Zamtocabtagene Autoleucel, a Tandem CD20-CD19 (directed) CAR-T Cell Therapy, for Treatment of Second Line (2L) Transplant-ineligible, High Risk, Relapsed/Refractory (R/R) Large B Cell Non-Hodgkin Lymphoma (NHL): Primary Analysis of the Randomized, Pivotal DALY 2-EU Study

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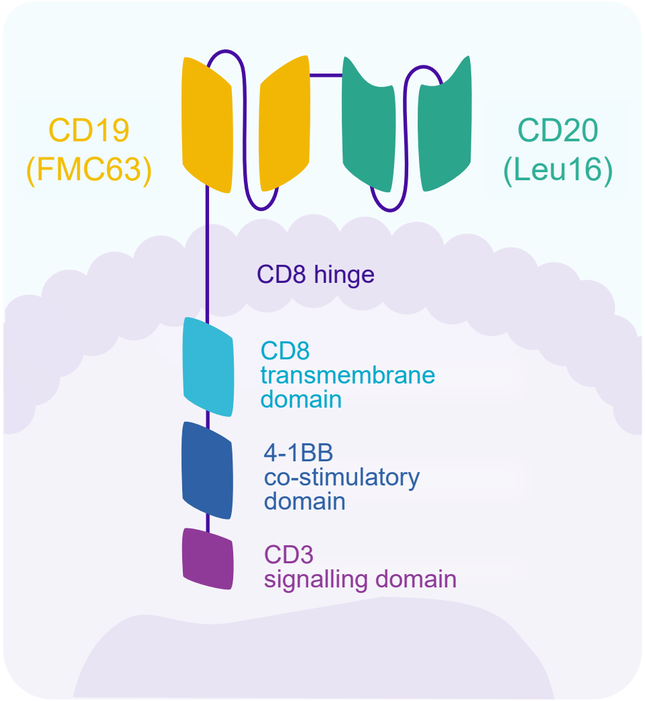
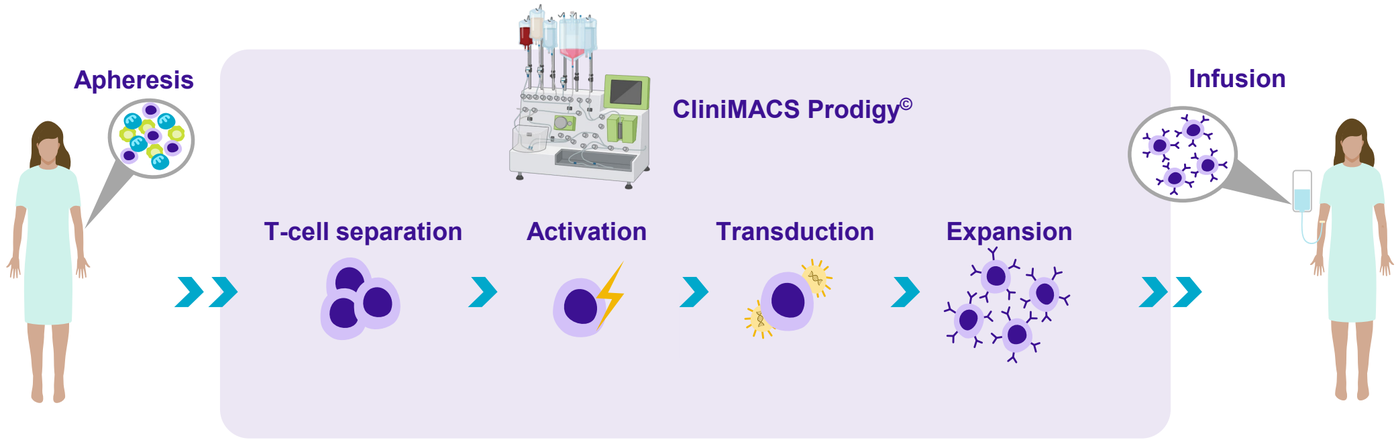
Zamtocabtagene autoleucel (zamto-cel): a novel tandem CD20-CD19 (directed) CAR-T cell therapy

Tandem CD20-CD19 (directed) CAR-T cell[1] therapy



Produced using a fully automated system and administered as a fresh (non-cryopreserved) formulation[2]



Manufacturing time	**12 days**
Vein-to-vein time	**13–15 days**

CAR, chimeric antigen receptor; CD, cluster of differentiation.

1 Majzner R, and Mackall C. Cancer Discov. 2018;8:1219–26; 2. Shah N, et al. Blood 2024;144;suppl. 1:68–70.

Introduction

- Efficacy of anti-CD19 CAR-T cell therapies for 2L in patients with high-risk[a] r/r LBCL has been demonstrated in randomized studies only for transplant-eligible patients[1,2]
- However, the level of evidence for CAR-T cell therapies should be strengthened for transplant-ineligible patients[3-6]
- **The tandem CD20-CD19 directed CAR-T cell product zamto-cel** has shown:
  - **Improved efficacy and safety** over CD19 CAR-T cell constructs in preclinical models[7]
  - **High response rates and durable remissions** with low incidence of CRS and/or ICANS in early clinical evaluation[8,9]
- **Zamto-cel was compared to R-GemOx in transplant-ineligible r/r LBCL patients in the randomized DALY 2-EU study (NCT04844866)**[10]

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; R-GemOx, rituximab gemcitabine oxaliplatin.

1. Westin JR, et al. N Engl J Med. 2023;389(2):148–57; 2. Abramson JS, et al. Lancet. 2024;404(10466):1940–54; 3. Sehgal A, et al. Lancet Oncol. 2022;23(8):1066–77; 4. Harrysson S, et al. Br J Haematol. 2022;198(2):267–77; 5. Houot R, et al. Nat Med. 2023;29(10):2593–2601; 6. Douglas M. J Adv Pract Oncol. 2020;11(5):521–8; 7. Schneider D, et al. J Immunotherapy. 2017;5:422; 8. Shah N, et al. Nat Med. 2020;26:1589–1575; 9. Borchmann P, et al. Presented at EHA 2022. June 9–17. Vienna, Austria; 10. ClinicalTrials.gov. NCT04844866.

