Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

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†A complete list of the TRANSFORM study sites is provided in the appendix

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Summary

Background Patients with large B-cell lymphoma (LBCL) primary refractory to or relapsed within 12 months of first-line therapy are at high risk for poor outcomes with current standard of care, platinum-based salvage immunochemotherapy and autologous haematopoietic stem cell transplantation (HSCT). Lisocabtagene maraleucel (liso-cel), an autologous, CD19-directed chimeric antigen receptor (CAR) T-cell therapy, has previously demonstrated efficacy and manageable safety in third-line or later LBCL. In this Article, we report a prespecified interim analysis of liso-cel versus standard of care as second-line treatment for primary refractory or early relapsed (within 12 months after response to initial therapy) LBCL.

Methods TRANSFORM is a global, phase 3 study, conducted in 47 sites in the USA, Europe, and Japan, comparing liso-cel with standard of care as second-line therapy in patients with primary refractory or early (≤12 months) relapsed LBCL. Adults aged 18–75 years, Eastern Cooperative Oncology Group performance status score of 1 or less, adequate organ function, PET–positive disease per Lugano 2014 criteria, and candidates for autologous HSCT were randomly assigned (1:1), by use of interactive response technology, to liso-cel (100×10^6 CAR$^+$ T cells intravenously) or standard of care. Standard of care consisted of three cycles of salvage immunochemotherapy delivered intravenously—R-DHAP (rituximab 375 mg/m^2 on day 1, dexamethasone 40 mg on days 1–4, two infusions of cytarabine 2000 mg/m^2 on day 2, and cisplatin 100 mg/m^2 on day 1), R-ICE (rituximab 375 mg/m^2 on day 1, ifosfamide 5000 mg/m^2 on day 2, etoposide 100 mg/m^2 on days 1–3, and carboplatin area under the curve 5 [maximum dose of 800 mg] on day 2), or R-GDP (rituximab 375 mg/m^2 on day 1, dexamethasone 40 mg on days 1–4, gemcitabine 1000 mg/m^2 on days 1 and 8, and cisplatin 75 mg/m^2 on day 1)—followed by high-dose chemotherapy and autologous HSCT in responders. Primary endpoint was event-free survival, with response assessments by an independent review committee per Lugano 2014 criteria. Efficacy was assessed per intention-to-treat (ie, all randomly assigned patients) and safety in patients who received any treatment. This trial is registered with ClinicalTrials.gov, NCT03575351, and is ongoing.

Findings Between Oct 23, 2018, and Dec 8, 2020, 232 patients were screened and 184 were assigned to the liso-cel (n=92) or standard of care (n=92) groups. At the data cutoff for this interim analysis, March 8, 2021, the median follow-up was 6·2 months (IQR 4·4–11·5). Median event-free survival was significantly improved in the liso-cel group (10·1 months [95% CI 6·1–not reached]) compared with the standard-of-care group (2·3 months [2·2–4·3]; stratified hazard ratio 0·35; 95% CI 0·23–0·53; stratified Cox proportional hazards model one-sided p<0·0001). The most common grade 3 or worse adverse events were neutropenia (74 [80%] of 92 patients in the liso-cel group *vs* 46 [51%] of 91 patients in the standard-of-care group), anaemia (45 [49%] *vs* 45 [49%]), thrombocytopenia (45 [49%] *vs* 58 [64%]), and prolonged cytopenia (40 [43%] *vs* three [3%]). Grade 3 cytokine release syndrome and neurological events, which are associated with CAR T-cell therapy, occurred in one (1%) and four (4%) of 92 patients in the liso-cel group, respectively (no grade 4 or 5 events). Serious treatment-emergent adverse events were reported in 44 (48%) patients in the liso-cel group and 44 (48%) in the standard-of-care group. No new liso-cel safety concerns were identified in the second-line setting. There were no treatment-related deaths in the liso-cel group and one treatment-related death due to sepsis in the standard-of-care group.

Interpretation These results support liso-cel as a new second-line treatment recommendation in patients with early relapsed or refractory LBCL.

Funding Celgene, a Bristol-Myers Squibb Company.

Introduction

Although many patients with large B-cell lymphoma (LBCL) are cured or achieve long-term remission after rituximab and anthracycline-containing first-line immunochemotherapy, patients with primary refractory disease or relapse within 12 months after first-line treatment often have poor outcomes with second-line immunochemotherapy-based approaches.[1] The standard treatment for patients with relapsed or refractory LBCL after initial immunochemotherapy is platinum-based salvage immunochemotherapy followed by high-dose chemotherapy and autologous haematopoietic stem cell transplantation (HSCT) in responding patients.[2,3] Although 50–60% of patients with relapsed or refractory LBCL are candidates for second-line salvage immunochemotherapy and would theoretically proceed to transplant, about 30% receive stem cell transplantation[1,4,5] and only a proportion of those patients achieve long-term remission. Importantly, the subgroup of patients with primary refractory or early relapsed LBCL have a particularly poor outcome.[5]

Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, defined composition, 4–1BB chimeric antigen receptor (CAR) T-cell product administered at equal target doses of $CD8^+$ and $CD4^+$ CAR^+ T cells. Liso-cel demonstrated efficacy and a manageable safety profile as third-line or later treatment in adult patients with relapsed or refractory LBCL in the TRANSCEND NHL 001 trial (NCT02631044).[6]

The objective of the phase 3 TRANSFORM trial was to compare the efficacy and safety of liso-cel with the current standard of care (three cycles of salvage platinum-based immunochemotherapy followed by high-dose chemotherapy and autologous HSCT for patients in complete response or partial response after salvage therapy) as second-line therapy in patients with primary refractory or early relapsed LBCL intended for autologous HSCT.

Methods

Study design and participants

We conducted a pivotal, global, randomised, open-label, phase 3 study of liso-cel in adults with relapsed or refractory LBCL from 47 medical cancer centres in the USA, Europe, and Japan (appendix pp 5–6). Eligible patients were aged 18–75 years, considered candidates for autologous HSCT, had LBCL refractory to or relapsed within 12 months after initial response to first-line therapy including an anthracycline and an anti-CD20 monoclonal antibody, Eastern Cooperative Oncology Group performance status score of 1 or less, adequate organ function, and PET-positive disease per Lugano 2014 criteria[7] before randomisation. No minimum absolute lymphocyte count was required for enrolment. Histologies were determined locally and subsequently confirmed by a central laboratory and were diffuse LBCL (DLBCL) not otherwise specified; DLBCL transformed from indolent non-Hodgkin lymphoma; high-grade

Research in context

Evidence before this study

We searched PubMed from Oct 23, 2000, to Oct 23, 2018, with the terms "CD19" AND "chimeric antigen receptor" AND "lymphoma" AND "second-line", without language or study type restrictions. Our search identified no published clinical data on autologous, CD19-directed chimeric antigen receptor (CAR) T-cell therapies in the second-line large B-cell lymphoma (LBCL) setting and only one review article discussing the potential for CAR T-cell therapy in the first-line or second-line settings for B-cell haematological malignancies. Salvage chemotherapy with platinum-based regimens followed by autologous haematopoietic stem cell transplantation has been the standard of care for patients with LBCL in the second-line treatment setting for the past two decades. However, only patients who respond to salvage chemotherapy can proceed to transplantation such that not all patients with LBCL in this setting benefit from standard of care. The subset of patients with LBCL that is primary refractory to or relapsed within 12 months after first-line therapy often have poor outcomes with standard of care, which underscores a critical unmet need.

Added value of this study

The results of the phase 3 TRANSFORM study represent a clinically meaningful advancement in effective second-line treatment options for patients with relapsed or refractory LBCL. Only a minority of these patients benefited from salvage immunochemotherapy followed by autologous haematopoietic stem cell transplantation, which has remained the standard of care for decades. This study also contributes information to investigations into the impact of different autologous, CD19-directed CAR T-cell products, enrolment criteria, and study designs to help explain the differences in clinical trial outcomes among three recent phase 3 studies evaluating these therapies as second-line treatment for LBCL.

Implications of all the available evidence

The TRANSFORM study supports a change in clinical practice for treatment of patients with refractory or relapsed LBCL within 12 months after first-line therapy. This recommendation aligns with the latest update of clinical treatment guidelines for this patient population in the second-line setting.

