Zamtocabtagene autoleucel, a tandem CD20–CD19-directed CAR T-cell therapy, for second line treatment of large B-cell lymphoma in patients ineligible for transplantation (DALY 2-EU): primary analysis of an open-label, multicentre, randomised phase 2 study

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Summary

Background Anti-CD19 CAR T-cell therapy is the standard second-line treatment for patients with relapsed or refractory large B-cell lymphoma. However, there is no evidence from randomised controlled trials in patients ineligible for transplantation. To address this gap, we compared zamtocabtagene autoleucel (zamto-cel), a CAR T-cell therapy directed at CD20 and CD19, with rituximab–gemcitabine–oxaliplatin (R-GemOx) chemoimmunotherapy in patients ineligible for transplantation with relapsed or refractory large B-cell lymphoma.

Methods DALY 2-EU is an open-label, multicentre, randomised, phase 2 trial conducted at 45 centres across 12 countries in Europe. Eligible patients were adults (aged ≥18 years) with second-line relapsed or refractory large B-cell lymphoma confirmed histologically who were ineligible for transplantation and had received first-line chemoimmunotherapy containing a combination of an anthracycline-based regimen and an anti-CD20 monoclonal antibody, with Eastern Cooperative Oncology Group performance status score of 2 or less. Patients were randomly assigned (1:1) to zamto-cel (single intravenous infusion of $2·5\times10^6$ fresh (ie, non-cryopreserved) CAR T-cells per kg, capped at 100 kg, produced in a closed automated system) or R-GemOx (rituximab [375 mg/m² intravenously on day 1], gemcitabine [1000 mg/m² intravenously on day 1 or 2], and oxaliplatin [100 mg/m² intravenously on day 1 or 2] administered for up to eight 14-day cycles). Randomisation was done with an interactive web response system and stratified by age, gender, lactate dehydrogenase, International Prognostic Index, histology, time to relapse after the start of first-line therapy, and country. The primary endpoint was event-free survival assessed by a masked independent review committee and compared all patients randomly assigned to the zamto-cel and R-GemOx groups using a one-sided log-rank test. Safety was assessed in all patients who received study treatment. This ongoing trial is registered with ClinicalTrials.gov (NCT04844866).

Findings Between Oct 14, 2021, and Jul 16, 2024, 219 patients were screened and 160 were randomly assigned to zamto-cel (n=82) and R-GemOx (n=78). The median age was 74·0 years (IQR 70·5–77·0). Patients were predominantly male (100 [63%] of 160 were men and 60 [38%] women) and White (91 [57%]), with race not reported for 64 (40%). Median vein-to-vein time for zamto-cel was 15 days (IQR 15–16). With a median follow-up of 17·0 months (IQR 9·0–22·8), event-free survival was longer in the zamto-cel group than in the R-GemOx group (6·21 months [95% CI 3·84–13·77] *vs* 2·53 months [1·97–3·35]; HR 0·39 [95% CI 0·27–0·58]; p<0·0001). Grade 3 or higher treatment-emergent adverse events occurred in 63 (83%) of 76 with zamto-cel and in 65 (86%) of 76 with R-GemOx. The most common grade 3–4 adverse events were neutropenia (28 [37%] with zamto-cel and 17 [22%] with R-GemOx), anaemia (11 [14%] and 12 [16%]), and decreased neutrophil count (20 [26%] and seven [9%]). Serious adverse events occurred in 31 (41%) patients with zamto-cel and 50 (66%) with R-GemOx, most commonly malignant neoplasm progression (11 [14%] and 38 [50%]), cytokine release syndrome (CRS; six [8%] and none), and immune effector cell-associated neurotoxicity syndrome (four [5%] and none). Treatment-related deaths occurred in two (3%) of 82 patients with zamto-cel (due to CRS and haemophagocytic lymphohistiocytosis) and in one (1%) of 78 with R-GemOx (malignant lymphoma progression).

Interpretation The risk–benefit ratio observed in the DALY 2-EU study supports consideration of zamto-cel as a second-line standard treatment option for patients with relapsed or refractory large B-cell lymphoma who are ineligible for transplantation.

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Introduction

Anti-CD19 CAR T-cell therapies have transformed the treatment landscape of relapsed or refractory large B-cell lymphoma.[1–3] In the second-line setting, randomised phase 3 trials have shown superior event-free survival with CAR T-cell therapy compared with standard-of-care high-dose chemotherapy with autologous stem cell support in patients with early relapsed or primary refractory disease.[4,5] However, in the second-line setting for patients ineligible for transplantation, only single-arm phase 2 studies have been conducted.[6,7]

Zamtocabtagene autoleucel (zamto-cel) is an autologous, ex vivo-generated CAR T-cell therapy comprising T cells enriched for CD4 and CD8 cells and genetically modified to express a bispecific tandem CD20 and CD19 CAR. The construct incorporates sequentially linked, single-chain variable fragments derived from Leu16 (targeting CD20) and FMC63 (targeting CD19), together with a 4-1BB costimulatory domain and a CD3 signalling domain. Dual targeting of CD20 and CD19 could mitigate antigen escape, improve the quality of response, and modify the toxicity profile as shown in mouse models.[8,9] Zamto-cel has shown high response rates and durable remissions in the US-based phase 1/2 DALY 1 (NCT03870945) and phase 2 DALY II (NCT04792489) studies.[10,11]

Consequently, in the DALY 2-EU trial, we aimed to compare the efficacy and safety of zamto-cel with rituximab–gemcitabine–oxaliplatin (R-GemOx) as a second-line treatment in patients with relapsed or refractory large B-cell lymphoma who were ineligible for transplantation.

Methods

Study design and patients

DALY 2-EU is an open-label, multicentre, randomised, phase 2 trial of zamto-cel versus R-GemOx (primary

Research in context

Evidence before this study

Large B-cell lymphoma is a rapidly growing haematological malignancy, predominantly affecting older adults with a median age of 68 years at first diagnosis and increasing incidence with age. To contextualise the current treatment landscape, we searched PubMed for reports of CAR T-cell therapy in second-line treatment for large B-cell lymphoma published from database inception to Jan 31, 2026, without language or study type restrictions. This search identified pivotal, randomised trials (TRANSFORM [NCT03575351] and ZUMA-7 [NCT03391466]) that showed superior efficacy of anti-CD19 CAR T-cell therapy over immunochemotherapy followed by high-dose chemotherapy and autologous stem-cell transplantation in patients who were eligible for transplantation. However, patients who are ineligible for transplantation (usually older than 70 years or with comorbidities) represent more than half of the relapsed or refractory large B-cell lymphoma patient population. At the time of trial design, there was no established standard of care for patients with relapsed or refractory large B-cell lymphoma who are ineligible for transplantation. Treatment was heterogenous and largely palliative, with platinum-based chemoimmunotherapy regimens such as rituximab–gemcitabine–oxaliplatin (R-GemOx) widely used as benchmark for disease control and tolerability, despite being unsuitable for some patients. At that time, only polatuzumab vedotin had conditional marketing authorisation in the EU, whereas other targeted therapies were not yet approved or widely implemented. These factors supported a trial design prospectively powered against R-GemOx with inclusion of a limited number of patients treated with polatuzumab-based therapy for contextualisation only. In this population, single-arm studies investigating CAR T-cell therapy (PILOT [NCT03483103] and ALYCANTE [NCT04531046]) have reported efficacy and safety outcomes; however, the relative benefit over established therapies is unknown.

Added value of this study

To our knowledge, DALY 2-EU is the first randomised trial of CAR T-cell therapy in patients with relapsed or refractory (≤24 months after start of first-line therapy) large B-cell lymphoma ineligible for transplantation. This study evaluated zamto-cel, a tandem CD20–CD19-directed CAR T-cell product, administered as a fresh formulation (ie, non-cryopreserved) after a fixed 12-day manufacturing process and a short vein-to-vein time of 15 days. The DALY 2-EU trial enrolled an older study population with high-risk disease features. Zamto-cel showed significant and clinically meaningful superior efficacy compared with R-GemOx, a prospectively selected comparator reflecting standard clinical practice at the time of study design.

Implications of all the available evidence

Taken together with existing evidence supporting CAR T-cell therapy in second-line relapsed or refractory large B-cell lymphoma, the results of the DALY 2-EU trial support consideration of zamto-cel as a second-line treatment option for patients with relapsed or refractory large B-cell lymphoma who are ineligible for transplantation. Further follow-up and additional studies are needed to define durability of benefit, generalisability to a broader patient population, the role of dual-antigen targeting in reducing antigen escape, and the optimal treatment sequencing.

analysis) or chemoimmunotherapy with R-GemOx or polatuzumab vedotin, bendamustine, and rituximab (Pola-BR; secondary analysis) in patients with relapsed or refractory large B-cell lymphoma who were ineligible for transplantation (appendix 1 p 2). In this Article, we report the results of the primary analysis. Patients were recruited at 45 academic medical centres, university hospitals, and specialised haematology–oncology centres across 12 European countries (appendix 1 pp 4–6).