DALY 2-EU study design (N=168): a randomized, multicenter, open-label trial (NCT04844866)

Key eligibility criteria

- Histologically proven DLBCL and other entities[a]
- r/r within 24 months from start of 1L chemoimmunotherapy
- ASCT-ineligible
- ECOG PS ≤ 2

R 1:1

Zamto-cel group

LA

Lympho-depletion (day -5 to -3) prior to infusion → **Zamto-cel** single IV infusion (fresh)

Patients in crossover group to zamto-cel:
- Relapse or progression occurred within ≤1 year of randomization
- Failure to achieve a PR or CR in ≥8 weeks

→ Lympho-depletion → **Zamto-cel** single IV infusion (fresh)

Comparator group

LA

R-GemOx 14-day cycles, Cycles 1–4 → **R-GemOx** 14-day cycles, Cycles 5–8

Pola-BR 21-day cycles, Cycles 1–3[b] → Pola-BR 21-day cycles, Cycles 4–6[b]

Week 8

Follow-up

Key endpoints

Primary
- EFS by IRC

Secondary
- PFS by IRC
- BCRR by IRC
- DoCR by IRC
- OS using RPSFT

Safety
- Type, frequency, and severity of AEs, SAEs, AESIs

Optional corticosteroid bridging therapy for high disease burden
- Oral or IV prednisone 50–100 mg or dexamethasone 30–40 mg QD for up to 4 days
- Stopped ≥7 days before leukapheresis and/or >72 hours before zamto-cel infusion

[a] As per 4th WHO classification (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; [b] Results of the Pola-BR group were not part of the primary analysis and are not discussed in this presentation.
AE, adverse event; AESI, adverse event of special interest; ASCT, autologous stem-cell transplant; BCRR, best complete response rate; CR, complete response; DoCR, duration of complete response; IRC, independent review committee; LA, leukapheresis; Pola-BR, polatuzumab vedotin-bendamustine-rituximab; PR, partial response; R, randomization; R-GemOx, rituximab-gemcitabine-oxaliplatin; RPSFT, rank-preserving structural failure time; SAE, serious adverse event.
ClinicalTrials.gov. NCT04844866.

DALY 2-EU:
statistical assumptions and predefined analysis populations

Main statistical assumptions

Analysis of primary endpoint EFS (by IRC) in Intent-to-treat (ITT)/Full analysis set (FAS) (zamto-cel vs. R-GemOx):

- EFS was defined as the time between the date of randomisation and the date of objective disease progression, failure to achieve PR or CR at or beyond Week 8 after randomisation leading to a new anti-lymphoma therapy or death of any cause, whichever occurred first
- Assumed median EFS 6.25 vs. 3.25 months
- Hazard ratio 0.52, power ≥93%, 1-sided alpha of 0.025
- Sample size needed for primary analysis: 160 patients

Predefined analysis populations

ITT/FAS:

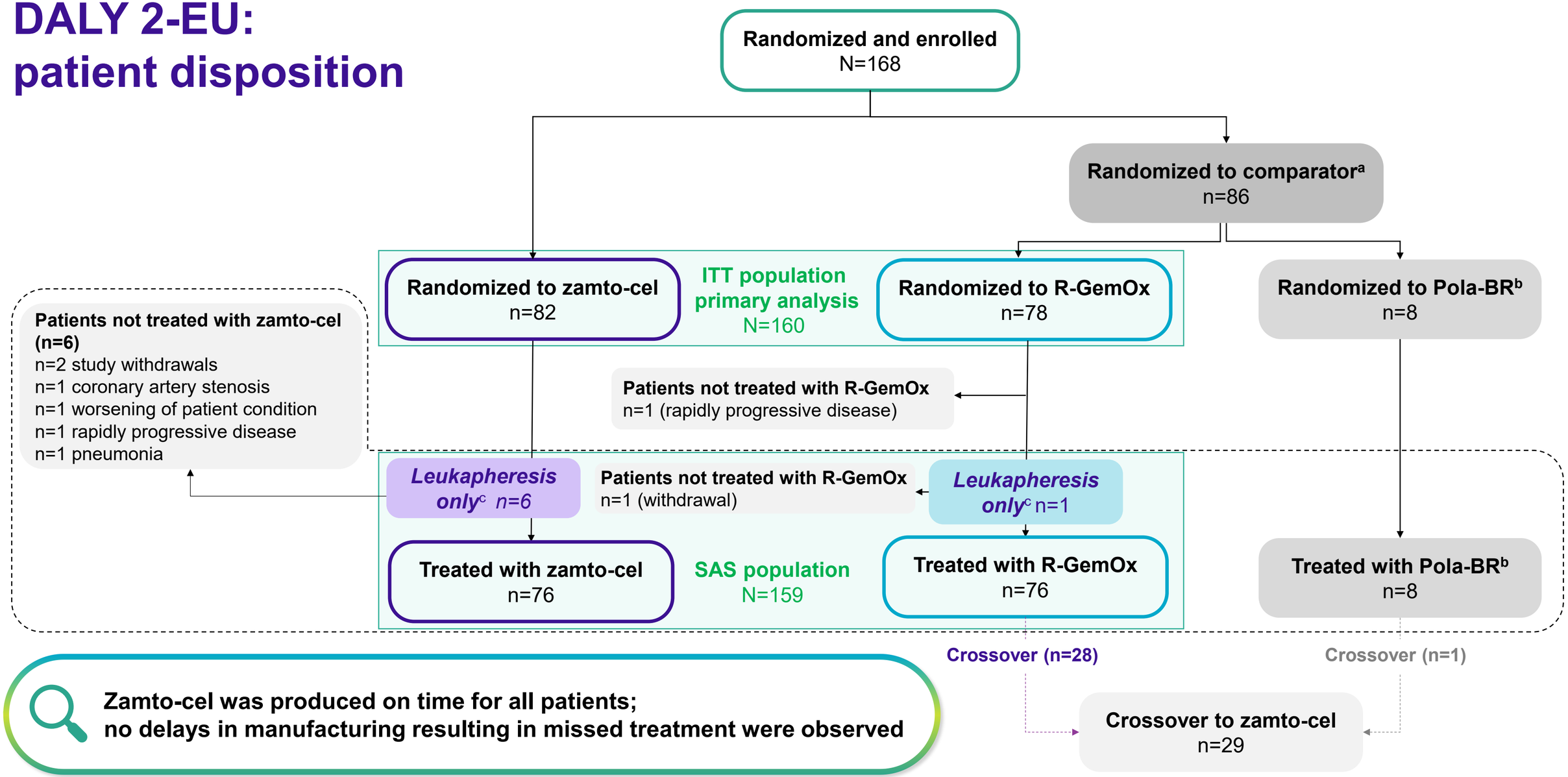
- All randomized patients
- **Modified ITT (mITT) / Modified FAS (mFAS):** Patients with evidence of disease at baseline (PET-CT by IRC) and ≥1 valid post-baseline efficacy assessment