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See Online for appendix

B-cell lymphoma with rearrangements of *MYC* and either *BCL2*, *BCL6*, or both with DLBCL histology; primary mediastinal B-cell lymphoma; T-cell histiocyte-rich LBCL; or follicular lymphoma grade 3B (per World Health Organization 2016 classification).[8] Patients with secondary central nervous system lymphoma were allowed. A full list of inclusion and exclusion criteria is available in the appendix (pp 7–10).

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Institutional review boards at participating institutions approved the study protocol and amendments. All patients provided written informed consent.

Randomisation and masking

All patients were enrolled by the study investigators and underwent leukapheresis before being randomly assigned (1:1) to either the liso-cel group or the standard-of-care group. Randomisation was done with a permuted-blocks method (dynamic block size: block size of 4 with probability of 0·75 and block size of 6 with probability of 0·25) with interactive response technology managed by an external vendor (Endpoint, San Francisco, CA, USA) and stratified by response to first-line therapy (relapsed *vs* refractory) and secondary age-adjusted International Prognostic Index (sAAIPI; 0–1 *vs* 2–3).

Procedures

All patients underwent leukapheresis, irrespective of group assignment, to collect autologous peripheral blood mononuclear cells via venous catheter for manufacture of liso-cel.

Patients in the liso-cel group received lymphodepleting chemotherapy (intravenous fludarabine 30 mg/m² and intravenous cyclophosphamide 300 mg/m² daily) for 3 days followed by liso-cel. Patients received liso-cel as two sequential intravenous infusions of $CD8^+$ and $CD4^+$ CAR^+ T cells at a total target dose of 100×10^6 CAR^+ T cells. Non-conforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered safe for infusion. Patients were allowed to receive one cycle of bridging therapy with one of the three defined salvage immunochemotherapy regimens allowed in the standard-of-care group per investigator discretion during liso-cel manufacturing. Disease status in these patients was reassessed by PET per independent review committee (IRC) after bridging therapy, before beginning lymphodepleting chemotherapy with intravenous fludarabine 30 mg/m² and cyclophosphamide 300 mg/m² daily for 3 days. Only fludarabine dose modification was allowed per protocol based on renal function. Patients in the standard-of-care group received three cycles of R-DHAP (intravenous rituximab 375 mg/m² on day 1, dexamethasone 40 mg on days 1–4, two infusions of cytarabine 2000 mg/m² on day 2, and cisplatin 100 mg/m² on day 1), R-ICE (intravenous rituximab 375 mg/m² on day 1, ifosfamide 5000 mg/m² on day 2, etoposide 100 mg/m² on days 1–3, and carboplatin area under the curve 5 [maximum dose 800 mg] on day 2), or R-GDP (intravenous rituximab 375 mg/m² on day 1, dexamethasone 40 mg on days 1–4, gemcitabine 1000 mg/m² on days 1 and 8, and cisplatin 75 mg/m² on day 1) per investigator choice; responding patients (complete or partial response) were to proceed to one cycle of high-dose chemotherapy (intravenous carmustine 300 mg/m² on day 1, etoposide 200 mg/m² on days 2–5, cytarabine 200 mg/m² on days 2–5, and melphalan 140 mg/m² on day 6) and autologous HSCT. Dose modifications were permitted for adverse events and premedication and were done according to site standards, local label indications, and investigator's decision (protocol; appendix pp 51–230).

Investigators could switch a patient's regimen within one of the three protocol-defined salvage regimens (ie, R-DHAP, R-ICE, or R-GDP) in case of toxicity or unsatisfactory response (for example, stable disease after one to two cycles of salvage chemotherapy). A switch within one of the three defined regimens was allowed to maximise a patient's chance to receive the full three cycles of salvage immunochemotherapy before declaring failure of the treatment, which was not considered an event-free survival event. If requested by the investigator, patients in the standard-of-care group were allowed to cross over to receive liso-cel as third-line treatment upon approval of the sponsor based on IRC confirmation of one of the following criteria: complete or partial response not achieved after three cycles of immunochemotherapy, progressive disease at any time, or need to start a new antineoplastic therapy due to absence of complete response after 18 weeks post-randomisation. These patients are referred to herein as the crossover subgroup and were not considered part of the liso-cel group. Patients could discontinue the treatment period, defined as the period from randomisation to week 18, or post-treatment follow-up period, defined as the period from week 18 to month 36, but continue to be followed up for overall survival. The survival follow-up was defined from month 36 until the last patient last visit.

Efficacy assessments were done by investigators and an IRC according to the Lugano 2014 criteria,[7] based on radiographic tumour evaluation by diagnostic quality CT or MRI scans (chest, neck, abdomen, and pelvis) and PET scans, at weeks 9 (5 weeks after liso-cel infusion and after three cycles of immunochemotherapy) and 18 (14 weeks after liso-cel infusion and 8 weeks after the start of high-dose chemotherapy for the standard-of-care group) and months 6, 9, 12, 18, 24, and 36 from

randomisation. Unscheduled assessments were allowed if deemed necessary by the investigator.

Adverse events were assessed by study investigators. Adverse events were captured from time of randomisation onward in both groups and include adverse events reported in the liso-cel group during bridging therapy. Cytokine release syndrome was graded per Lee 2014 criteria.[9] All other adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, including neurological events, which were defined as investigator-identified neurological adverse events related to liso-cel.

Cellular kinetics were analysed in peripheral blood samples by droplet digital polymerase chain reaction to detect the liso-cel CAR transgene (Molecular MD, Portland, OR, USA). B-cell aplasia, defined as less than 3% CD19$^+$ peripheral blood lymphocytes,[10] was assessed by an exploratory, validated flow cytometry method (Charles River Laboratories; Reno, NV, USA for American sites and Edinburgh, UK for European sites) of peripheral blood samples.

Outcomes

The primary endpoint was event-free survival per IRC. Event-free survival was defined as the time from randomisation to death from any cause, progressive disease, failure to achieve complete or partial response by 9 weeks after randomisation, or start of new antineoplastic therapy due to efficacy concerns, whichever occurred first. Patients who did not experience an event-free survival event were to be censored at the last adequate IRC disease assessment.

Key secondary endpoints were complete response rate (defined as the proportion of patients achieving a complete response from randomisation up to 3 years after randomisation) and progression-free survival (defined as the time from randomization to progressive disease or death from any cause, whichever occurs first) per IRC, and overall survival (defined as the time from randomisation to death due to any cause). Other secondary endpoints were duration of response (defined as time from first response to disease progression, start of new antineoplastic therapy due to efficacy concerns, or death from any cause); overall response rate (defined as the percentage of patients achieving an objective response of partial response or better); event-free survival, progression-free survival, and overall survival rates at 6, 12, 24, and 36 months after randomisation; clinical, histological, and molecular subgroup analyses, including receipt of bridging therapy; and rate of completion of high-dose chemotherapy and autologous HSCT. Data at 24 months and 36 months are not yet available.

Additional secondary endpoints of health-related quality of life, progression-free survival on next line of treatment, and response 3 months after autologous HSCT will be reported separately.

Secondary safety outcomes included the type, frequency, and severity of adverse events, laboratory abnormalities, and hospital resource use.

Exploratory endpoints included cellular kinetics (maximum expansion in the blood [C_{max}], time to C_{max} [t_{max}], and area under the curve from 0 to 28 days post-infusion [AUC_{0-28d}]) in the liso-cel group and crossover subgroup and enumeration of B cells to provide B-cell aplasia pharmacodynamic biomarker data resulting from liso-cel treatment. Efficacy and safety outcomes, the same ones as for the primary analysis, for the crossover subgroup were also captured. A full list of endpoints can be found in the appendix (p 16–17).

Statistical analysis

The study was designed to have a power of 90% at one-sided 2·5% significance level to identify an approximate 81% increase in median event-free survival for the liso-cel group compared with the standard-of-care group (equivalent to a hazard ratio [HR] of 0·55). Given an expected randomisation rate of up to 12 patients per month, a 20% drop out rate before first response assessment, and a yearly dropout rate of 10% (30% cumulative), 182 patients were expected to be randomly assigned to treatment and 215 patients to be screened (screen failure rate of 15%).