Eligible patients were adults (aged ≥18 years) with histologically confirmed large B-cell lymphoma, an estimated life expectancy of more than 3 months, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, use of a previous first-line chemoimmunotherapy containing an anthracycline-based regimen and an anti-CD20 monoclonal antibody, and relapsed or refractory disease. Refractory disease was defined as no complete response to first-line therapy, progressive disease after two or more cycles of first-line therapy, stable disease after four cycles of first-line therapy, a partial response as the best response after six or more cycles, or biopsy-proven persistent disease for 24 months or less from the start of first-line therapy. Relapsed disease was defined as complete remission to first-line therapy followed by biopsy-proven progression within 24 months or less after first-line therapy. Eligible histological diagnoses were based on WHO's 2016 classification[12] and included diffuse large B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma with *MYC* and *BCL2* or *BCL6* (or both) rearrangements, and disease transformed from a previous low-grade lymphoma. Local histological diagnoses were reassessed by independent central pathology assessments. Patients were required to have one or more transplant-ineligibility criteria: 18 years or older with previous autologous stem cell transplantation (as first-line consolidation) or a haematopoietic cell transplantation-specific comorbidity index score greater than 3, or 65 years or older with at least one comorbidity, including impaired cardiac function, impaired renal function, impaired pulmonary function or dyspnoea on slight activity, or ECOG performance score of more than 1; patients 70 years or older were eligible irrespective of comorbidities. Patients who had received more than one line of treatment for diffuse large B-cell lymphoma, or any other experimental treatment within the previous 4 weeks or five half-lives (whichever was longer), were excluded (appendix 1 pp 8–9). No cancer survivors or patient representatives were involved in the study design, conduct, data analysis or interpretation, or writing of the report. Patients provided written informed consent before any study-related procedures. Gender (male, female, or diverse), race, and ethnicity were self-reported.

A major protocol amendment (dated Feb 9, 2023, 16 months after the start of recruitment) allowed for the inclusion of patients with relapsed disease confirmed within 24 months from the start of first-line therapy (previously ≤12 months from the completion of the first-line therapy). The amendment also introduced a one-sided crossover from the comparator group to zamto-cel for patients who relapsed or progressed within 1 year of randomisation or did not reach a partial or complete response at or beyond 8 weeks after randomisation.

See Online for appendix 1

The study was conducted in accordance with the Declaration of Helsinki, International Council of Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. Principal investigators obtained Independent Ethical Committees approval (appendix 1 p 7). This ongoing trial is registered with ClinicalTrials.gov (NCT04844866) and EudraCT (2020-003908-14). The study protocol and statistical analysis plan are available in appendix 2.

See Online for appendix 2

Randomisation and masking

An interactive web response system randomly allocated eligible patients (1:1) to receive either zamto-cel or chemoimmunotherapy (ie, R-GemOx or Pola-BR at the investigator's discretion). Up to 10% of patients randomised to the comparator group could receive Pola-BR. The randomisation sequence was generated by an external vendor using a biased-coin minimisation algorithm (probability 0·80 *vs* 0·20) to balance treatment allocation across stratification factors. Stratification factors were age, gender, lactate dehydrogenase, International Prognostic Index (IPI), histology, time to relapse after the start of first-line therapy, and country (appendix 1 p 3). Participants and investigators were unmasked to group assignment. An Independent Review Committee (IRC) that was masked to group assignments evaluated efficacy outcomes. Data were analysed—as prespecified in the statistical analysis plan, which was finalised before the random assignment of the first participant—by an external service provider who was unmasked to group assignment.

Procedures

Patients randomly assigned to the zamto-cel group had leukapheresis. After a protocol amendment, leukapheresis was also offered to the comparator group. Holding and bridging therapy was not allowed in the zamto-cel group except for corticosteroids for 4 days. Lymphodepleting chemotherapy with cyclophosphamide (300 mg/m²) and fludarabine (30 mg/m²) was administered over 3 days during CAR T-cell manufacturing, starting 5 days before the zamto-cel infusion (ie, on day −5, day −4, and day −3). Zamto-cel was manufactured in a 12-day process on the CliniMACS Prodigy machine (Miltenyi Biotec, Bergisch Gladbach, Germany) and administered as a single, fresh (ie, non-cryopreserved), intravenous infusion of $2{\cdot}5\times10^6$ CAR-transduced autologous T cells per kg bodyweight,

capped at 100 kg. Follow-up is ongoing and for up to 6 years per patient (appendix 1 p 3).

Comparator therapy comprised up to eight 14-day cycles of R-GemOx (rituximab 375 mg/m² intravenously on day 1, gemcitabine 1000 mg/m² intravenously on day 1 or 2, and oxaliplatin 100 mg/m² intravenously on day 1 or 2), or six 21-day cycles of Pola-BR (polatuzumab vedotin 1·8 mg/kg intravenously on day 1, bendamustine 90 mg/m² intravenously on days 1 and 2, and rituximab 375 mg/m² intravenously on day 1). After a protocol amendment, patients randomised to the comparator group with progressive disease or insufficient clinical response could crossover for zamto-cel treatment after sponsor approval. Comparator dose modifications followed the Summary of Product Characteristics and institutional standards.

Efficacy was assessed locally with diagnostic CT or MRI scans and PET-CT scans until disease progression, the withdrawal of consent, the initiation of a new antilymphoma therapy, or death. PET scans were performed at similar follow-up timepoints in both groups: 8 weeks after the reference timepoint (ie, leukapheresis and start of first chemotherapy cycle) and at weeks 16, 26, 38, 50, and 74, and approximately at years 2, 3, 4, and 5 after the reference timepoint. Response was assessed per the Lugano classification[13] criteria by an IRC masked to the study treatment. A baseline sum of the products of perpendicular diameters of 5000 mm² or more, calculated from CT-based target lesion measurements, was used as a predefined descriptive measure of morphological tumour burden. Patients with stable disease or disease progression could be further treated at the investigator's discretion.

Adverse events and treatment-emergent adverse events were reported, continuously recorded in the electronic case report form, coded centrally according to the Medical Dictionary for Regulatory Activities version 28.0 or higher, and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; version 5.0) by investigators or delegated site staff. Treatment-emergent adverse events were defined as adverse events occurring up to 90 days after zamto-cel infusion and before the start date of new antilymphoma therapy, and from the first chemoimmunotherapy dose to 30 days after the end of the last comparator treatment cycle or date of crossover approval and starting before the start date of new anti-lymphoma therapy (appendix 1 p 10). Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per American Society for Transplantation and Cellular Therapy and NCI CTCAE criteria by investigators or delegated site staff (appendix 1 pp 11–12).[14] Protocol-defined CRS symptoms included fever (ie, temperature ≥38°C), hypotension (graded by vasopressor requirement), and hypoxia (graded by oxygen support requirement). CRS grades were established from the most severe event of hypotension or hypoxia. Protocol-defined ICANS symptoms were assessed across five domains: immune effector cell-associated encephalopathy score (ie, cognitive function), depressed consciousness, seizures, motor findings, and raised intracranial pressure (ie, cerebral oedema). ICANS grades were established from the most severe event across all domains. Zamto-cel-specific adverse events of special interest included grade 3 or higher CRS or ICANS, secondary malignancies, life-threatening infections, and new-onset autoimmune diseases. Adverse events of special interest in both groups included relapse or disease progression and death from any cause. Cytopenias were identified based on laboratory values from haematology assessments. Prolonged cytopenias were defined as grade 3 or higher anaemia, neutropenia, or thrombocytopenia present at day 28 after infusion; delayed cytopenias were defined as grade 3 or higher anaemia, neutropenia, or thrombocytopenia with onset between days 28 and 90 after infusion. Hypogammaglobulinaemia was defined as IgG less than 4 g/L. B-cell aplasia was defined as fewer than 5 B cells per µL. Laboratory testing, including pregnancy testing, serology, clinical chemistry, haematology, coagulation, inflammatory markers, and COVID-19 testing, was done per the protocol.

Patients were able to withdraw from study participation at any time and for any reason, including changes rendering them unsuitable for cell infusion at the judgement of the investigator, adverse events, withdrawal of consent, loss to follow-up, or pregnancy. Patients discontinuing prematurely were encouraged to continue follow-up assessments.

Outcomes

The primary endpoint was IRC-assessed event-free survival, defined as the time from randomisation to objective disease progression, not reaching partial response or complete response at or beyond week 8 after randomisation leading to initiation of new antilymphoma therapy, or death from any cause, whichever occurred first. Key secondary efficacy endpoints were IRC-assessed progression-free survival, IRC-assessed best complete response until week 24 (in zamto-cel) or week 26 (in R-GemOx), IRC-assessed duration of complete response, and overall survival. Progression-free survival was defined as the time from randomisation to objective disease progression or death from any cause, whichever occurred first. Best complete response rate was defined as the proportion of patients with at least one complete response assessment up to week 24 in the zamto-cel treatment group and week 26 in the R-GemOx treatment group. Duration of complete response was defined as the time from first complete response to objective disease progression or death from any cause, whichever occurred first. Overall survival was defined as the time from randomisation to death from any cause.