Safety analysis set (SAS):

- Includes patients randomized to zamto-cel or R-GemOx/Pola-BR who received study treatment
  - → Zamto-cel: Patients who had leukapheresis
  - → R-GemOx/Pola-BR: Patients who had leukapheresis and/or who received their first dose of chemotherapy
- Patients in comparator arm could **crossover** to zamto-cel if they relapsed or progressed within ≤1 year of randomization, or failed to achieve a PR or CR in ≥8 weeks

CR, complete response; EFS, event-free survival; (m)FAS, (modified) full analysis set; IRC, independent review committee; (m)ITT, (modified) intent-to-treat; PET-CT, positron emission tomography-computed tomography; Pola-BR, polatuzumab vedotin, bendamustine and rituximab; PR, partial response; R-GemOx, rituximab gemcitabine oxaliplatin; SAS, safety analysis set.

DALY 2-EU: patient disposition



Zamto-cel was produced on time for all patients; no delays in manufacturing resulting in missed treatment were observed

[a] It was at the Investigator's discretion which of the two predefined comparator regimens was indicated for the participant and should be administered; [b] The secondary analysis of the primary endpoint compared zamto-cel with the complete comparator arm (patients treated with R-GemOx and Pola-BR) in the ITT population, provided that the primary analysis was significant; the results of this analysis will be reported separately; [c] Patients who were randomised and received leukapheresis without study drug treatment were not included in the analysis of the safety population in this presentation

ITT, intent-to-treat; Pola-BR, polatuzumab vedotin-bendamustine-rituximab; R-GemOx, rituximab-gemcitabine-oxaliplatin; SAS, safety analysis set; zamto-cel, zamtocabtagene autoleucel.

DALY 2-EU baseline characteristics were balanced: an elderly population with high-risk characteristics

Characteristic (ITT population)		Zamto-cel, n (%) (n=82)	R-GemOx, n (%) (n=78)
Median age, years (range)		74.5 (19, 87)	74.0 (55, 86)
Age, ≥75 years		41 (50)	33 (42)
Sex, male		52 (63)	48 (62)
ECOG PS	0	24 (29)	31 (40)
	1	33 (40)	31 (40)
	2	25 (31)	16 (21)
Histological diagnosis by investigator assessment	DLBCL (NOS)	62 (76)	48 (62)
	HGBL	5 (6)	9 (12)
	Other[a]	15 (18)	20 (26)
	Missing/not confirmed	0	1 (1)

Characteristic (ITT population)		Zamto-cel, n (%) (n=82)	R-GemOx, n (%) (n=78)
Previous response status			
Refractory[b]		42 (51)	47 (60)
Relapsed / time to relapse after start of 1L	≤12 months	20 (24)	18 (23)
	>12 – ≤18 months	11 (13)	8 (10)
	>18 – ≤24 months	6 (7)	5 (6)
	Missing	3 (4)	0
LDH	≤1x ULN	42 (51)	27 (35)
	>1x ULN	37 (45)	47 (60)
	Missing	3 (4)	4 (5)
Modified Ann Arbor Stage	III + IV	55 (67)	52 (67)
IPI score	0–2	35 (43)	33 (42)
	3–5	47 (57)	45 (58)

[a] Other included high-grade BCL NOS (zamto-cel: 5 [6%], R-GemOx: 8 [10%]), primary thymic large mediastinal BCL (zamto-cel: 1 [1%], R-GemOx: 1 [1%]), and disease transformed from an earlier diagnosis of low-grade lymphoma into DLBCL with disease progression after systemic treatment (zamto-cel: 9 [11%], R-GemOx: 11 [14%]). [b] Refractory based on the investigator assessement. Values are n (%) unless otherwise specified.

DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group performance status; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; ITT, intent-to-treat; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; ULN, upper limit of normal; R-GemOx, rituximab gemcitabine oxaliplatin; SPD, sum of perpendicular diameters.

DALY 2-EU:
transplant-ineligibility (TI) criteria and distribution

Age ≥18 years AND one criteria:

- Prior ASCT (as 1L consolidation)
  OR
- HCT-CI >3

Age ≥65 years AND one or more criteria:

- Impaired cardiac function (LVEF <50%)