The primary analysis will be conducted when 119 event-free survival events have occurred. Event and censoring rules for event-free survival and progression-free survival are shown in the appendix (pp 18–22). Two interim efficacy analyses, at 60% and 80% of the planned event-free survival information fraction, were included in the study, and an O'Brien-Fleming boundary alpha spending function was used to control the type I error. For the prespecified interim analysis reported in this Article, planned at 80% and performed at 82% of the 119 events needed for the primary analysis, the null hypothesis (ie, no difference in study treatments) was to be rejected if the p value associated to the test was less than 0·012. If the null hypothesis was rejected for event-free survival, hypothesis testing on complete response rate, progression-free survival, and overall survival could be performed hierarchically to control the overall type I error rate. Patients in the crossover subgroup continued to be followed for overall survival in the standard-of-care group. To adjust for the confounding effect of patients in the standard-of-care group crossing over to receive liso-cel, prespecified supportive analyses of overall survival were conducted, using both two-stage estimator and rank-preserving structural failure time models.

Analysis sets are defined in the appendix (p 15). The intention-to-treat (ITT) set was the primary efficacy analysis set and included all randomly assigned patients. The safety set for the liso-cel group comprised patients who had received any study treatment, which included bridging therapy if needed, lymphodepleting chemotherapy, and

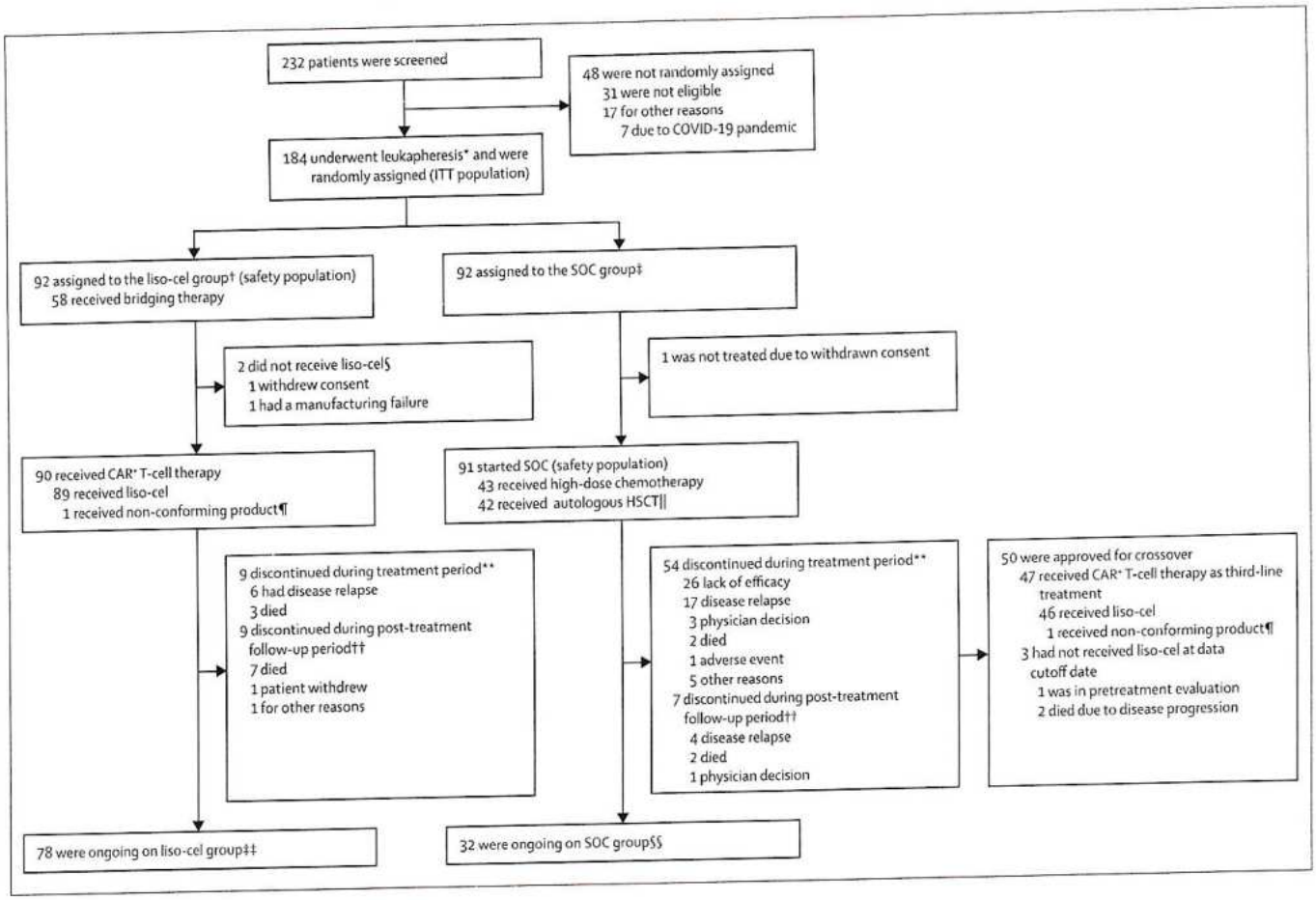

Figure 1: **Trial profile**
CAR=chimeric antigen receptor. HSCT=haematopoietic stem cell transplantation. ITT=intention-to-treat. Liso-cel=lisocabtagene maraleucel. SOC=standard of care. *During screening, patients provided informed consent and were assessed for eligibility, underwent leukapheresis, and subsequent randomisation. †Patients received lymphodepleting chemotherapy followed by liso-cel infusion; bridging therapy was allowed per protocol. ‡Patients received three cycles of SOC salvage immunochemotherapy followed by high-dose chemotherapy and autologous HSCT. §Patients received bridging therapy and, therefore, were included in the safety analysis set. ¶Non-conforming product was defined as any product wherein one of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel but was considered safe for infusion. ||The patient received all high-dose chemotherapy drugs but had not yet received autologous HSCT because the patient received the last dose of high-dose chemotherapy on March 8, 2021, the cutoff date of this interim analysis. **Patients could discontinue the treatment period, defined as the period from randomisation to week 18, but continue to be followed for overall survival. ††Patients could discontinue the post-treatment follow-up period, defined as the period from week 18 to month 36, but continue to be followed for overall survival. ‡‡12 patients ongoing in the treatment period, 65 ongoing in the post-treatment follow-up period, and one ongoing in the survival follow-up. §§Ten patients ongoing in the treatment period, 21 ongoing in the post-treatment follow-up period, and one ongoing in the survival follow-up.

liso-cel or non-conforming product. The standard-of-care safety set comprised patients who received any treatment (eg, salvage immunochemotherapy with or without high-dose chemotherapy or autologous HSCT). For time-to-event endpoints, the Kaplan-Meier product limit method was used to extract summary information, including time-to-event rates (eg, 6-month event-free survival rate) and median survival times together with two-sided 95% CIs. Greenwood's formula was used to estimate the 95% CIs for time-to-event rates. HR and p value were estimated from a stratified Cox proportional hazards model (stratification factors correspond with those used for randomisation). The proportional hazard assumption was evaluated via inspection of Schoenfeld residuals. For binary endpoints such as complete response, the frequency distributions are provided as summary information with 95% CIs calculated using the approximation to the normal distribution. Cochran-Mantel-Haenszel tests were used for analysis and calculation of p values.

Prespecified efficacy subgroup analyses were performed using baseline demographic and disease characteristics (see appendix pp 13–14 for detailed list). Forest plots for subgroups were developed for primary and key secondary efficacy endpoints.

An independent Data Safety Monitoring Board reviewed cumulative study data, conduct of the trial was overseen by a Scientific Steering Committee, and IRC was established to review efficacy data related to disease response assessments.