Best objective response, defined as the best objective response in the time between the date of randomisation and the date of objective disease progression, the start of new antilymphoma therapy, or the date of death from any cause, is the only other secondary efficacy endpoint reported in this paper (appendix 1 pp 13–16). Safety endpoints were the proportions of adverse events, serious adverse events, and adverse events of special interest, as well as hospitalisations, days at an intensive care unit (ICU), use of tocilizumab or high-dose corticosteroids, and requirements for transfusions, antimicrobial therapy, or immunoglobulin substitution.

Exploratory endpoints included tumour CD19 and CD20 expression in case of relapse after zamto-cel treatment, and cellular kinetics and dynamics in the zamto-cel and crossover cohort. CD19 and CD20 expression were assessed with H-scores, calculated as the percentage of positive cells multiplied by staining intensity (1+, 2+, or 3+); positivity was defined as an H-score of 5 or higher, with dual CD19 and CD20 positivity defined as an H-score of 5 or higher for both markers (appendix 1 p 20). Other prespecified secondary and exploratory endpoints (appendix 1 pp 13–16) are not reported in this Article and will be addressed in future publications.

Statistical analysis

A planned sample size of 168 patients provided at least 93% power to detect differences in event-free survival, assuming a median event-free survival of 3·25 months for R-GemOx, 6·00 months for Pola-BR, and 6·25 months for zamto-cel, and a hazard ratio (HR) of 0·52 for zamto-cel versus R-GemOx.

The full analysis set included all randomly assigned patients (ie, intention-to-treat analysis) by allocated treatment group and was used for efficacy analyses. The modified full analysis set included patients with evidence of disease at baseline and at least one valid efficacy assessment after baseline and was used for sensitivity analyses. Safety analyses used the safety analysis set, which included all patients who received any amount of the study drug, according to treatment received (appendix 1 p 21). The comparator group was defined as all patients allocated to one of the two prespecified comparator regimens: R-GemOx or Pola-BR.

The primary analysis (event-free survival: zamto-cel versus R-GemOx) was conducted after all patients completed the 6-month visit, were lost to follow-up, or had died. We estimated treatment effects on event-free survival as HRs with 95% CIs using Cox proportional hazards models with IPI, histology, and time to relapse after first-line therapy as covariates. Treatment effects were tested statistically with a stratified log-rank test. A post-hoc sensitivity analysis was conducted with a Cox proportional hazard model adjusting for all stratification factors used in the biased coin minimisation algorithm. Zamto-cel was compared with the comparator group only if the primary analysis was significant. Superiority required a one-sided p value of ≤0·025.

Key secondary endpoints were analysed hierarchically (appendix 1 pp 3–4). Progression-free survival and duration of complete response were assessed with the stratified log-rank approach. Best complete response rates (at week 24 or 26) were compared with a one-sided stratified Cochran–Mantel–Haenszel test with relative risks and 95% CIs. Overall survival was analysed with a rank-preserving structural failure time model. Other endpoints were descriptive. Prespecified secondary analyses of efficacy endpoints based on investigator assessment were conducted with the same statistical methods as the corresponding independent review committee-assessed analyses. Adverse events were summarised by frequency and percentage in treated patients. No imputation was applied for time-to-event endpoints; missing responses were treated as non-responses. We conducted analyses using SAS (version 9.4 or higher).

Censoring rules for the time-to-event endpoints are provided in appendix 1 (pp 17–19). Prespecified event and censoring rules for all time-to-event endpoints are provided in appendix 1 (p 31).

Role of the funding source

The funder of the study participated in the study design, data collection, data analysis, data interpretation, and the writing of the paper.

Results

Between Oct 14, 2021, and July 16, 2024, 168 (77%) of 219 screened patients were randomised in the DALY 2-EU trial, with 51 deemed ineligible (48 due to screening failure [appendix 1 p 26] and three were not randomly assigned). 82 patients were assigned to the zamto-cel group and 78 to the R-GemOx group (figure 1). Patients were predominantly male (100 [63%] of 160 were men and 60 [38%] were women) and White (91 [57%], five [3%] other, and 64 [40%] with race not reported). Baseline demographic and disease characteristics were balanced and represented an older population (median age 74·0 years [IQR 70·5–77·0]) with high-risk disease characteristics as indicated by an IPI score of 3–5 in 92 (58%) of 160 patients and including 107 (67%) patients with advanced-stage disease (stage III or IV). High tumour burden, defined as a sum of the products of perpendicular diameters greater than 5000 mm², was observed in 45 (28%) of 160 patients. An ECOG performance status score of 2 was present in 41 (26%) of 160 patients with an imbalance in the treatment groups (25 [30%] of 82 in the zamto-cel group and 16 [21%] of 78 in the R-GemOx group). Most patients (110 [69%]) had diffuse large B-cell lymphoma not otherwise specified, as per local assessment (table 1; appendix 1 pp 22–24). Of the 82 patients in the zamto-cel group who met at

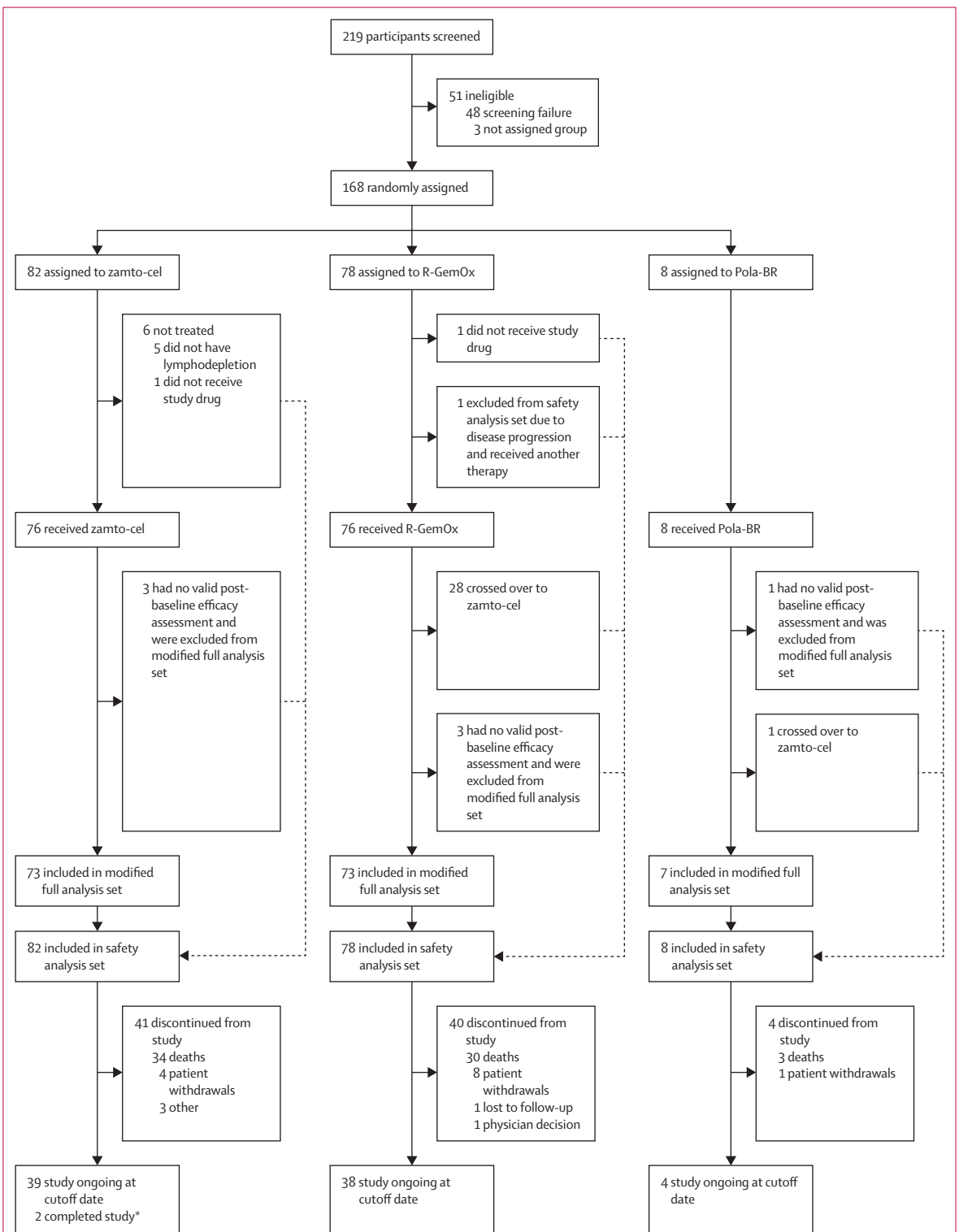

Figure 1: **Trial profile**
*For these two patients, trial completion refers to the completion of all protocol-specified assessments up to the end of follow-up, which was approximately 2 years from informed consent.