OR

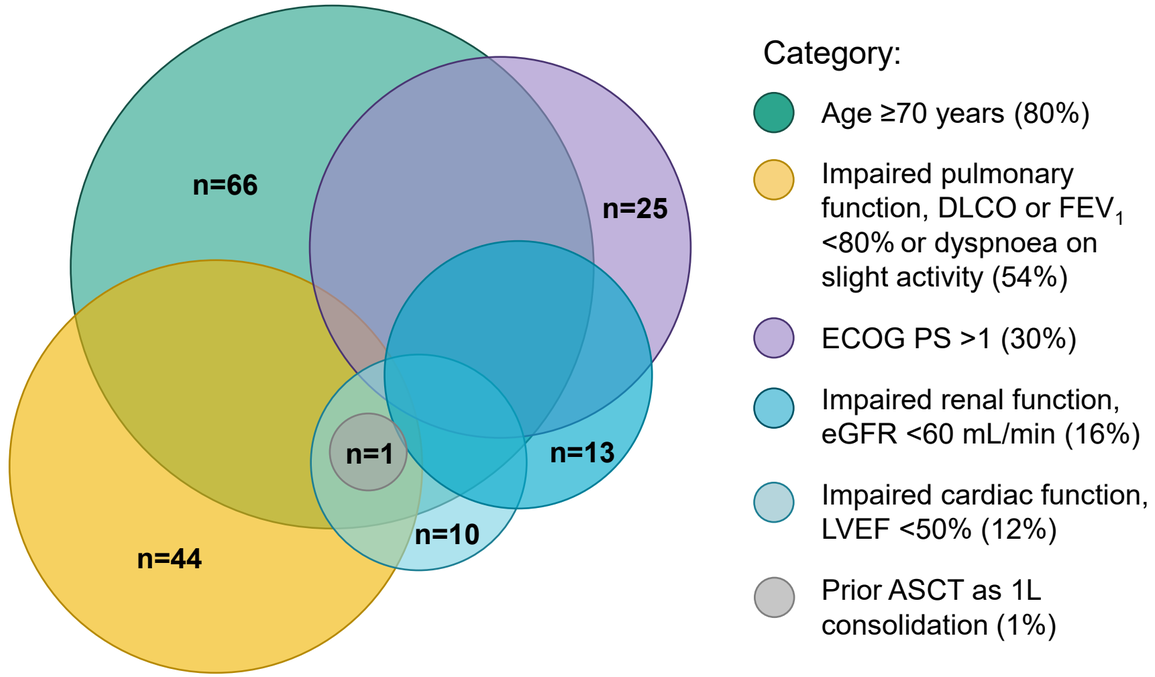
- Impaired renal function (eGFR <60 mL/min) **OR**
- Impaired pulmonary function (FEV1 <80%) or dyspnea on slight activity

OR

- ECOG PS >1

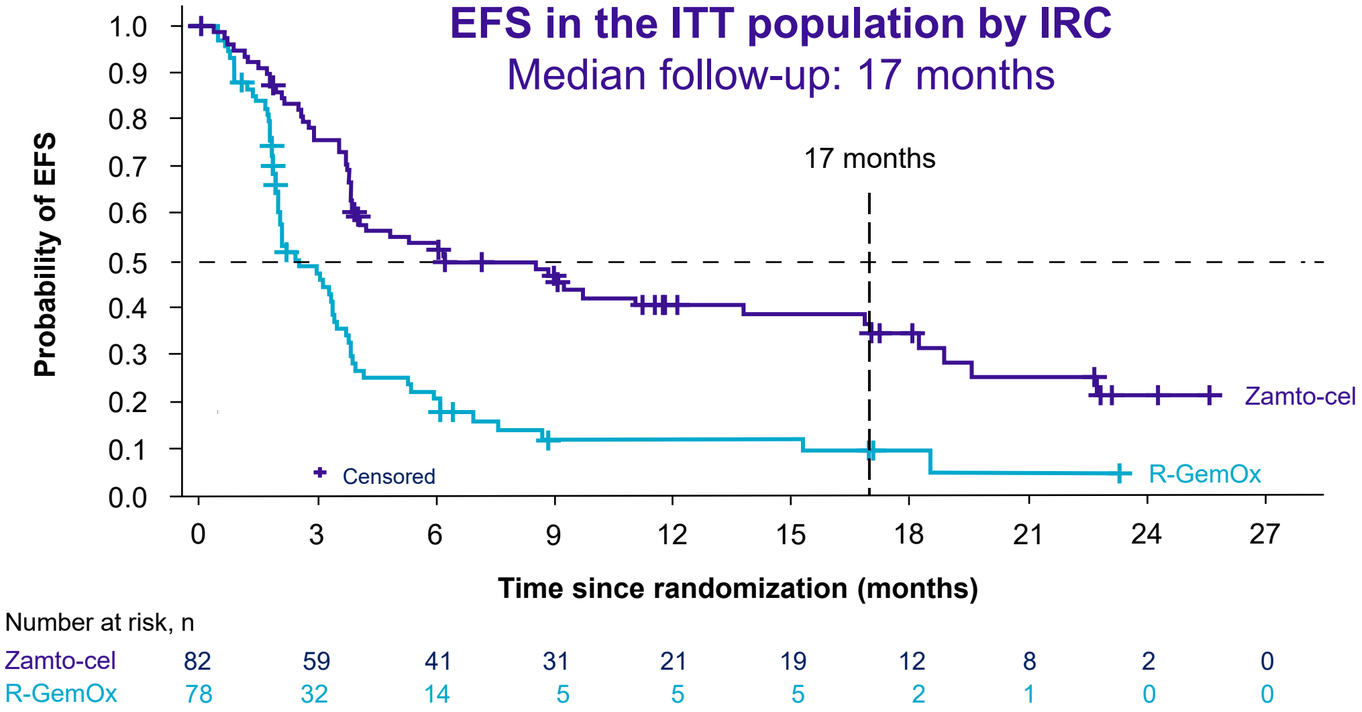
Age ≥70 years

Prevalence of TI criteria in the zamto-cel arm (n=82)



ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; HCT-CI, Hematopoietic cell transplantation-specific comorbidity index; HDC, high-dose chemotherapy; LVEF, left ventricular ejection fraction. DLCO, diffusing capacity for carbon monoxide; FEV1, first second of forced expiration