	Liso-cel group (n=92)	Standard-of-care group (n=92)
Sex		
Male	44 (48%)	61 (66%)
Female	48 (52%)	31 (34%)
Age, years		
Median (IQR)	60 (53·5–67·5)	58·0 (42·0–65·0)
<65	56 (61%)	67 (73%)
≥65 to <75	36 (39%)	23 (25%)
≥75	0	2 (2%)
Race		
American Indian or Alaskan native	0	0
Asian	10 (11%)	8 (9%)
Black or African American	4 (4%)	3 (3%)
Native Hawaiian or other Pacific Islander	0	0
White	54 (59%)	55 (60%)
Not collected or reported*	22 (24%)	25 (27%)
Other	2 (2%)	1 (1%)
Hispanic or Latino ethnic group		
Yes	3 (3%)	3 (3%)
No	65 (71%)	62 (67%)
Not reported*	24 (26%)	26 (28%)
Unknown	0	1 (1%)
Large B-cell lymphoma subtypes		
DLBCL not otherwise specified	53 (58%)	49 (53%)
DLBCL transformed from indolent lymphomas†	7 (8%)	8 (9%)
Follicular lymphoma grade 3B	1 (1%)	0
HGBCL with gene rearrangements in *MYC* and *BCL2*, *BCL6*, or both‡	22 (24%)	21 (23%)
Double-hit rearrangements	9 (10%)	14 (15%)
Triple-hit rearrangements	13 (14%)	7 (8%)
PMBCL	8 (9%)	10 (11%)
THRBCL	1 (1%)	4 (4%)
Cell of origin		
Germinal centre B cell	45 (49%)	40 (43%)
Activated B cell, non-germinal centre B cell	21 (23%)	29 (32%)
Unknown	25 (27%)	23 (25%)
Missing	1 (1%)	0
ECOG performance status at screening		
0	48 (52%)	57 (62%)
1	44 (48%)	35 (38%)
Creatinine clearance, mL/min	107·1 (90·0–123·6)	113·4 (88·2–140·4)
Left ventricular ejection fraction, %	61% (56–65)	60% (55–63)
Secondary AAIPI		
0 or 1	56 (61%)	55 (60%)
2 or 3	36 (39%)	37 (40%)
Previous response status		
Refractory§	67 (73%)	68 (74%)
Relapsed¶	25 (27%)	24 (26%)
Ann Arbor stage‖		
1	8 (9%)	14 (15%)
2	16 (17%)	15 (16%)
3	18 (20%)	13 (14%)
4	50 (54%)	50 (54%)
Number of extranodal involvement sites	1 (0–2)	1 (0–2)
SPD, cm²	11·4 (5·3–35·0)	15·7 (10·4–30·8)
SPD >50 cm²	10 (11%)	10 (11%)
LDH**≥500 units per L	10 (11%)	11 (12%)
Bone marrow involvement (known or suspected)	9 (10%)	13 (14%)
Secondary CNS lymphoma	1 (1%)	3 (3%)
Never achieved complete response or partial with first-line therapy (chemotherapy refractory)	25 (27%)	18 (20%)
Best response to first-line therapy		
Complete response	30 (33%)	28 (30%)
Partial response	36 (39%)	45 (49%)
Stable disease	7 (8%)	5 (5%)
Progressive disease	18 (20%)	13 (14%)
Not evaluable	1 (1%)	1 (1%)
Time from initial diagnosis to randomisation, months	7·6 (6·0–11·2)	7·9 (5·8–10·5)

Data are n (%) or median (IQR). AAIPI=age-adjusted International Prognostic Index. DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. HGBCL=high-grade B-cell lymphoma. LDH=lactate dehydrogenase. Liso-cel=lisocabtagene maraleucel. PMBCL=primary mediastinal large B-cell lymphoma. SPD=sum of the product of perpendicular diameters. THRBCL=T-cell histiocyte-rich large B-cell lymphoma. *Not reported in some countries due to privacy requirements. †11 patients had DLBCL transformed from follicular lymphoma (five in the liso-cel group and six in the standard-of-care group), three patients had DLBCL transformed from marginal zone lymphoma (two in the liso-cel group and one in the standard-of-care group), and one patient in the standard-of-care group had transformation from other types of B-cell lymphomas. ‡FISH results were assessed locally but subsequently confirmed by a central laboratory. §Defined as stable disease, progressive disease, partial response, or complete response with relapse less than 3 months after first-line therapy. ¶Defined as complete response with relapse on or after 3 months within 12 months after first-line therapy. ‖Assessed at the time of screening. **Threshold initially defined in the TRANSCEND NHL 001 study.[5]

Table 1: **Demographics and baseline disease characteristics (intention-to-treat)**

The relationship between cellular kinetic parameters (C_{max}, t_{max}, and AUC_{0-28d}) and dichotomous parameters, such as response, complete response rate, cytokine release syndrome, and neurological events, were assessed by Wilcoxon rank sum tests (prespecified analyses). The relationship between cellular kinetic parameters and time-to-event parameters, such as event-free survival and progression-free survival, were assessed by univariable Cox proportional hazards models (prespecified analyses).

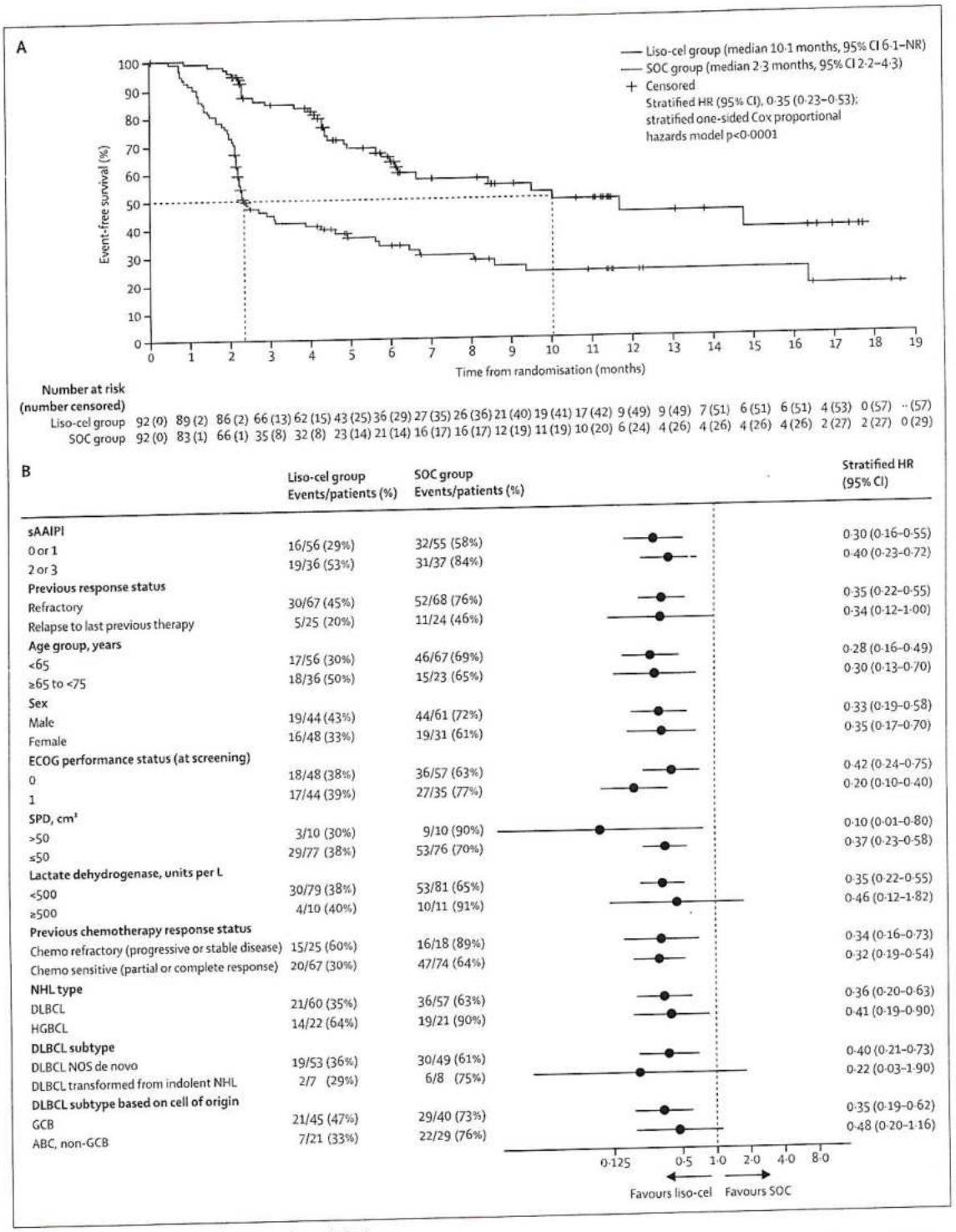

Figure 2: **Event-free survival (intention-to-treat population)**
(A) Kaplan-Meier of event-free survival per independent review committee (primary endpoint). (B) subgroup analysis of event-free survival per independent review committee. Event-free survival is defined as the time from randomisation to death from any cause, progressive disease, not achieving a complete or partial response by 9 weeks post-randomisation, or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first. ABC=activated B cell. DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Group. GCB=germinal centre B cell. HGBCL=high-grade B-cell lymphoma. HR=hazard ratio. Liso-cel=lisocabtagene maraleucel. NHL=non-Hodgkin lymphoma. NOS=not otherwise specified. NR=not reached. sAAIPI=secondary age-adjusted International Prognostic Index. SOC=standard of care. SPD=sum of the product of perpendicular diameters.