	Zamto-cel (n=82)	R-GemOx (n=78)
Gender		
Male	52 (63%)	48 (62%)
Female	30 (37%)	30 (38%)
Age, years		
Median (IQR)	74·5 (71·0–78·0)	74·0 (70·0–77·0)
18–64	2 (2%)	5 (6%)
65–74	39 (48%)	40 (51%)
75–84	40 (49%)	32 (41%)
≥85	1 (1%)	1 (1%)
Race*		
White	44 (54%)	47 (60%)
Other	4 (5%)	1 (1%)
Not reported	34 (41%)	30 (38%)
Ethnicity*		
Hispanic or Latino	1 (1%)	2 (3%)
Not Hispanic or Latino	42 (51%)	41 (53%)
Not reported	39 (48%)	35 (45%)
ECOG performance status score		
0	24 (29%)	31 (40%)
1	33 (40%)	31 (40%)
2	25 (30%)	16 (21%)
Histological large B-cell lymphoma diagnosis by investigator assessment		
DLBCL not otherwise specified	62 (76%)	48 (62%)
HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements with DLBCL, blastoid, or intermediate histology or HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangement	5 (6%)	9 (12%)
Disease transformed from an earlier diagnosis of low-grade lymphoma into DLBCL with DLBCL disease progression subsequent to DLBCL-directed systemic treatment	9 (11%)	11 (14%)
Other	6 (7%)	10 (13%)
Cell of origin, by Hans classifier		
Non-germinal centre type	42 (51%)	36 (46%)
Germinal centre type	37 (45%)	38 (49%)
Missing	3 (4%)	4 (5%)
Previous response status		
Refractory‡	42 (51%)	47 (60%)
Not refractory	40 (49%)	31 (40%)
Time to relapse after the start of first-line therapy†		
≤12 months	20/40 (50%)	18/31 (58%)
>12 to ≤18 months	11/40 (28%)	8/31 (26%)
>18 to ≤24 months	6/40 (15%)	5/31 (16%)
Missing	3/40 (8%)	0

(Table 1 continues in next column)

(Continued from previous column)

	Zamto-cel (n=82)	R-GemOx (n=78)
SPD, mm²	2383·5 (1085·0–5340·0)	3315·4 (1472·0–5239·1)
SPD ≥5000 mm²	23 (28%)	22 (28%)
Number of extranodal involvement sites		
≤1	54 (66%)	52 (67%)
≥2	28 (34%)	26 (33%)
Modified Ann Arbor stage		
I to II	27 (33%)	26 (33%)
III to IV	55 (67%)	52 (67%)
International Prognostic Index score		
0–2	35 (43%)	33 (42%)
3–5	47 (57%)	45 (58%)
Left ventricular ejection fraction	59% (55–64)	59% (54–63)
<50%	10 (12%)	10 (13%)
FEV_1 (% predicted)	98·0 (82·0–108·0)	90·5 (76·5–105·0)
>70%	68/81 (84%)	67 (86%)
50–70%	12/81 (15%)	8 (10%)
<50%	1/81 (1%)	3 (4%)
Haematopoietic cell transplantation-specific comorbidity index score		
0–1	24 (29%)	25 (32%)
≥2	46 (56%)	48 (62%)
Missing	12 (15%)	5 (6%)
Lactate dehydrogenase		
≤2 × ULN	68 (83%)	64 (82%)
>2 × ULN	11 (13%)	10 (13%)
Missing	3 (4%)	4 (5%)
CD19 positivity		
Yes (H-Score CD19 ≥5)	78 (95%)	72 (92%)
No (H-Score CD19 <5)	1 (1%)	1 (1%)
Missing	3 (4%)	5 (6%)
CD20 positivity		
Yes (H-Score CD20 ≥5)	77 (94%)	72 (92%)
No (H-Score CD20 <5)	3 (4%)	3 (4%)
Negative CD19 and CD20	0	0
Missing	2 (2%)	3 (4%)
Bridging therapy with corticosteroids	17 (21%)	1 (1%)

Data are n (%) or median (IQR). DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. FEV_1=forced expiratory volume in 1 s. HGBCL=high-grade B-cell lymphoma. SPD=sum of perpendicular diameters. ULN=upper limit of normal. *Per US Census Bureau classifications. †Denominators represent the numbers of patients with relapse.

Table 1: **Demographic and baseline clinical characteristics**

least one transplant-ineligibility criterion, 66 (80%) were 70 years or older and 44 (54%) had impaired pulmonary function. Baseline haematological parameters are summarised in appendix 1 (p 25). Analyses of the comparator group (R-GemOx plus Pola-BR) are reported in appendix 1 (pp 23–24, 35–36, 38).

Zamto-cel was manufactured from the initial leukapheresis on the first attempt for all patients intended

to receive zamto-cel and was administered in 76 (93%) of 82 patients in this group at a median dose of $2·3×10^6$ zamto-cel CAR T-cells/kg (IQR 2·22–2·39). All randomly assigned patients received the fresh formulation of zamto-cel, whereas four crossover patients received a cryopreserved product. The median vein-to-vein time (leukapheresis to infusion) was 15 days (IQR 15–16) with a time between randomisation and infusion of 20 days (range 17–21). Of the six patients who did not receive zamto-cel, five did not proceed to lymphodepletion and one underwent lymphodepletion but did not receive the zamto-cel infusion. The reasons for not receiving zamto-cel were consent withdrawal in two patients, disease progression in three, and pneumonia in one. R-GemOx was administered in 76 (97%) of 78 patients in the R-GemOx group, and the median number of cycles administered was 4·0 (IQR 3·0–6·5), with 14 (18%) patients receiving eight cycles. Dose adjustments occurred in 24 (32%) of 76 patients and were most frequently related to oxaliplatin in 22 (29%) patients, mainly due to the onset or worsening of polyneuropathy. Of the two patients who did not receive R-GemOx, one withdrew consent and one had disease progression and received another therapy. Study treatment exposure and corticosteroid administration before study treatment are detailed in appendix 1 (pp 27–30).

Data cutoff was Jan 15, 2025. The median event-free survival was significantly longer in the zamto-cel group than in the R-GemOx group (6·21 months [95% CI 3·84–13·77] *vs* 2·53 months [1·97–3·35]; HR 0·39 [95% CI 0·27–0·58]; p<0·0001) after a median follow-up of 17·0 months (IQR 9·0–22·8; figure 2; table 2; appendix 1 p 31). Proportional hazards assumptions were evaluated with log-minus-log survival plots, which showed parallel curves across groups, supporting that the proportional hazards assumption was met. This benefit was shown across most prespecified subgroup analyses (appendix 1 p 32). A sensitivity analysis to the primary analysis, adjusting for the full set of minimisation factors, did not yield any statistically or clinically relevant