DALY 2-EU primary endpoint: significant EFS benefit with zamto-cel



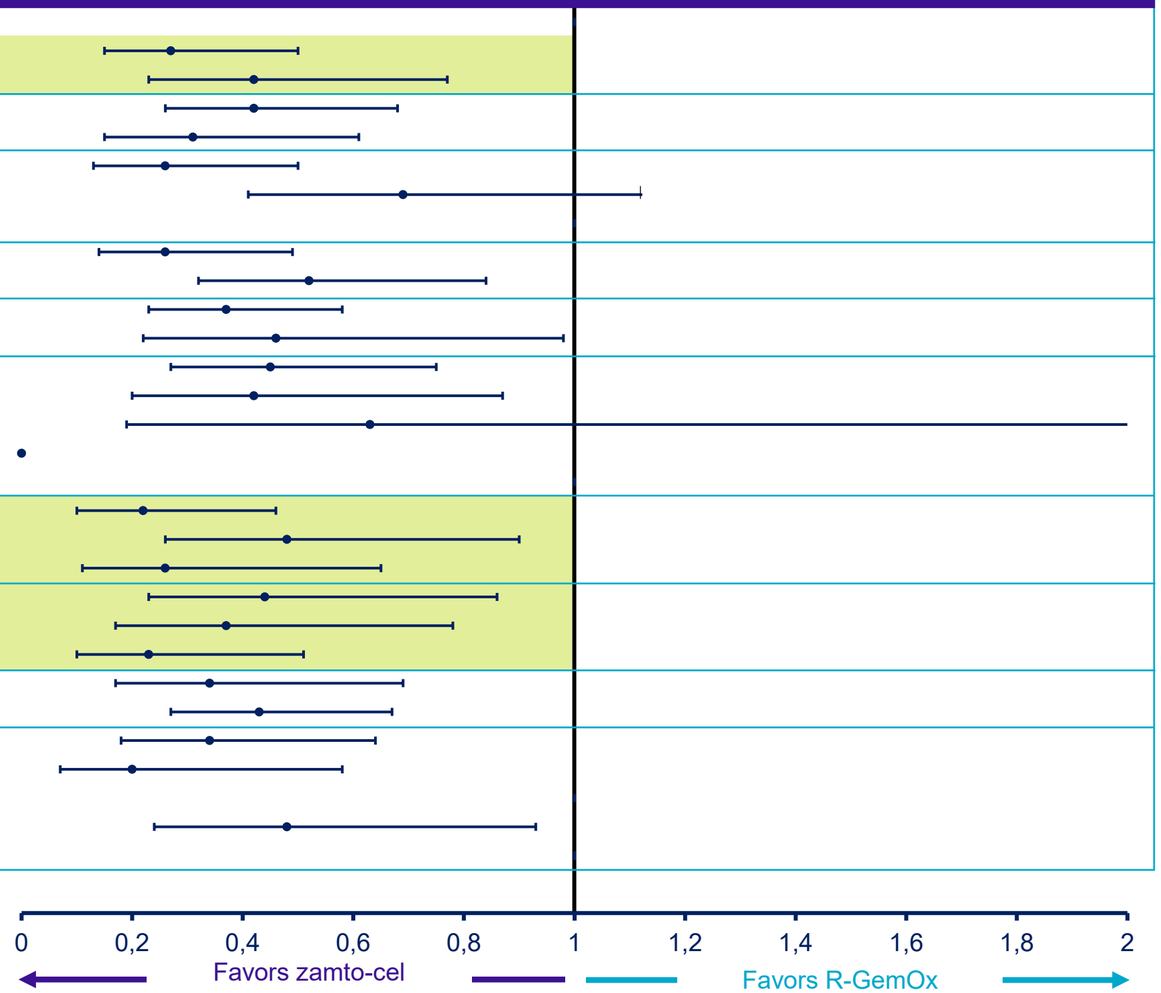
Primary endpoint	Zamto-cel (n=82)	R-GemOx (n=78)
EFS based on IRC assessment[a]		
Median EFS, months (95% CI)	6.21 (3.84, 13.77)	2.53 (1.97, 3.35)
Patients with events, n (%)	52 (63.4)	63 (80.8)
HR (95% CI) p-value	0.39 (0.27, 0.58) p<0.0001	

Zamto-cel arm demonstrated highly statistically significant and clinically meaningful superiority over R-GemOx for EFS, with a HR of 0.39

All p-values are one-sided. [a]EFS was defined as the time between the date of randomization and the date of objective disease progression, failure to achieve PR or CR at or beyond Week 8 after randomization leading to a new anti-lymphoma therapy or death of any cause, whichever occurs first. Treatment effects were estimated as HRs with 95% CIs using a Cox proportional hazards models. P-value was from the log-rank test stratified by IPI. Superiority was concluded if the 1-sided p-value was ≤0.025. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; R-GemOx, rituximab gemcitabine oxaliplatin.

DALY 2-EU subgroup analyses: superior EFS in zamto-cel consistent across majority of subgroups