	Liso-cel group (n=92)	Standard-of-care group (n=92)	Stratified HR (95% CI)*	p value
Event-free survival based on IRC assessment (primary endpoint)				
Number of patients with events (%)	35 (38%)	63 (68%)	..	..
Median (95% CI), months†	10·1 (6·1–NR)	2·3 (2·2–4·3)	0·35 (0·23–0·53)	<0·0001
6-month rate (95% CI‡)	63·3% (52·0–74·7)	33·4% (23·0–43·8)	..	..
12-month rate (95% CI‡)	44·5% (29·4–59·6)	23·7% (13·4–34·1)	..	..
Complete response rate§ based on IRC assessment (key secondary endpoint)				
n (%, 95% CI)	61 (66%; 56–76)	36 (39%; 29–50)	..	<0·0001
Progression-free survival based on IRC assessment (key secondary endpoint)				
Number of patients with events (%)	28 (30%)	43 (47%)	..	..
Median (95% CI), months†	14·8 (6·6–NR)	5·7 (3·9–9·4)	0·41 (0·25–0·66)	0·0001
6-month rate (95% CI‡)	69·4% (58·1–80·6)	47·8% (35·0–60·6)	..	..
12-month rate (95% CI‡)	52·3% (36·7–67·9)	33·9% (20·1–47·7)	..	..
Overall survival (key secondary endpoint)				
Number of patients with events (%)	13 (14%)	24 (26%)	..	..
Median (95% CI), months	NR (15·8–NR)	16·4 (11·0–NR)	0·51 (0·26–1·00)	0·026
6-month rate (95% CI‡)	91·8% (85·4–98·2)	89·4% (82·9–96·0)	..	..
12-month rate (95% CI‡)	79·1% (67·1–91·1)	64·2% (50·5–77·9)	..	..
Overall response rate (secondary endpoint)				
n (%, 95% CI)	79 (86%; 77–92)	44 (48%; 37–59)	..	..
Best response since randomisation				
Complete response	61 (66%)	36 (39%)	..	..
Partial response	18 (20%)	8 (9%)	..	..
Stable disease	4 (4%)	21 (23%)	..	..
Progressive disease	6 (7%)	24 (26%)	..	..
Not evaluable	3 (3%)	3 (3%)	..	..
Duration of response for patients who achieved a complete response				
Number of patients with events (%)	14 (15%)	12 (13%)	..	..
Duration (95% CI), months	NR (6·8–NR)	14·5 (4·7–NR)	0·65 (0·30–1·43)	..
6-month duration (95% CI‡)	71·0% (56·1–86·0)	65·9% (47·2–84·5)	..	..
12-month duration (95% CI‡)	62·1% (44·6–79·6)	54·7% (33·7–75·7)	..	..

HR=hazard ratio. IRC=independent review committee. Liso-cel=lisocabtagene maraleucel. NR=not reached. *Based on a stratified Cox proportional hazards model. †Median estimates of time to event are from Kaplan-Meier product-limit estimates. ‡Based on Greenwood's formula. §Based on Cochran-Mantel-Haenszel test.

Table 2: **Summary of primary and key secondary efficacy outcomes (intention-to-treat population)**

All p values are reported as two-sided without multiplicity adjustment. Statistical significance was defined as p value of less than 0·05 in these exploratory analyses. All statistical analyses were done with SAS, version 9.4.

This trial is registered at ClinicalTrials.gov, NCT03575351.

Role of the funding source

The funder had a role in study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit.

Results

Between Oct 23, 2018, and Dec 8, 2020, 232 patients were screened and 184 were randomly assigned to the liso-cel (n=92) or standard of care (n=92) group, corresponding to the ITT population (figure 1). Reasons for screen failures are summarised in the appendix (p 23). The data cutoff date of this interim analysis at 82% event-free survival information fraction was March 8, 2021; the median follow-up was 6·2 months (IQR 4·4–11·5). Baseline demographic and disease characteristics were generally balanced between treatment groups (table 1). Most patients (n=160, 87%) had DLBCL (not otherwise specified or transformed from follicular lymphoma; 117 [64%]) or high-grade B-cell lymphoma (43 [23%]), 135 (73%) were refractory to first-line therapy, 61 (33%) were at least 65 years of age, and 73 (40%) had an sAAIPI of at least 2.

Of the 92 patients assigned to the liso-cel group, 89 (97%) received liso-cel infusion and one (1%) received a non-conforming product. Exposure to liso-cel is shown in the appendix (p 24). Two patients were not treated with liso-cel but did receive bridging therapy (one withdrew consent in the context of rapid progression and one had manufacturing failure). 58 (63%) patients in the liso-cel group received bridging therapy, mostly due to high tumour burden or rapid

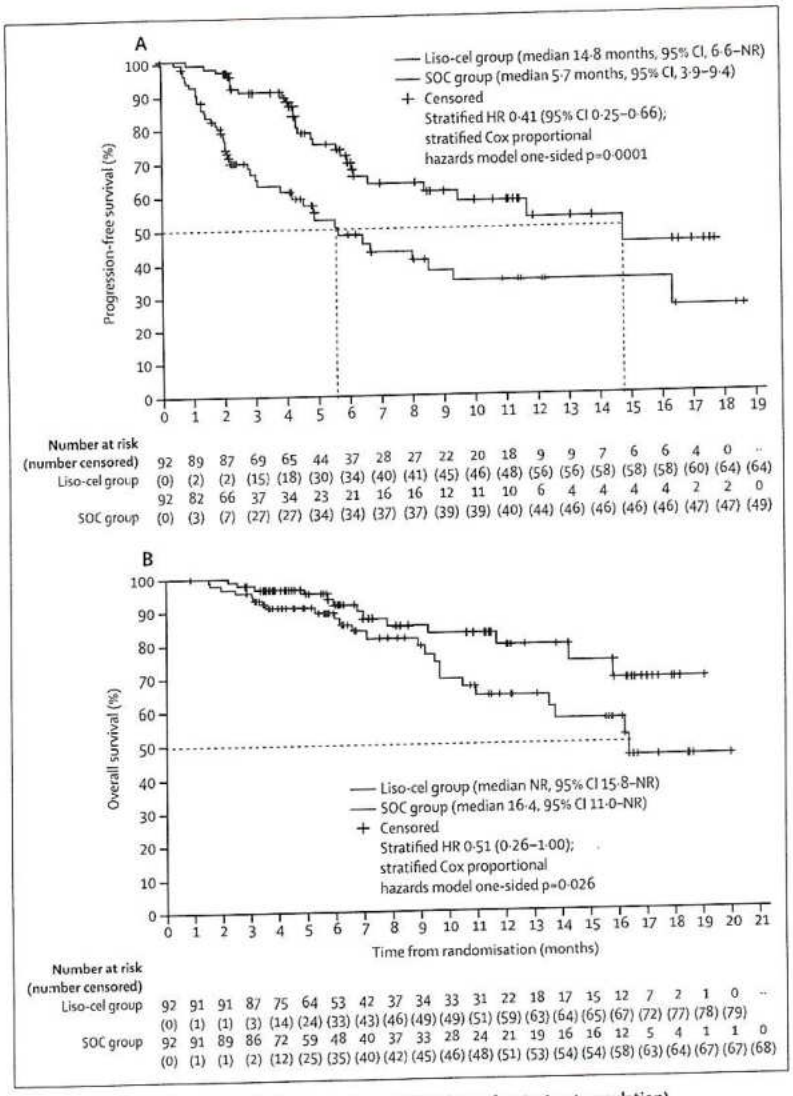

Figure 3: **Progression-free survival (A) and overall survival (B; intention-to-treat population)**
Progression-free survival is defined as the time from randomisation to death from any cause or progressive disease, whichever occurs first. Overall survival is defined as the time from randomisation to death from any cause. HR=hazard ratio. Liso-cel=lisocabtagene maraleucel. NR=not reached. SOC=standard of care.