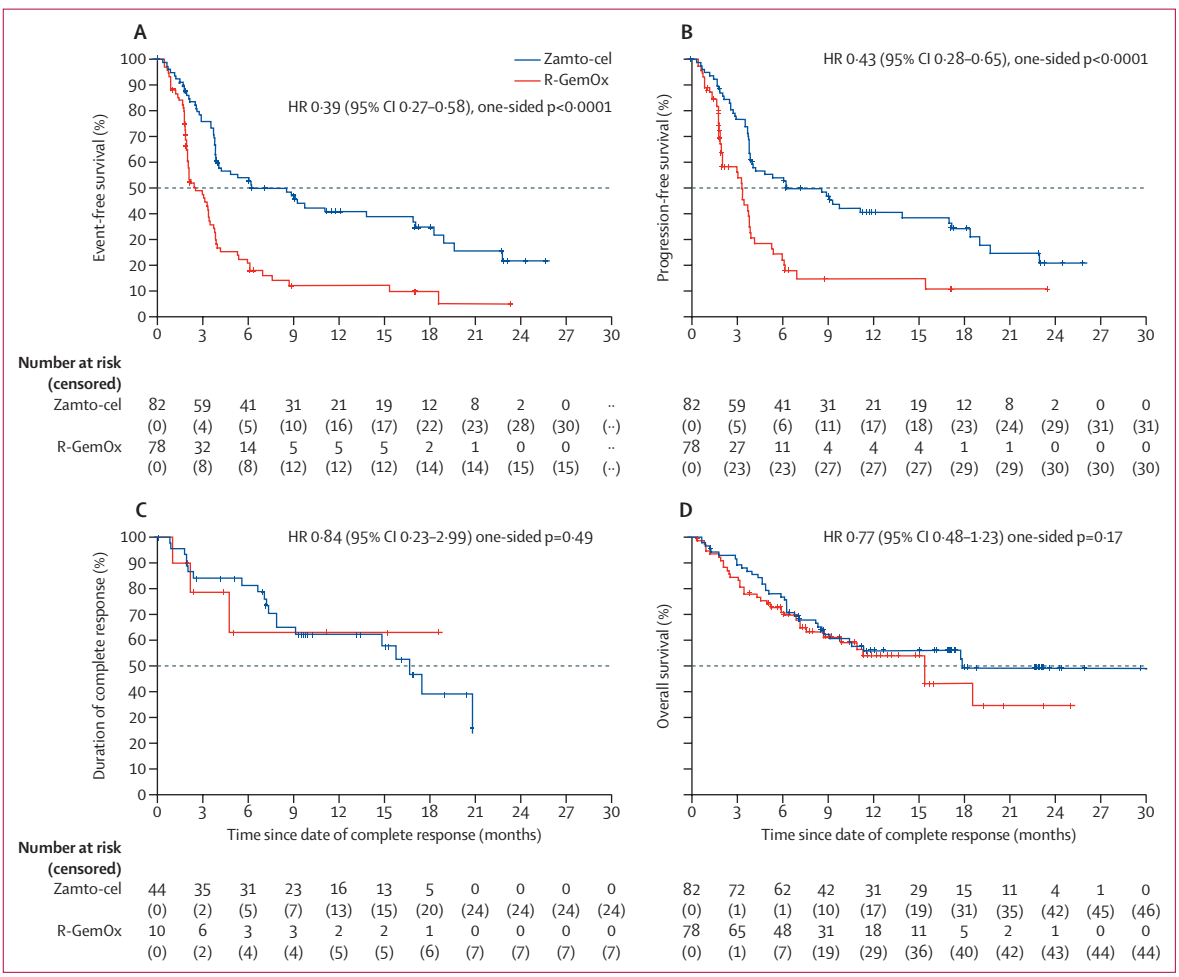

Figure 2: **Kaplan–Meier estimates of independent review committee-assessed time-to-event endpoints**
(A) Event-free survival. (B) Progression-free survival. (C) Duration of complete response. (D) Overall survival by rank-preserving structural failure time. HR=hazard ratio.

changes to the results of the primary analysis model (appendix 1 p 33).

Confirmatory testing of key secondary endpoints was conducted following statistical significance of the primary and secondary analysis of the primary endpoint (appendix 1 p 33). The median progression-free survival was significantly longer in the zamto-cel group than in the R-GemOx group (8·51 months [95% CI 3·84–16·82]

	Zamto-cel (n=82)	R-GemOx (n=78)	Stratified HR or RR (95% CI)	One-sided p value
Primary endpoint				
Event-free survival based on IRC assessment				
Patients with events	52 (63%)	63 (81%)	NA	NA
Death	8/52 (15%)	12/63 (19%)	NA	NA
Disease progression	44/52 (85%)	44/63 (70%)	NA	NA
Did not reach partial or complete response at or beyond week 8, leading to the initiation of new antilymphoma therapy	0	7/63 (11%)	NA	NA
Median event-free survival (95% CI), months	6·21 (3·84–13·77)	2·53 (1·97–3·35)	HR 0·39 (0·27–0·58)	<0·0001
Post-hoc sensitivity analysis	NA	NA	HR 0·34 (0·23–0·51)*	<0·0001*
6-month rate (95% CI)	54% (42–64)	21% (12–31)	NA	NA
12-month rate (95% CI)	41% (29–52)	12% (5–21)	NA	NA
Key secondary endpoints				
Progression-free survival based on IRC assessment				
Patients with events	51 (62%)	48 (62%)	NA	NA
Death	7/51 (14%)	4/48 (8%)	NA	NA
Disease progression	44/51 (86%)	44/48 (92%)	NA	NA
Median (95% CI), months	8·51 (3·84–16·82)	3·35 (2·04–3·81)	HR 0·43 (0·28–0·65)	<0·0001
6-month rate (95% CI)	54% (43–65)	23% (13–35)	NA	NA
12-month rate (95% CI)	41% (30–52)	16% (7–28)	NA	NA
Best complete response rate until week 24 in zamto-cel or week 26 in R-GemOx based on IRC assessment				
Patients with confirmed complete response (95% CI)	40 (49%; 37·58–60·08)	11 (14%; 7·26–23·83)	RR 3·45 (1·91–6·21)	<0·0001
Duration of complete response based on IRC assessment				
Patients with confirmed complete response	44 (54%)	10 (13%)	NA	NA
Median duration (95% CI), months	16·59 (7·82–not calculable)	Not calculable (0·95–not calculable)	HR 0·84 (0·23–2·99)	0·49
6-month rate (95% CI)	81% (66–90)	63% (22–87)	NA	NA
12-month rate (95% CI)	62% (45–75)	63% (22–87)	NA	NA
Overall survival via RPSFT				
Patients with events	36 (44%)	34 (44%)	NA	NA
Median (95% CI), months	17·81 (9·07–not calculable)	15·28 (8·67–not calculable)	HR 0·77 (0·48–1·23)	0·17
6-month rate (95% CI)	77% (66–84)	70% (58–79)	NA	NA
12-month rate (95% CI)	56% (44–66)	54% (40–66)	NA	NA
Other secondary endpoints				
Best objective response based on IRC assessment				
Best objective response, complete response, or partial response	59 (72%)	35 (45%)	RR 1·63 (1·23–2·17)	0·0001
Complete response	44 (54%)	11 (14%)	NA	NA
Partial response	15 (18%)	24 (31%)	NA	NA
Stable disease	3 (4%)	10 (13%)	NA	NA
Progressive disease	13 (16%)	26 (33%)	NA	NA
Not evaluable	0	0	NA	NA
Missing	7 (9%)	7 (9%)	NA	NA

Data are n (%) unless otherwise specified. Treatment effects on time-to-event endpoints were estimated as HRs with 95% CIs with Cox proportional hazards models with International Prognostic Index, histology, and time to relapse after first-line therapy as covariates. Treatment effects were tested statistically with a stratified log-rank test; proportional hazards assumptions were formally assessed. Best complete response rate was analysed with a one-sided stratified Cochran–Mantel–Haenszel test, with missing responses imputed as non-response. Overall survival was analysed with the RPSFT model adjusted for treatment switching. HR=hazard ratio. IRC=independent review committee. NA=not applicable. RPSFT=rank-preserving structural failure time. RR=relative risk. *Post-hoc sensitivity analysis with a Cox proportional hazard model adjusting for the full set of stratification factors.

Table 2: **Summary of efficacy results**

vs 3·35 months [2·04–3·81]; HR 0·43 [95% CI 0·28–0·65]; p<0·0001), (figure 2; table 2). No significant difference in overall survival between zamto-cel and R-GemOx was observed (figure 2; table 2). The best complete response rate was higher with zamto-cel than with R-GemOx (40 [49%] of 82 *vs* 11 [14%] of 78; p<0·0001), whereas no significant difference in the median duration of complete response was observed (HR 0·84 [95% CI 0·23–2·99]; p=0·49; figure 2; table 2).

The best objective response rate was higher in the zamto-cel group than in the R-GemOx group (59 [72%] of 82 *vs* 35 [45%] of 78). 44 (54%) patients had complete remission in the zamto-cel group compared with 11 (14%) patients in the R-GemOx group. In the modified full analysis set, 44 (60%) of 73 patients in the zamto-cel group had a complete response compared with 11 (15%) of 73 patients in the R-GemOx group (appendix 1 p 33). Investigator-assessed efficacy outcomes are reported in appendix 1 (p 34). Similar efficacy benefits were observed for zamto-cel when compared with the comparator group (appendix 1 pp 35–36). 38 (46%) of 82 patients in the zamto-cel group and 36 (46%) of 78 patients in the R-GemOx group received further therapies off-protocol (appendix 1 p 37).

Almost all patients receiving study treatment had a treatment-emergent adverse event (zamto-cel: 75 [99%] of 76; R-GemOx: 76 [100%] of 76]; table 3; appendix 1 p 38). CRS was the most common treatment-emergent adverse event with zamto-cel (59 [78%]), whereas anaemia was the most frequent with R-GemOx (26 [34%]). 31 (41%) patients in the zamto-cel group and 50 (66%) in the R-GemOx group had a serious treatment-emergent adverse event. The most common serious treatment-emergent adverse event in both groups was malignant neoplasm progression (11 [14%] in the zamto-cel group and 38 [50%] in the R-GemOx group; a full list is available in appendix 1 [pp 39–40]). Treatment-emergent deaths occurred in eight (10%) of 82 in the zamto-cel group and eight (10%) of 78 in the R-GemOx group (appendix 1 p 38), mainly due to disease progression (four patients in each group). According to investigator assessment, treatment-related deaths occurred in two (3%) patients with zamto-cel (CRS and haemophagocytic lymphohistiocytosis) and one (1%) with R-GemOx (malignant lymphoma progression).