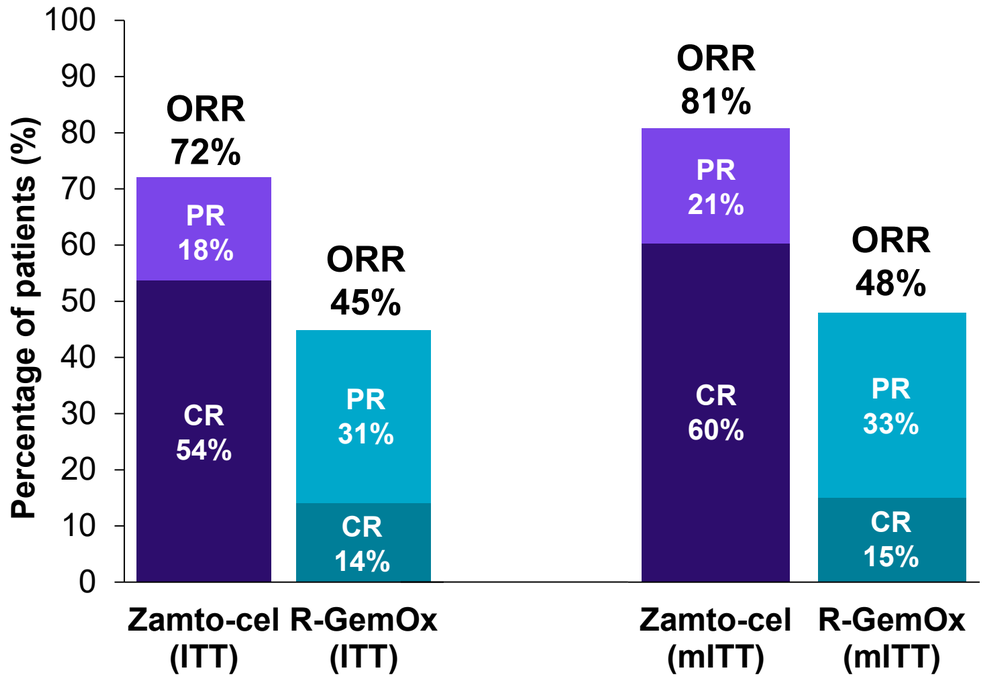
Subgroup		Event/count (ITT) Zamto-cel	R-GemOx	HR (95% CI)
	≤64 years	1/2	4/5	NC
Age, years	65–74 years	24/39	32/40	0.27 (0.15, 0.50)
	≥75 years	27/41	27/33	0.42 (0.23, 0.77)
Gender	Male	35/52	30/48	0.42 (0.26, 0.68)
	Female	17/30	23/30	0.31 (0.15, 0.61)
LDH	≤1x ULN	21/42	21/27	0.26 (0.13, 0.50)
	>1x ULN	29/37	33/42	0.69 (0.41, 1.14)
	Missing	2/3	9/9	NC
IPI score	0–2	17/35	27/33	0.26 (0.14, 0.49)
	3–5	35/47	36/45	0.52 (0.32, 0.84)
Histology by local assessment	DLBCL NOS	40/62	40/48	0.37 (0.23, 0.58)
	Other	12/20	23/30	0.46 (0.22, 0.98)
Time to relapse	Refractory[a]	28/42	38/47	0.45 (0.27, 0.75)
	≤12 months	15/20	16/18	0.42 (0.20, 0.87)
	>12 – ≤18 months	7/11	6/8	0.63 (0.19, 2.09)
	>18 – ≤24 months	0/6	3/5	0.00 (0.00, NC)
	Missing	2/3	0/0	NC
ECOG PS	0	13/24	26/31	0.22 (0.10, 0.46)
	1	22/33	25/31	0.48 (0.26, 0.90)
	2	17/25	12/16	0.26 (0.11, 0.06)
SPD, mm^2	≤2000	22/38	18/24	0.44 (0.23, 0.86)
	>2000 – <5000	15/21	25/32	0.37 (0.17, 0.78)
	≥5000	15/23	20/22	0.23 (0.10, 0.51)
Ann Arbor Stage	I–II	15/27	19/26	0.34 (0.17, 0.69)
	III–IV	37/55	44/52	0.43 (0.27, 0.67)
Best response to 1L treatment	CR	23/35	24/28	0.34 (0.18, 0.64)
	PR	10/18	10/15	0.20 (0.07, 0.58)
	Stable disease	2/2	2/4	NC
	Progressive disease	18/26	25/29	0.48 (0.24, 0.93)
	Missing	0/1	2/2	NC



[a] Refractory disease defined as no CR to 1L therapy. DLBCL NOS, diffuse large B-cell lymphoma not otherwise specified; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; CR, complete response; NC, not calculated; ULN, upper limit of normal; R-GemOx, rituximab gemcitabine oxaliplatin; SPD, sum of perpendicular diameters.

DALY 2-EU secondary endpoints: CR rate in zamto-cel 3.8x higher than R-GemOx

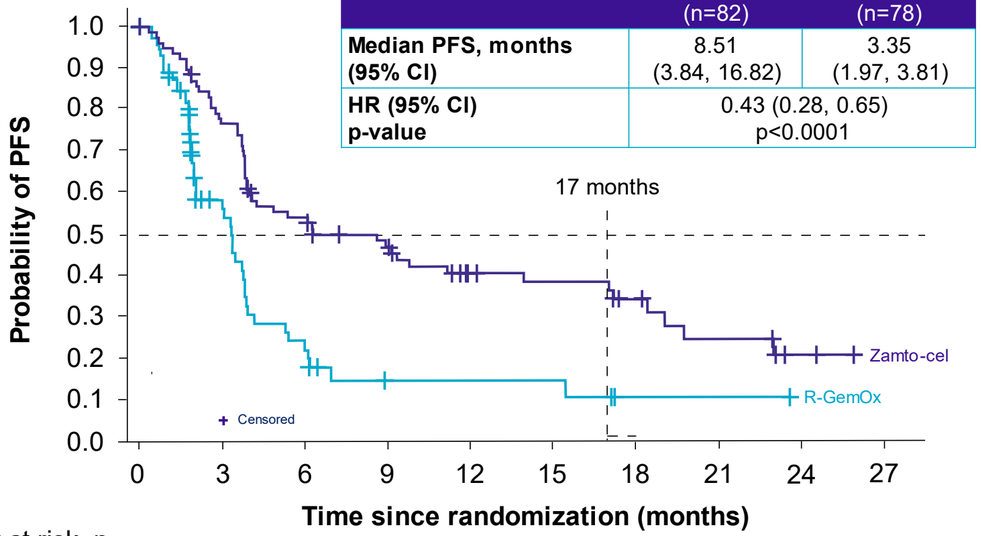
Response rates in the ITT and mITT populations



Median PFS by IRC

Median follow-up: 17 months

	Zamto-cel (n=82)	R-GemOx (n=78)
Median PFS, months (95% CI)	8.51 (3.84, 16.82)	3.35 (1.97, 3.81)
HR (95% CI) p-value	0.43 (0.28, 0.65) p<0.0001	