disease progression per investigator assessment (appendix p 25). Of the 58 patients receiving bridging therapy, 53 (91%) received one cycle of bridging therapy and five (9%) received more than one cycle (considered to be protocol deviations), four due to delay in the manufacturing process and one due to investigator decision. 19 (21%) received liso-cel in the outpatient setting. The median time from leukapheresis to product availability was 26 days (IQR 22–30; range 19–84), from leukapheresis to infusion of liso-cel was 36 days (IQR 34–41; range 25–91), and from randomisation to infusion of liso-cel was 34 days (IQR 31–36; range 24–104). Turnaround time of liso-cel manufacturing by region is shown in the appendix (p 26).

Of the 92 patients randomised to the standard-of-care group, 91 (99%) patients received salvage immunochemotherapy; 12 patients switched salvage regimens (appendix p 27). Of the 91 patients who received salvage immunochemotherapy, 43 (47%) were considered to have a response by the investigator and proceeded to high-dose-chemotherapy, with 39 (43%) of these patients having an IRC-confirmed response (per IRC, 28 achieved a complete response, 11 achieved a partial response, while four had stable disease). At the time of this data cutoff, 42 (46%) patients had received autologous HSCT, and one patient had just completed all high-dose chemotherapy drugs and was expected to go on to receive autologous HSCT after the data cutoff. 50 patients in the standard-of-care group were approved for crossover, with 40 (80%) patients crossing over during salvage immunochemotherapy and ten (20%) after high-dose chemotherapy or autologous HSCT. Reasons for crossover included disease progression (n=36), suboptimal response (ie, stable disease after three cycles of salvage immunochemotherapy or no complete response after autologous HSCT; n=8), and relapse (n=6; appendix p 38). Of the 50 patients approved for crossover, 46 received liso-cel, and one received a non-conforming product. Three patients were not treated with liso-cel; two died of rapid disease progression before receiving the infusion and one was still in the pretreatment evaluation period at the data cutoff date.

In this prespecified interim analysis, at the time of data cutoff, there were 35 patients with event-free survival events in the liso-cel group and 63 patients in the standard-of-care group. Median event-free survival was significantly improved in the liso-cel group (10·1 months [95% CI 6·1–not reached]) compared with the standard-of-care group (2·3 months [2·2–4·3]; stratified HR 0·35; 95% CI 0·23–0·53; one-sided p<0·0001; figure 2A, table 2). Event-free survival rates at 6 months were 63% (95% CI 52–75%) for the liso-cel group and 33% (95% CI 23–44%) for the standard-of-care group. Liso-cel demonstrated clinical benefit over standard of care in nearly all prespecified subgroups analysed based on stratified HRs of event-free survival (figure 2B).

Treatment with liso-cel also resulted in a higher complete response rate (61 [66%] of 92 patients; 95% CI 56–76) than standard of care (36 [39%] of 92 patients; 29–50; p<0·0001; table 2). Patients who achieved a complete response in the liso-cel group had longer median duration of response than those in the standard-of-care group (median not reached [95% CI 6·8–not reached] *vs* 14·5 months [4·7–not reached]). The overall response rate was 86% (79 patients; 95% CI 77–92%) in the liso-cel group and 48% (44 patients; 37–59%) in the standard-of-care group.

At the time of this analysis, there were 28 progression-free survival events in the liso-cel group and 43 in the standard-of-care group. A statistically significant

	Liso-cel group (n=92)		Standard-of-care group (n=91)	
	Grade 1–2	Grade ≥3	Grade 1–2	Grade ≥3
Any treatment-emergent adverse event	90 (98%)	85 (92%)	90 (99%)	79 (87%)
Any serious treatment-emergent adverse event	24 (26%)	31 (34%)	16 (18%)	39 (43%)
Deaths due to treatment-emergent adverse event	NA	1 (1%)*	NA	2 (2%)*
Most common treatment-emergent adverse events (occurring in ≥10% of patients in either group)				
Neutropenia	43 (47%)	74 (80%)	17 (19%)	46 (51%)
Anaemia	36 (39%)	45 (49%)	34 (37%)	45 (49%)
Thrombocytopenia	30 (33%)	45 (49%)	35 (38%)	58 (64%)
Nausea	49 (53%)	3 (3%)	52 (57%)	3 (3%)
Cytokine release syndrome	45 (49%)	1 (1%)	0	0
Prolonged cytopenia†	NA	40 (43%)	NA	3 (3%)
Headache	39 (42%)	4 (4%)	19 (21%)	1 (1%)
Fatigue	36 (39%)	0	34 (37%)	2 (2%)
Constipation	31 (34%)	2 (2%)	22 (24%)	0
Diarrhoea	23 (25%)	0	37 (41%)	3 (3%)
Decreased appetite	21 (23%)	1 (1%)	26 (29%)	3 (3%)
Pyrexia	27 (29%)	0	21 (23%)	0
Lymphopenia	8 (9%)	23 (25%)	4 (4%)	8 (9%)
Dizziness	20 (22%)	0	13 (14%)	0
Hypokalaemia	16 (17%)	4 (4%)	19 (21%)	4 (4%)
Insomnia	19 (21%)	0	11 (12%)	0
Hypotension	18 (20%)	3 (3%)	4 (4%)	0
Vomiting	18 (20%)	1 (1%)	21 (23%)	2 (2%)
Back pain	14 (15%)	1 (1%)	15 (16%)	2 (2%)
Peripheral oedema	15 (16%)	1 (1%)	16 (18%)	0
Leukopenia	9 (10%)	14 (15%)	6 (7%)	11 (12%)
Febrile neutropenia	4 (4%)	11 (12%)	3 (3%)	19 (21%)
Hypomagnesaemia	13 (14%)	0	19 (21%)	1 (1%)
Abdominal pain	11 (12%)	3 (3%)	11 (12%)	1 (1%)
Arthralgia	13 (14%)	0	9 (10%)	0
Cough	13 (14%)	0	8 (9%)	0
Dyspnoea	12 (13%)	1 (1%)	7 (8%)	1 (1%)
Bone pain	12 (13%)	0	9 (10%)	0
Tremor	11 (12%)	1 (1%)	0	0
Myalgia	11 (12%)	1 (1%)	4 (4%)	0
Asthenia	9 (10%)	1 (1%)	8 (9%)	0
Hypertension	9 (10%)	4 (4%)	6 (7%)	1 (1%)
Tachycardia	9 (10%)	0	10 (11%)	0
Peripheral sensory neuropathy	7 (8%)	0	11 (12%)	0
Hypophosphataemia	6 (7%)	3 (3%)	10 (11%)	6 (7%)
Dyspepsia	5 (5%)	0	10 (11%)	0
Stomatitis	5 (5%)	0	9 (10%)	2 (2%)
Mucosal inflammation	4 (4%)	0	11 (12%)	3 (3%)

Data are n (%) of patients with grade 1–2 or grade 3 or worse treatment-emergent adverse events. A patient might be counted twice, once in the grade 1–2 group and once in the grade ≥3 group if multiple events or multiple occurrences of the same event were reported as grade 1–2 and grade 3 or worse. CAR=chimeric antigen receptor. Liso-cel=lisocabtagene maraleucel. Treatment-emergent adverse events were defined as adverse events occurring or worsening on or after the date of randomisation and within 90 days after the last treatment (ie, CAR T-cell infusion in the liso-cel group or the last dose of chemotherapy in the standard-of-care group). NA=not applicable (only grade 5). *The treatment-emergent adverse event leading to death in one patient in the liso-cel group was failure to thrive in the context of disease progression; treatment-emergent adverse events leading to death reported in patients treated with standard of care included sepsis and acute respiratory distress syndrome; only includes deaths reported after randomisation and within 90 days after the last treatment cycle. †Defined as grade 3 or worse central laboratory results at 35 days after liso-cel infusion or after the start of the last chemotherapy in the standard-of-care group.