In the zamto-cel group, all-grade CRS was observed in 59 (78%) of 76 patients, with a maximum of grade 1 CRS observed in 35 (46%), a maximum of grade 2 in 20 (26%), and a maximum of grade 3 or higher in four (5%). Tocilizumab was administered in 29 (38%) patients and corticosteroids were administered in 14 (18%). All-grade ICANS was observed in eight (11%) patients, with maximum of grade 1 in four (5%), maximum of grade 2 in three (4%), and maximum of grade 3 in one (1%). Consistent with the low incidence and severity of ICANS, corticosteroids were administered in six (8%) patients. With respect to haematological toxicity, prolonged cytopenias were observed in ten (13%) patients with zamto-cel (table 4; appendix 1 p 42) and two (3%) patients with R-GemOx. At baseline, B-cell aplasia (ie, <5 B cells per µL) was present in 72 (95%) of 76 patients and declined over time to 48 (63%) at week 16 after leukapheresis. The highest incidence of hypogammaglobulinaemia (IgG <4 g/L) was observed at week 10 after leukapheresis, affecting 16 (21%) patients (appendix 1 p 43); three (4%) of these patients received immunoglobulin replacement therapy administered according to institutional standards from onset until the resolution of hypogammaglobulinaemia.

All-grade infections and infestations occurred in 34 (45%) of 76 patients with zamto-cel and 23 (30%) of 76 patients with R-GemOx (appendix 1 p 44). COVID-19 was the most common infection-related treatment-emergent adverse event, occurring in six (8%) patients with zamto-cel and in nine (12%) patients with R-GemOx. Grade 3 or higher treatment-emergent infections and infestations occurred in 14 (18%) patients with zamto-cel and ten (13%) with R-GemOx (appendix 1 p 44).

ICU admissions within 7 months of randomisation (excluding prophylactic ICU surveillance) were reported in six (8%) of 76 patients with zamto-cel and three (4%) of 76 patients with R-GemOx, with a median duration of 8 days (IQR 2–12) with zamto-cel and 2 days (IQR 1–11) with R-GemOx (appendix 1 p 45). Of 54 patients in the comparator group with crossover option, 31 (57%) met the eligibility criteria and were approved for the one-sided crossover, of whom 29 (28 [37%] from the R-GemOx group and one [13%] from the Pola-BR group) received zamto-cel treatment. Based on investigator assessments, the best objective response was observed in 23 (79%) of 29 patients (95% CI 60·3–92·0), including 19 (66%) with a complete response (appendix 1 p 46). Safety outcomes were generally consistent with those observed in the overall study population; however, a lower incidence of CRS was observed in the crossover population than in the main population, with 14 (48%) of 29 in the crossover population having any grade CRS and two (7%) having events of grade 3 or higher. All-grade ICANS occurred in five (17%) patients, with grade 3 or higher ICANS reported in one (3%).

12 (16%) patients in the zamto-cel group who had disease progression after treatment underwent biopsies with central assessment for both CD19 and CD20 expression. CD19 and CD20 losses (ie, H-score of <5 at follow-up assessment if H-score was >5 at screening) were each observed in one (8%) of 12 patients. No double antigen losses were observed.

Discussion

To our knowledge, DALY 2-EU is the first randomised study comparing second-line CAR T-cell therapy (zamto-cel) with chemoimmunotherapy (R-GemOx) in patients ineligible for transplantation. Zamto-cel

showed a significant and clinically relevant benefit in event-free survival with a HR of 0·39, and the efficacy was consistent across key subgroups, including both high-risk disease and patient characteristics. Zamto-cel treatment was associated with low rates of severe CRS or ICANS, despite a population of patients at high risk. In addition, automated manufacturing allowed rapid production of zamto-cel and treatment of almost all patients.

The DALY 2-EU study included an older patient population at very high risk of second-line treatment failure, as indicated by the high prevalence of refractory disease (56%), IPI scores of 3–5 (58%), and ECOG performance status scores of 2 (26%). Treatment with the standard regimen R-GemOx in the modified full analysis set achieved a complete response rate of 15%, which is lower than reported in previous studies[15–17] and reflects the very high-risk population enrolled in this trial. In the modified full analysis set, treatment with zamto-cel increased the complete response rate to 60%. CAR T-cell therapies directed only at CD19 have also shown efficacy in phase 2 trials in patients ineligible for transplantation; however, differences in study designs and included patient populations make direct comparisons difficult.[6,7] In 61 patients who received lisocabtagene maraleucel, a complete response rate of 54% (95% CI 41–67) and a 12-month event-free survival rate of 47% (33–59) were reported.[7] Consistent with these findings, a real-world comparative analysis of lisocabtagene maraleucel against conventional chemotherapy in the PILOT study showed superior outcomes with CAR T-cell therapy in patients ineligible for transplantation with large B-cell lymphoma

	Zamto-cel (n=76)					R-GemOx (n=76)				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Missing	Grade 1–2	Grade 3	Grade 4	Grade 5	Missing
Any treatment-emergent adverse event	12 (16%)	17 (22%)	33 (43%)	13 (17%)	0	10 (13%)	31 (41%)	20 (26%)	14 (18%)	1 (1%)
Blood and lymphatic system disorders										
Neutropenia	2 (3%)	7 (9%)	21 (28%)	0	0	4 (5%)	8 (11%)	9 (12%)	0	0
Anaemia	8 (11%)	11 (14%)	0	0	0	14 (18%)	12 (16%)	0	0	0
Thrombocytopenia	6 (8%)	4 (5%)	2 (3%)	0	0	4 (5%)	7 (9%)	6 (8%)	0	0
Leukopenia	2 (3%)	3 (4%)	7 (9%)	0	0	1 (1%)	5 (7%)	2 (3%)	0	0
Lymphopenia	1 (1%)	1 (1%)	6 (8%)	0	0	1 (1%)	0	1 (1%)	0	0
Febrile neutropenia	0	4 (5%)	0	0	0	0	0	0	0	0
Hypofibrinogenaemia	1 (1%)	1 (1%)	0	0	0	0	0	0	0	0
Leukocytosis	0	1 (1%)	0	0	0	0	0	0	0	0
Pancytopenia	0	1 (1%)	0	0	0	0	0	0	0	0
Investigations										
Neutrophil count decreased	3 (4%)	4 (5%)	16 (21%)	0	0	0	6 (8%)	1 (1%)	0	0
Platelet count decreased	4 (5%)	3 (4%)	3 (4%)	0	0	5 (7%)	3 (4%)	3 (4%)	0	0
Alanine aminotransferase increased	4 (5%)	1 (1%)	0	0	0	8 (11%)	3 (4%)	0	0	0
White blood cell count decreased	1 (1%)	3 (4%)	7 (9%)	0	0	0	4 (5%)	0	0	0
Aspartate aminotransferase increased	2 (3%)	0	0	0	0	7 (9%)	3 (4%)	0	0	0
Oxygen saturation decreased	8 (11%)	1 (1%)	1 (1%)	1 (1%)	0	0	0	0	0	0
Lymphocyte count decreased	0	1 (1%)	6 (8%)	0	0	1 (1%)	1 (1%)	0	0	0
C-reactive protein increased	3 (4%)	3 (4%)	0	0	1 (1%)	0	1 (1%)	0	0	0
T-lymphocyte count decreased	2 (3%)	2 (3%)	4 (5%)	0	0	0	0	0	0	0
CD4 lymphocytes decreased	1 (1%)	2 (3%)	4 (5%)	0	0	0	0	0	0	0
CD8 lymphocytes decreased	1 (1%)	2 (3%)	3 (4%)	0	0	0	0	0	0	0
Natural killer cell count decreased	0	1 (1%)	3 (4%)	0	1 (1%)	0	0	0	0	0
Serum ferritin increased	0	2 (3%)	0	0	2 (3%)	1 (1%)	0	0	0	0
Gamma-glutamyltransferase increased	1 (1%)	0	0	0	0	2 (3%)	1 (1%)	0	0	0
Monocyte count decreased	0	3 (4%)	1 (1%)	0	0	0	0	0	0	0
CD19 lymphocytes decreased	2 (3%)	0	1 (1%)	0	1 (1%)	0	0	0	0	0
Blood creatinine increased	1 (1%)	2 (3%)	0	0	0	1 (1%)	0	0	0	0
Blood IgG decreased	1 (1%)	1 (1%)	0	0	0	0	0	0	0	0
Blood glucose increased	0	1 (1%)	0	0	0	0	0	0	0	0
Blood magnesium decreased	0	1 (1%)	0	0	0	0	0	0	0	0
Procalcitonin increased	0	1 (1%)	0	0	0	0	0	0	0	0
Ejection fraction decreased	0	0	0	0	0	0	0	1 (1%)	0	0

(Table 3 continues on next page)