Number at risk, n

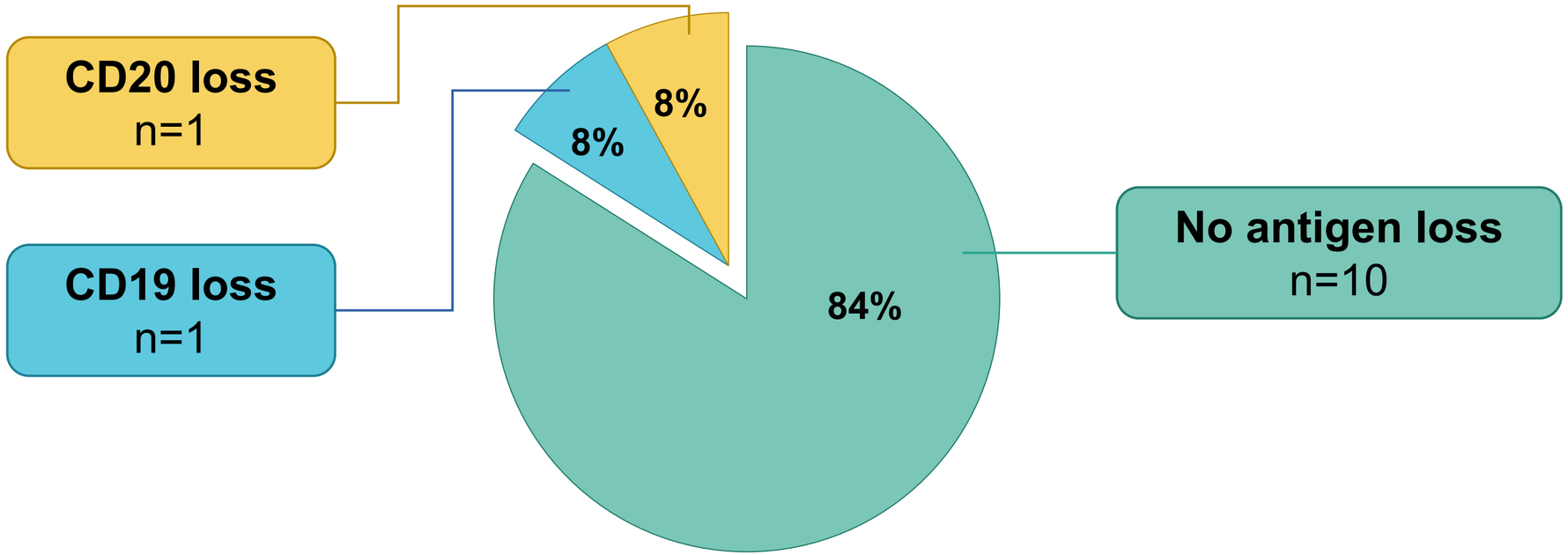
Zamto-cel	82	59	41	31	21	19	12	8	2	0
R-GemOx	78	27	11	4	4	4	1	1	0	0

- ✓ **PFS (HR [95% CI]: 0.43 [0.28, 0.65]; p<0.0001) for zamto-cel was statistically superior**
- ✓ **Zamto-cel demonstrated higher CR rate vs. R-GemOx**

CR, complete response; HR, hazard ratio; IRC, independent review committee; (m)ITT, (modified) intent-to-treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response; R-GemOX, rituximab gemcitabine oxaliplatin.

DALY 2-EU:
antigen loss does not appear to be a driver of progression

Number of tumors with CD19 and/or CD20 evaluation at progression (n=12)



None of the patients tested experienced dual CD19/CD20 antigen loss

DALY 2-EU: zamto-cel showed a manageable safety profile

TEAEs, n (%)	Zamto-cel (n=76)	R-GemOx (n=76)
Patients experiencing any TEAE	75 (98.7)	76 (100)
Patients experiencing any Grade ≥3 TEAE	63 (82.9)	65 (85.5)
TEAEs related to R-GemOx	0	69 (90.8)
TEAEs related to zamto-cel	69 (89.5)	0
AEs related to lymphodepletion	71 (93.4)	0
Prolonged cytopenias Grade ≥3 day 1-28	10 (13.2)	2 (2.6)
Delayed cytopenias Grade ≥3 day 29-90	8 (10.5)	30 (39.5)
Hypogammaglobulinemia[a]	4 (5.3)	0
Treatment-related deaths, n[b]	2[c]	0

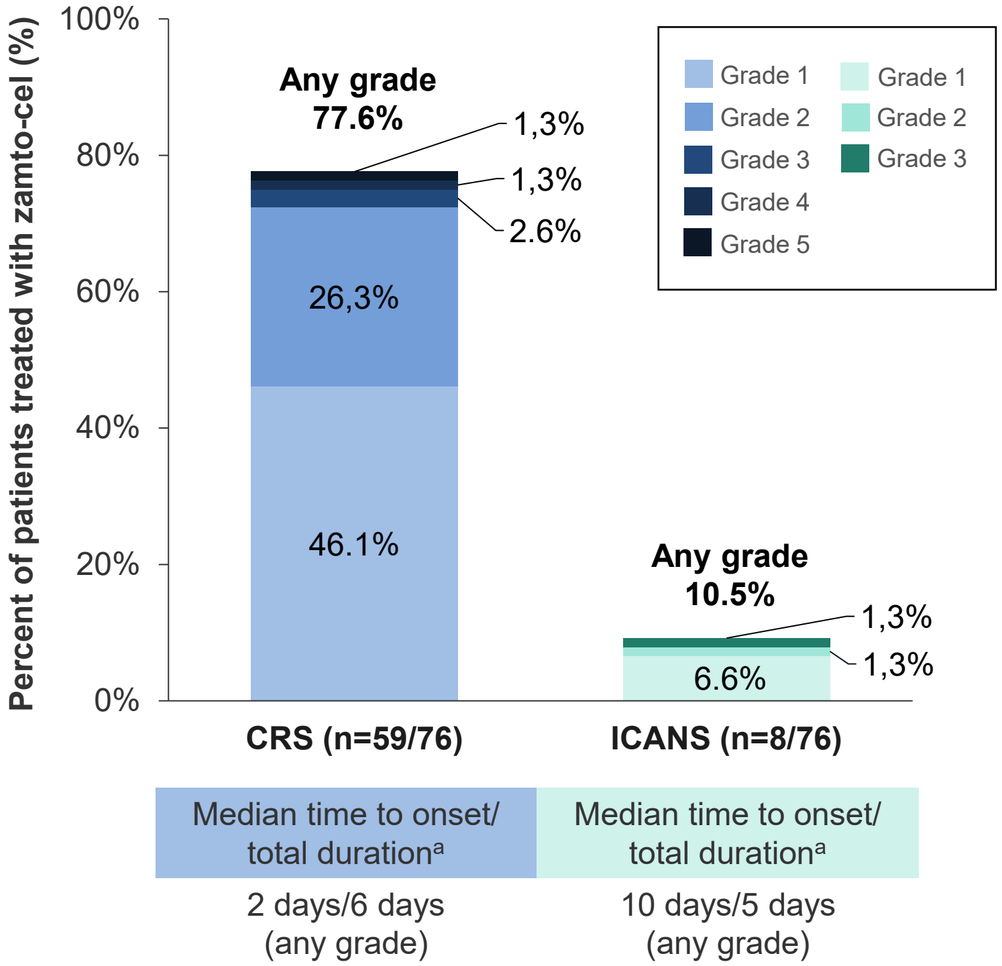
Clinically relevant TEAEs, n (%)	Zamto-cel (n=76)		R-GemOx (n=76)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
CAR-T associated				
CRS	59 (77.6)	4 (5.3)	0	0
ICANS	8 (10.5)	1 (1.3)	0	0
Hematologic				
Anemia	19 (25.0)	11 (14.5)	26 (34.2)	12 (15.8)
Neutropenia	30 (39.5)	28 (36.8)	21 (27.6)	17 (22.4)
Leukopenia	12 (15.8)	10 (13.2)	8 (10.5)	7 (9.2)
Thrombocytopenia	12 (15.8)	6 (7.9)	17 (22.4)	13 (17.1)
Other				
Nausea	11 (14.5)	0	19 (25.0)	0
Peripheral neuropathy	0	0	12 (15.8)	0
Infections CTCAE	34 (44.7)	14 (18.4)	23 (30.3)	10 (13.2)
HLH	2 (2.6)	2 (2.6)	1 (1.3)	1 (1.3)

