronchitis	1 (3.4)	
Septic shock	1 (3.4)	
Clinically relevant hematologic TEAEs, n (%)	**Any grade**	**Grade ⩾3**
Anemia	14 (48.3)	4 (13.8)
Neutropenia	16 (55.2)	9 (31.0)
Leukopenia	3 (10.3)	-
Thrombocytopenia	9 (31.0)	4 (13.8)

AE, adverse event; TEAE, treatment-emergent adverse event; zamto-cel, zamtocabtagene autoleucel.
Patients with multiple events within a category are counted only once in this category. AEs with multiple continuous events within one preferred term per patient are only counted once with the maximum attributes.

Figure 2. Bridging Therapies Used[a] (Crossover Full Analysis Population; n=30)

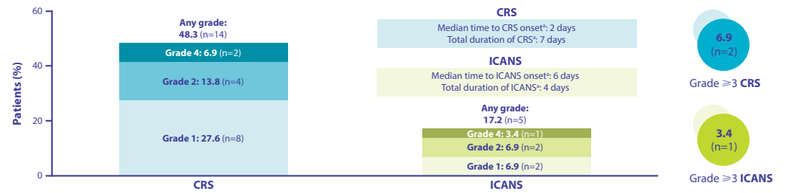


[a]Patients could have received more than one type of bridging therapy.

Figure 3. A) BOR and B) Estimated Survival and Efficacy Rates in the Crossover Population (Crossover Efficacy Population; n=29)

BOR, best objective response; CI, confidence interval; EFS, event-free survival; OS, overall survival; PFS, progression-free survival.

Figure 4. Rates of Severe CRS and ICANS in the Crossover Population (Crossover Safety Population; n=29)



CRS, cytokine release syndrome; ICANS, immune cell-associated neurotoxicity syndrome.
[a]Any grade. If a patient has multiple events, the event with the longest duration is taken.

CONCLUSIONS

- **In this 3L setting, most intended patients received zamto-cel.**
- **Analysis of this mainly refractory 3L patient population revealed clinically meaningful efficacy of zamto-cel with low rates of severe CRS and ICANS, consistent with 2L treatment with zamto-cel.**

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Zamtocabtagene autoleucel (zamto-cel) is an investigational product and is not approved for therapeutic use in any country.

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