Table 3: **Treatment-emergent adverse events (safety set)**

	Liso-cel group (n=92)
Patients with ≥1 treatment-emergent adverse event of special interest	83 (90%)
Cytokine release syndrome*	
Any grade	45 (49%)
Grade 1	34 (37%)
Grade 2	10 (11%)
Grade 3	1 (1%)
Grade 4–5	0
Time to onset, days	5 (3–8)
Time to resolution, days	4 (2–5)
Neurological events†	
Any grade	11 (12%)
Grade 1	5 (5%)
Grade 2	2 (2%)
Grade 3	4 (4%)‡
Grade 4–5	0
Time to onset, days	11 (10–17)
Time to resolution, days	6 (2–19)
Clinical management of cytokine release syndrome	
Tocilizumab, corticosteroids, or both	21 (23%)
Tocilizumab only	9 (10%)
Tocilizumab and corticosteroids	12 (13%)
Corticosteroids only	0
Vasopressors	0
Clinical management of neurological events	
Tocilizumab, corticosteroids, or both	7 (8%)
Tocilizumab only	1 (1%)§
Tocilizumab and corticosteroids	0
Corticosteroids only	6 (7%)
Number of tocilizumab doses per patient	
1	12 (13%)
2	4 (4%)
3	3 (3%)
>3	3 (3%)

Data are n (%) or median (IQR). Liso-cel=lisocabtagene maraleucel. *Graded according to the Lee 2014 criteria.[3] †Defined as investigator-identified neurological adverse event related to liso-cel and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. ‡Grade 3 events reported: encephalopathy (n=1), mental status change (n=1), aphasia and tremor (n=1), and aphasia and muscular weakness (n=1). §This patient received one dose of tocilizumab as treatment for a neurological event (dizziness).

Table 4: **Treatment-emergent adverse events of special interest in the liso-cel group**

improvement in progression-free survival was observed in the liso-cel group compared with standard of care (stratified HR 0·41; 95% CI 0·25–0·66; p=0·0001; figure 3A). There were 13 deaths in the liso-cel group and 24 deaths in the standard-of-care group. Overall survival was longer in the liso-cel group than in the standard-of-care group (stratified HR 0·51 [95% CI 0·26–1·00]; p=0·026; figure 3B). To adjust for the confounding effect of patients in the standard-of-care group crossing over to receive liso-cel, results of the prespecified supportive analyses of overall survival showed a difference in overall survival in favour of the liso-cel group from both the two-stage estimator model (stratified HR 0·32; 95% CI 0·16–0·64) and the rank-preserving structural failure time model (stratified HR 0·27; 95% CI 0·12–0·62; appendix p 28).

We conducted a prespecified subgroup analysis to assess the contribution of bridging therapy on efficacy in the liso-cel group (appendix p 29); nine patients had PET-negative disease after bridging therapy before receiving liso-cel. The results showed a consistent benefit of liso-cel over standard of care for both patients who received bridging therapy and those who did not.

No patients in either group discontinued treatment due to toxicity. No patients in the liso-cel group had dose modifications for toxicity. In the standard-of-care group, four patients switched salvage regimens for an adverse event (appendix p 27), and dose modification for toxicity was reported in three patients who received R-DHAP, in five patients who received R-ICE, in three patients who received R-GDP, and in one patient who received high-dose chemotherapy.

The majority of patients in both groups had a treatment-emergent adverse event (table 3; appendix pp 30–31). The most common grade 3 or worse adverse events were neutropenia (74 [80%] of 92 patients in the liso-cel group *vs* 46 (51%) of 91 patients in the standard-of-care group), anaemia (45 [49%] *vs* 45 [49%]), thrombocytopenia (45 [49%] *vs* 58 [64%]), and prolonged cytopenia (40 [43%] *vs* 3 [3%]).

Any grade serious treatment-emergent adverse events were reported in 44 (48%) patients in the liso-cel group (grade ≥3 in 31 [34%] patients) and 44 (48%) in the standard-of-care group (grade ≥3 in 39 [43%] patients). The most frequently reported serious adverse events reported in the liso-cel group were cytokine release syndrome (12 [13%]), febrile neutropenia (seven [8%]), and pyrexia (six [7%]). The most frequently reported serious adverse events in the standard-of-care group were febrile neutropenia (nine [10%]), pyrexia (seven [8%]), acute kidney injury (five [5%]), and neutropenia (four [4%]).

There were 13 (14%) deaths in the liso-cel group; seven from lymphoma progression, four from COVID-19, one from a grade 5 treatment-emergent adverse event (failure to thrive after disease progression), and one from an unknown cause. There were 24 (26%) deaths in the standard-of-care group; 13 from lymphoma progression (nine in the crossover subgroup), one from COVID-19, six from grade 5 treatment-emergent adverse events (sepsis [n=3], acute respiratory distress syndrome [n=1], cardiac arrest [n=1], and multiorgan failure [n=1]), and four from unknown causes. No deaths were considered related to study treatment (appendix p 32).

Any-grade cytokine release syndrome was reported in 45 (49%) patients in the liso-cel group (table 4; appendix p 33). The majority were grade 1 (34 [37%]) and grade 2 (10 [11%]), with only one (1%) event of

grade 3 cytokine release syndrome and no grade 4 or 5 events. The median time from liso-cel infusion to onset and resolution of any-grade cytokine release syndrome was 5 days (IQR 3–8) and 4 days (2–5), respectively. Cytokine release syndrome was managed with tocilizumab, corticosteroids, or both in 21 (23%) patients (table 4). No patients received vasopressors for cytokine release syndrome.

Any-grade neurological events were reported in 11 (12%) patients in the liso-cel group; five (5%) had grade 1, two (2%) had grade 2, and four (4%) had grade 3 events; no grade 4 or 5 neurological events were reported (table 4; appendix p 34). Grade 3 neurological events included one patient each with encephalopathy, mental status change, aphasia and tremor, and aphasia and muscular weakness. The median time to onset and resolution of any-grade neurological events was 11 days (IQR 10–17) and 6 days (2–19), respectively. Neurological events were managed with tocilizumab, corticosteroids, or both in seven (8%) patients (table 4).

Prolonged cytopenias (defined as grade ≥3 anaemia, neutropenia, thrombocytopenia, or all not resolved at 35 days after liso-cel infusion or after start of the last chemotherapy in the standard-of-care group) were reported in 40 patients (43%) in the liso-cel group and three (3%) patients in the standard-of-care group (appendix p 35). In the liso-cel group, 73% of prolonged cytopenias resolved to grade 2 or better within 2 months after onset of prolonged cytopenia (ie, within 3 months after liso-cel infusion). Severe (grade ≥3) infections were reported in 14 patients (15%) in the liso-cel group and 19 patients (21%) in the standard-of-care group. Febrile neutropenia was reported in 14 patients (15%) in the liso-cel group (grade ≥3 in 11 [12%] patients) and 22 patients (24%) in the standard-of-care group (grade ≥3 in 19 [21%] patients; table 3).

Hospital resource utilisation in the liso-cel and standard-of-care groups and in patients who received liso-cel in the outpatient setting are summarised in the appendix (pp 36–37). Four patients in each group were admitted to the intensive care unit (ICU) during initial hospitalisation, including two patients with grade 3 neurological events of altered mental status and tremors in the liso-cel group (appendix p 36). Among the 19 patients who received liso-cel in the outpatient setting, 13 were hospitalised after liso-cel infusion (median time of 9 days post-infusion [IQR 4–19]), with ten due to adverse events. No outpatient was admitted to the ICU (appendix p 37).

Results of the prespecified exploratory analyses for the crossover subgroup are summarised in the appendix (pp 38–44, 49). The group of patients in the standard-of-care group who crossed over to receive liso-cel as third-line therapy comprised a high proportion of patients with refractory disease (43 [86%] of 50 patients), had a best response of partial response or less to first-line therapy (40 [80%]), or an Eastern Cooperative Oncology Group performance status of 1 or worse at time of crossover (30 [60%]). The overall response rate and complete response rate per investigator assessment after liso-cel infusion for the crossover subgroup were 48% (22 patients; 95% CI 33–63) and 39% (18 patients; 25–55), respectively. The safety outcomes were consistent with the overall study results, including a low incidence of severe cytokine release syndrome and neurological events.