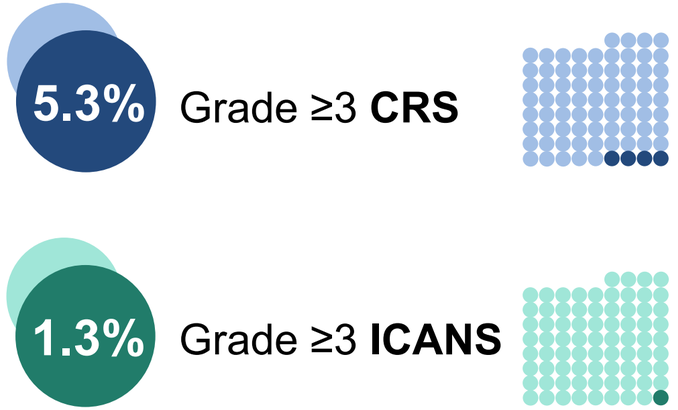
Zamto-cel was well tolerated in this elderly population

[a] Three patients received immunoglobulin substitution. [b] Any treatment-related death that occurred between the day of zamto-cel infusion and up to 90 days after zamto-cel infusion (zamto-cel group) or between the day of the first dose of SoC therapy to whichever occurs first: 30 days after the end of the last cycle of SoC therapy or date of approval of crossover. [c] Treatment-related deaths due to CRS (n=1) and HLH / meningitis (n=1). AE, adverse event; AESI, adverse events of special interest; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; R-GemOx, rituximab gemcitabine oxaliplatin; SAS, safety analysis set; TEAE, treatment-emergent adverse event.

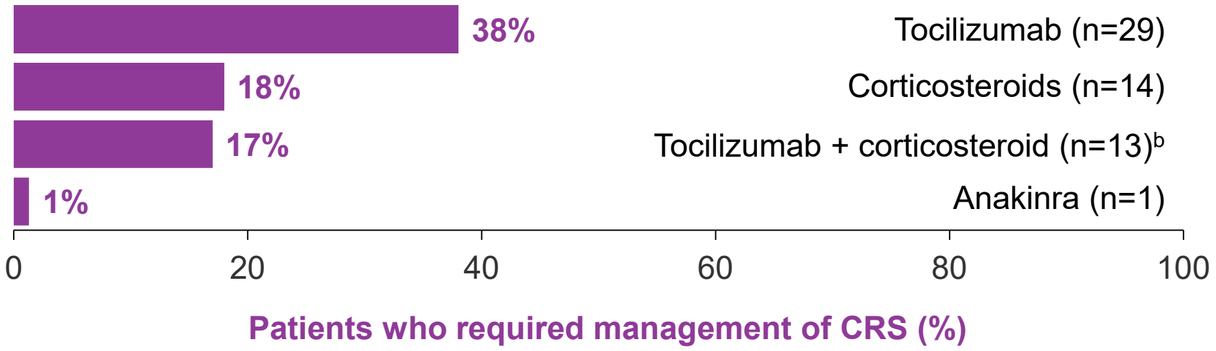
DALY 2-EU:
zamto-cel was well tolerated, with low rates of severe CRS and ICANS

Rates of CRS and ICANS in patients treated with zamto-cel





Management of CRS in patients treated with zamto-cel



[a] Total duration includes gaps between episodes. [b] The 13 patients that received tocilizumab + corticosteroid combination therapy were also counted individually for both tocilizumab (n=13/29) and corticosteroid (n=13/14). AE, adverse event; AESI, adverse events of special interest; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; c R-GemOx, rituximab gemcitabine oxaliplatin.

DALY 2-EU: Summary and conclusions

Zamto-cel:

- The first tandem CD20-CD19 (directed) fresh (non-cryopreserved) CAR-T cell product
- Short manufacturing time of **12 days**, with a vein-to-vein time of 13–15 days

DALY 2-EU:

- Zamto-cel demonstrated **significant and clinically meaningful superiority** over R-GemOx in transplant-ineligible patients at high risk for treatment failure independent of baseline patient and disease characteristics
  - ✓ **EFS HR 0.39, p<0.0001**
  - ✓ **CR rate 54% (ITT) / 60% (mITT)**
- Zamto-cel showed a manageable safety profile
  - ✓ Grade ≥3 CRS in 5.3% of patients (n=4)
  - ✓ Grade ≥3 ICANS in 1.3% patients (n=1, Grade 3)

The favorable risk/benefit profile of zamto-cel supports its use as a preferred 2L treatment option for patients with r/r LBCL and transformed lymphomas

CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; CRS, cytokine release syndrome; CRR, complete response rate; EFS, event-free survival; HR, hazard ratio; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; R-GemOx, rituximab gemcitabine oxaliplatin; r/r, relapsed/refractory

Acknowledgments

- We thank the patients and their families, investigators, and study teams involved in the DALY 2-EU clinical trial

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