	Zamto-cel (n=76)					R-GemOx (n=76)				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Missing	Grade 1–2	Grade 3	Grade 4	Grade 5	Missing
(Continued from previous page)										
Infections and infestations										
COVID-19	5 (7%)	0	1 (1%)	0	0	8 (11%)	1 (1%)	0	0	0
Pneumonia	1 (1%)	4 (5%)	0	0	0	1 (1%)	1 (1%)	0	0	0
Infection	2 (3%)	2 (3%)	0	0	0	0	2 (3%)	0	0	0
Urinary tract infection	1 (1%)	0	0	0	0	3 (4%)	2 (3%)	0	0	0
Cytomegalovirus infection reactivation	1 (1%)	1 (1%)	0	0	0	0	0	0	0	0
Sepsis	0	1 (1%)	0	0	0	0	1 (1%)	0	0	0
Staphylococcal infection	1 (1%)	1 (1%)	0	0	0	0	0	0	0	0
Bacteraemia	1 (1%)	0	0	0	0	0	1 (1%)	0	0	0
Gastroenteritis	1 (1%)	0	0	0	0	0	1 (1%)	0	0	0
Cellulitis	0	1 (1%)	0	0	0	0	0	0	0	0
Dermohypodermitis	0	1 (1%)	0	0	0	0	0	0	0	0
Encephalitis herpes	0	1 (1%)	0	0	0	0	0	0	0	0
Influenza	0	1 (1%)	0	0	0	0	0	0	0	0
Meningitis herpes	0	0	0	1 (1%)	0	0	0	0	0	0
Necrotising fasciitis	0	0	1 (1%)	0	0	0	0	0	0	0
Septic shock	0	0	0	1 (1%)	0	0	0	0	0	0
Bacterial infection	0	0	0	0	0	0	1 (1%)	0	0	0
Urinary tract infection bacterial	0	0	0	0	0	0	1 (1%)	0	0	0
Neoplasms: benign, malignant, and unspecified (including cysts and polyps)										
Malignant neoplasm progression	2 (3%)	1 (1%)	0	9 (12%)	0	8 (11%)	15 (20%)	4 (5%)	12 (16%)	5 (7%)
Tumour pain	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0
Cancer pain	0	1 (1%)	0	0	0	0	0	0	0	0
Lung neoplasm malignant	0	1 (1%)	0	0	0	0	0	0	0	0
Tumour pseudoprogression	0	1 (1%)	0	0	0	0	0	0	0	0
General disorders and administration site conditions										
Pyrexia	53 (70%)	5 (7%)	0	0	0	8 (11%)	0	0	0	0
Fatigue	9 (12%)	4 (5%)	0	0	0	10 (13%)	0	0	0	0
Asthenia	2 (3%)	1 (1%)	0	0	0	9 (12%)	2 (3%)	0	0	0
Metabolism and nutrition disorders										
Decreased appetite	9 (12%)	2 (3%)	0	0	0	9 (12%)	0	0	0	0
Hypokalaemia	9 (12%)	0	0	0	0	5 (7%)	2 (3%)	0	0	0
Hyperglycaemia	1 (1%)	2 (3%)	0	0	0	1 (1%)	1 (1%)	0	0	0
Hypophosphataemia	1 (1%)	0	0	0	0	2 (3%)	1 (1%)	0	0	0
Hyponatraemia	1 (1%)	1 (1%)	0	0	0	0	1 (1%)	0	0	0
Hypoalbuminaemia	1 (1%)	1 (1%)	0	0	0	0	0	0	0	0
Dehydration	0	1 (1%)	0	0	0	1 (1%)	0	0	0	0
Hypercalcaemia	0	0	1 (1%)	0	0	0	1 (1%)	0	0	0
Tumour lysis syndrome	0	0	0	0	0	0	1 (1%)	0	0	0
Hypophagia	0	1 (1%)	0	0	0	0	0	0	0	0
Cell death	0	0	0	0	0	0	1 (1%)	0	0	0
Immune system disorders										
Cytokine release syndrome	55 (72%)	2 (3%)	1 (1%)	1 (1%)	0	0	0	0	0	0
Hypogammaglobulinaemia	2 (3%)	1 (1%)	0	0	1 (1%)	0	0	0	0	0
Haemophagocytic lymphohistiocytosis	0	0	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0
Psychiatric disorders										
Delirium	3 (4%)	1 (1%)	0	0	0	0	0	0	0	0
Disorientation	0	2 (3%)	0	0	0	0	0	0	0	0
Anxiety	0	1 (1%)	0	0	0	0	0	0	0	0
Completed suicide	0	0	0	1 (1%)	0	0	0	0	0	0

(Table 3 continues on next page)

	Zamto-cel (n=76)					R-GemOx (n=76)				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Missing	Grade 1–2	Grade 3	Grade 4	Grade 5	Missing
(Continued from previous page)										
Vascular disorders										
Hypotension	19 (25%)	1 (1%)	0	1 (1%)	0	6 (8%)	0	0	0	0
Hypertension	3 (4%)	1 (1%)	0	0	0	4 (5%)	1 (1%)	0	0	0
Thrombophlebitis	0	1 (1%)	0	0	0	2 (3%)	0	0	0	0
Jugular vein thrombosis	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0
Capillary leak syndrome	0	1 (1%)	0	0	0	0	0	0	0	0
Nervous system disorders										
Neuropathy peripheral	0	0	0	0	0	12 (16%)	0	0	0	0
Polyneuropathy	0	0	0	0	0	12 (16%)	0	0	0	0
Paraesthesia	1 (1%)	0	0	0	0	10 (13%)	0	0	0	0
Immune effector cell-associated neurotoxicity syndrome	7 (9%)	1 (1%)	0	0	0	0	0	0	0	0
Peripheral sensory neuropathy	0	0	0	0	0	7 (9%)	1 (1%)	0	0	0
Somnolence	2 (3%)	2 (3%)	0	0	0	0	0	0	0	0
Syncope	0	1 (1%)	0	0	0	0	1 (1%)	0	0	0
Horner's syndrome	0	0	0	0	0	0	1 (1%)	0	0	0
Stupor	0	1 (1%)	0	0	0	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders										
Pleural effusion	1 (1%)	0	1 (1%)	0	0	1 (1%)	0	0	0	0
Haemoptysis	0	1 (1%)	0	0	0	0	0	0	0	0
Respiratory failure	0	0	1 (1%)	0	0	0	0	0	0	0
Tachypnoea	0	0	0	1 (1%)	0	0	0	0	0	0
Gastrointestinal disorders										
Nausea	11 (14%)	0	0	0	0	19 (25%)	0	0	0	0
Diarrhoea	9 (12%)	0	0	0	0	15 (20%)	0	0	0	0
Constipation	8 (11%)	0	0	0	0	6 (8%)	0	0	0	0
Abdominal pain upper	3 (4%)	1 (1%)	0	0	0	2 (3%)	1 (1%)	0	0	0
Rectal haemorrhage	0	1 (1%)	0	0	0	0	0	0	0	0
Gastric ulcer	0	0	0	0	0	0	1 (1%)	0	0	0
Upper gastrointestinal haemorrhage	0	0	0	0	0	0	1 (1%)	0	0	0
Renal and urinary disorders										
Acute kidney injury	1 (1%)	0	1 (1%)	0	0	1 (1%)	2 (3%)	0	0	0
Anuria	0	0	1 (1%)	0	0	0	0	0	0	0
Congenital, familial, and genetic disorders										
Congenital aplasia	0	0	1 (1%)	0	0	0	0	0	0	0
Injury, poisoning, and procedural complications										
Fall	6 (8%)	0	0	0	0	0	0	1 (1%)	0	0
Wrong product administered	0	0	0	0	0	0	1 (1%)	0	0	3 (4%)
Femur fracture	0	0	0	0	0	0	0	1 (1%)	0	0
Humerus fracture	0	0	0	0	0	0	0	1 (1%)	0	0
Pelvic fracture	0	0	0	0	0	0	0	1 (1%)	0	0
Vascular access site swelling	0	1 (1%)	0	0	0	0	0	0	0	0
Cardiac disorders										
Cardiac failure	0	0	0	0	0	0	1 (1%)	0	2 (3%)	0
Cardiac arrest	0	0	0	0	0	0	0	1 (1%)	0	0
Tachyarrhythmia	0	0	0	0	0	0	1 (1%)	0	0	0
Hepatobiliary disorders										
Drug-induced liver injury	0	0	0	0	0	1 (1%)	1 (1%)	0	0	0

(Table 3 continues on next page)

	Zamto-cel (n=76)					R-GemOx (n=76)				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Missing	Grade 1–2	Grade 3	Grade 4	Grade 5	Missing
(Continued from previous page)										
Musculoskeletal and connective tissue disorders										
Bone pain	0	0	0	0	0	0	1 (1%)	0	0	0
Sacral pain	0	0	0	0	0	0	1 (1%)	0	0	0
Product issues										
Device occlusion	1 (1%)	0	0	0	0	0	1 (1%)	0	0	0

Data are n (%). Treatment-emergent adverse events included grade 1 or 2 events that occurred in at least 10% of patients and all grade 3, 4, or 5 events. All terminology is from the Medical Dictionary for Regulatory Activities version 28.0. Patients could have had more than one adverse event and could therefore be counted under more than one preferred term.

Table 3: **Summary of treatment-emergent adverse events in patients who received study treatment (based on safety analysis set)**

	Zamto-cel (n=76)
CRS	
All grades	59 (78%)
Maximum grade 1	35 (46%)
Maximum grade 2	20 (26%)
Maximum grade 3	2 (3%)
Maximum grade 4	1 (1%)
Maximum grade 5	1 (1%)
Time to onset, days	2 (2–2)
Duration, days	3 (2–6)
ICANS	
All grades	8 (11%)
Maximum grade 1	4 (5%)
Maximum grade 2	3 (4%)
Maximum grade 3	1 (1%)
Maximum grade 4	0
Maximum grade 5	0
Missing	1 (1%)
Time to onset, days	10 (6–13)
Duration, days	5·5 (5–6)
Clinical management of CRS*	
Tocilizumab	29 (38%)
Corticosteroid	14 (18%)
Tocilizumab plus corticosteroid	13 (17%)
Anakinra	1 (1%)
Clinical management of ICANS	
Corticosteroid	6 (8%)
Levetiracetam	2 (3%)
Cytopenias	
Prolonged cytopenias grade ≥3	10 (13%)
Delayed cytopenias grade ≥3	8 (11%)

Data are n (%) or median (IQR). CRS=cytokine release syndrome. ICANS=immune effector cell-associated neurotoxicity syndrome. *Treatments are not mutually exclusive and patients could have received more than one treatment; only commonly reported CRS management interventions are reported here.

Table 4: **Summary of selected treatment-emergent adverse events in patients who received zamto-cel**

treated in the second-line setting.[18] The complete response rate with axicabtagene ciloleucel was high at 82·3% (95% CI not reported) and the 12-month event-free survival rate was 51·2% (38·2–62·8).[6] However, these results were accompanied by a non-relapse mortality of 9·7% and severe ICANS in 14·5% of patients.

Safety is a factor that requires special attention when treating older patients. Relatively low rates of ICANS have also been described for other dual-targeting CAR T-cell constructs;[19–21] these findings are likely influenced by multiple construct-related factors, including the costimulatory domain, beyond the dual-targeting approach. Furthermore, the low rates of severe CRS and ICANS in the DALY 2-EU trial were documented in a patient population with high tumour burden at baseline and without the use of holding or bridging therapy, thus at a high risk for the development of CAR T-cell-specific adverse events.[22,23] Severe CRS (2%) and ICANS (5%) were reported at similar ranges for lisocabtagene maraleucel in the PILOT study.[7] However, unlike the DALY 2-EU study, 52% of patients in the PILOT study received debulking chemotherapy before CAR T-cell therapy.

Another frequent and clinically relevant adverse event after CAR T-cell therapy is prolonged cytopenia. The incidence of prolonged cytopenia was lower with zamto-cel (ten [13%]) compared with the approximately 30% reported by other studies for CD19-directed CAR T-cell therapies.[2,6,7] However, severe infections were similar to other products in this indirect comparison.[2,6] This finding likely reflects the multifactorial nature of infectious complications after CAR T-cell therapy, which are not only driven by treatment-related factors, but also by patient-related risk factors such as age and comorbidities.[24,25] An important note is that the conduct of the DALY 2-EU trial coincided with the COVID-19 pandemic, which should be taken into account when interpreting infection-related adverse events and deaths.

Overall survival data are immature but show a numerical improvement in the zamto-cel group compared with R-GemOx. However, frequent use of CAR T-cell therapy after disease progression on standard-of-care treatment, either through study crossover or through commercially

available CAR T-cell therapies in subsequent treatment lines, is likely to affect the assessment of effects of zamto-cel on overall survival in this cohort.

When DALY 2-EU was designed, R-GemOx was considered an appropriate standard-of-care treatment for this population; however, studies have shown the superiority of bispecific antibody regimens.[15,26] In the STARGLO trial,[15] the anti-CD20 and CD3 antibody glofitamab in combination with GemOx (Glofit–GemOx) was evaluated versus R-GemOx in patients ineligible for transplantation with relapsed or refractory diffuse large B-cell lymphoma and a median age of 68 years. Transplantation ineligibility was driven by patients older than 70 years (42%) and notably the refusal of autologous stem-cell transplantation (35%). By contrast, DALY 2-EU enrolled an older population based on predefined medical criteria for transplantation ineligibility. Glofit–GemOx showed significantly improved overall survival and an HR for progression-free survival of 0·37 (95% CI 0·25–0·55). Based on these results, Glofit–GemOx was approved by the European Medicines Agency for second-line treatment of diffuse large B-cell lymphoma in patients ineligible for transplantation. However, these results did not provide sufficient evidence for the US Food and Drug Administration to support the treatment in the US patient population.[15,27] The SUNMO trial[26] evaluated the CD20 and CD3 bispecific antibody mosunetuzumab in combination with polatuzumab vedotin (Mosun–Pola) versus R-GemOx in patients ineligible for transplantation with relapsed or refractory large B-cell lymphoma and a median age of 62 years. Mosun–Pola also significantly improved progression-free survival over R-GemOx (HR 0·41 [95% CI 0·3–0·6]).[26] These results are in line with the HR of 0·43 (95% CI 0·28–0·65) observed for zamto-cel in DALY 2-EU. Similarly to the PILOT study, the definition of transplantation ineligibility in DALY 2-EU was based exclusively on predefined medical criteria, in contrast with STARGLO and SUNMO, in which non-clinical criteria such as patient refusal or logistical barriers were included. In addition, the patient populations of these studies differ. Patients enrolled in DALY 2-EU and treated with zamto-cel were older and more clinically fragile (25 [30%] with an ECOG performance status score of 2) than either STARGLO (10%) or SUNMO (13%). Moreover, combinations with GemOx or Mosun–Pola, as well as longer treatment duration, potentially increase toxicity and affect the risk–benefit ratio.

To our knowledge, DALY 2-EU is the first study to show the feasibility of so-called fresh-in and fresh-out (ie, non-cryopreserved) CAR T-cell therapy, eliminating the need for cryopreservation, with 76 (93%) patients receiving zamto-cel in the randomised setting. This high treatment rate was enabled by the automated and short production and vein-to-vein time.

For CD19 CAR T-cell therapies, the loss of CD19 has been identified as a relevant factor for treatment failure.[28] Although we observed no double antigen loss in patients who had disease progression after zamto-cel, numbers in this trial are too low to draw firm conclusions. There are several limitations of the DALY 2-EU trial. The small sample size prevents some subgroup analyses and might be insufficient to detect rare safety events. Secondly, the study design permitted crossover to zamto-cel or alternative CAR T-cell products in the comparator group, making the interpretation of overall survival in this trial difficult. Thirdly, the comparator treatment used in this trial, R-GemOx, is no longer considered standard of care; therefore, the relevance of our findings can only be assessed by indirect comparison with current treatment options. Finally, the follow-up duration was not sufficient to draw final conclusions on the durability of the observed remissions. Generalisability should be considered in relation to the study population and treatment setting. Extrapolation to patients not represented in the trial, including other rare large B-cell lymphoma entities or patients ineligible for transplantation, should be made with caution.

The strengths of the study include a randomised design that allows firm conclusions on the primary endpoint and key secondary endpoints. Secondly, the contribution of many centres highlights the feasibility of delivering a fresh-to-fresh CAR T-cell product. Thirdly, the study population of older patients with an impaired general condition and a high tumour burden lends validity to the study results for patients treated outside of clinical trials. Several future analyses of efficacy, safety, and cellular kinetics are planned after this primary report of the DALY 2-EU trial (appendix 1 p 47).

In summary, zamto-cel showed superior efficacy compared with R-GemOx in the DALY 2-EU trial, along with a safety profile similar to other CAR T-cell therapies. The risk–benefit ratio of zamto-cel supports its consideration as a standard treatment option in patients ineligible for transplantation with relapsed or refractory large B-cell lymphoma.

Contributors

PV, PBorc, UJ, FL, MJK, SH, and TO were involved in the design and conceptualisation of the work. PBorc, TvM, GI, PBori, PD, PM, LGo, ME, LGe, BvT, PN, NS, UJ, ATM, LGr, FL, JvD, MJK, JDR, and PV were involved in the provision of study materials or patient recruitment and data collection. PBorc, TvM, GI, PBori, PD, PM, LGo, ME, LGe, BvT, PN, NS, UJ, ATM, LGr, FL, JvD, MJK, JDR, and PV were involved in data acquisition. All authors were involved in data analysis and interpretation. All authors were involved in writing and agree to be accountable for all aspects of the work. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. PBorc, TvM, GI, PBori, PD, PM, LGo, ME, LGe, BvT, PN, NS, UJ, ATM, LGr, FL, JvD, MJK, JDR, CB, PP, PvH, SH, and PV directly accessed and verified the data.

Declaration of interests

GI has received consulting fees from Bristol Myers Squibb/Celgene, Regeneron, AbbVie, Gilead Sciences/Kite Pharma, Miltenyi Biotec, and Autolus; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie,

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Data sharing

De-identified individual participant data (including data dictionaries) reported in this Article can be made available to qualified researchers upon reasonable request, subject to review of a research proposal, a statistical analysis plan, and execution of a data access agreement. Data will become available beginning 6 months after marketing authorisation approval and can remain available for at least 3 years. Access might be granted to researchers whose proposed use of the data has been approved based on scientific merit and the intended use of the data, consistent with safeguarding the privacy of trial participants and the integrity of the study. Requests for access should be directed to waeln@miltenyi.com.

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