Among 83 patients who were evaluable for cellular kinetics in the liso-cel group, median t_{max} was 10 days (IQR 9–11, range 6–22), median C_{max} was 33 349 copies per µg (IQR 13 873–95 618), and the median AUC_{0-28d} after infusion was 270 345 day times copies per µg (IQR 111 550–793 716; appendix p 44). The association between liso-cel cellular kinetic parameters (C_{max}, t_{max}, and AUC_{0-28d}) and clinical efficacy (response, complete response, event-free survival, and progression-free survival) and safety (cytokine release syndrome and neurological events) in the liso-cel group are shown in the appendix (p 45–46). Persistence of liso-cel was observed up to 11 months after infusion (appendix p 47). The incidence of B-cell aplasia in evaluable patients at different timepoints in the liso-cel group is summarised in the appendix (p 48). 67 (81%) of 83 patients had B-cell aplasia at screening and 70 (96%) of 73 patients had B-cell aplasia before infusion; 68 (96%) of 71 patients had B-cell aplasia at 1 month and 58 (97%) of 60 patients had B-cell aplasia at 2 months. Cellular kinetics for the crossover subgroup were similar to those of the liso-cel group (appendix p 44).

Discussion

Liso-cel demonstrated superior clinical outcomes over standard of care and a manageable safety profile as second-line therapy in patients with early relapsed or refractory LBCL. Treatment with liso-cel resulted in a more than 4-times increase in median event-free survival, 27% higher complete response rate, and a more than 2·5-times increase in median progression-free survival compared with standard-of-care treatment. Overall survival data were immature because of the small number of deaths at the time of this interim analysis. In this disease setting, achieving a complete response after CAR T-cell therapy appears to be associated with achieving a durable response[11] and most patients achieve complete responses at the first disease assessment.[6,12,13] In TRANSFORM, patients in the liso-cel group had a statistically significantly higher complete response rate (66% *vs* 39%; p<0·0001) and longer median duration of response (not reached *vs* 14·5 months) than did those in the standard-of-care group. There were no new safety concerns associated with liso-cel in the second-line setting compared with the third-line or later setting (TRANSCEND NHL 001).[6] Grade 3 cytokine release syndrome (1%) and neurological events (4%) occurred infrequently, and no grade 4 or 5 cytokine release syndrome and neurological

events were reported. Prolonged cytopenia occurred in 43% of patients in the liso-cel group but resolved within 2 months after onset in most patients and did not lead to an increased risk of infections or febrile neutropenia compared with the standard-of-care group. ICU admission during initial hospitalisation was low (<5% of patients) in both groups. 21% of patients in the liso-cel group were treated in the outpatient setting.

To allow enrolment of patients with rapidly progressing disease, bridging therapy was allowed during CAR T-cell manufacturing in the liso-cel group. All patients, those who received bridging therapy and those who did not, derived a consistent clinically meaningful benefit over standard-of-care treatment.

There was a high rate of disease progression in the standard-of-care group compared with the liso-cel group. Early progression in the standard-of-care group was frequent and precluded proceeding to treatment with high-dose chemotherapy and autologous HSCT in more than half of the patients, requiring patients to move to third-line therapy.

The TRANSFORM results represent a clinically meaningful advancement in the second-line treatment of relapsed or refractory LBCL, where salvage immunochemotherapy followed by high-dose chemotherapy and autologous HSCT has remained the standard of care for decades. In three large phase 3 studies—CORAL,[1] LY.12,[4] and ORCHARRD[5]—with various immunochemotherapy regimens, efforts to improve the response to second-line salvage therapy along with the proportion of patients intended for autologous HSCT were largely unsuccessful, with no improvement in response rate between different immunochemotherapy regimens. In the CORAL,[1] LY.12,[4] and ORCHARRD[5] studies, a low percentage of patients were able to proceed to autologous HSCT, ranging from 35% to 50%. Overall, patients had poor outcomes, with low complete response rates and short progression-free survival, underscoring the need for a different modality of treatment in these patients. In the TRANSFORM study, in line with historical studies, 42 (46%) patients in the standard-of-care group proceeded to autologous HSCT of whom 39 (43%) patients had an IRC-confirmed response to salvage chemotherapy. In contrast to the standard-of-care group, nearly all patients in the liso-cel group were able to receive the full intended treatment, and most patients achieved meaningful clinical benefit with improvements in event-free survival, complete response rates, and progression-free survival. Patients who received liso-cel as third-line treatment in the crossover subgroup had similar safety outcomes but lower response rates than those in second line (liso-cel group). These initial results suggest the importance of treating this patient population with liso-cel earlier.

Early relapse (refractory disease or progression within 12 months) and sAAIPI scores of at least 2 and previous exposure to rituximab were previously identified as poor prognostic factors for achieving a response to salvage immunochemotherapy and overall survival in the CORAL study,[1] and progression-free survival and overall survival in the ORCHARRD study.[5] Overall response rates in patients with refractory disease or who relapsed within 12 months of first-line therapy ranged from 29% to 46% in these studies. In particular, patients relapsing within 12 months of rituximab-containing first-line therapy had a very poor prognosis,[1,5] underlining a crucial unmet need. In the ORCHARRD study, median progression-free survival in the high-risk versus standard-risk populations was approximately 2 months versus 24 months, and median overall survival was approximately 10 months versus not reached.[5]

There are two recent phase 3 reports (ZUMA-7 and BELINDA) of other CAR T-cell therapies (axicabtagene ciloleucel [axi-cel] and tisagenlecleucel, respectively) as second-line treatment versus standard of care in refractory or early relapsed transplant-intended patients with LBCL. Event-free survival was the primary endpoint in both studies. In ZUMA-7 (axi-cel), event-free survival was defined as the time from randomisation to the earliest date of disease progression according to the Lugano 2014 criteria,[7] the commencement of new therapy for lymphoma, death from any cause, or a best response of stable disease up to and including the response on the day 150 assessment after randomisation.[15] The median time from leukapheresis to product delivery to the trial site was 18 days, and the median time from randomisation to axi-cel infusion was 29 days (IQR 27–34). Axi-cel demonstrated superiority over standard of care for event-free survival (median 8·3 months *vs* 2·0 months; HR 0·40 [95% CI 0·31–0·51]; p<0·001) and objective response rate (83% *vs* 50%, complete response rate of 65% *vs* 32%), with a median follow-up of 24·9 months.[12] DLBCL or high-grade B-cell lymphoma were the most common disease subtypes (303 patients, 84%), 264 patients (74%) had disease refractory to first-line therapy, 109 (30%) patients were 65 years of age or older, and 161 (45%) patients had sAAIPI of at least 2. Bridging chemotherapy was not allowed except for glucocorticoids, which were administered in 36% of patients. Prohibition of bridging chemotherapy might have limited enrolment of patients with rapidly progressing disease in urgent need of therapy. In the axi-cel group, any-grade and grade 3 or worse cytokine release syndrome occurred in 92% and 6% of patients, respectively, whereas any-grade and grade 3 or worse neurological events occurred in 60% and 21% of patients, respectively. Overall, 25% of patients in the axi-cel group required ICU care.

In contrast, the primary analysis of the BELINDA (tisagenlecleucel) study showed no difference between tisagenlecleucel versus standard of care in event-free survival, defined as the time from randomisation to stable or progressive disease at or after the week 12 assessment per IRC according to the Lugano 2014 criteria[7] or death at any time.[14] Median event-free survival was 3·0 months in both groups (HR 1·07 [95% CI 0·82–1·40];

p=0·61), and overall response rate was 46% versus 43% and complete response rate was 28·4% versus 27·5% in the tisagenlecleucel and standard-of-care groups, respectively, after a median follow-up of 10·0 months.[14] DLBCL not otherwise specified or high-grade B-cell lymphoma were the most common disease types (279 patients, 87%), 214 patients (66·5%) had disease refractory to first-line therapy, and 100 patients (31%) were at least 65 years of age. Bridging chemotherapy with one of the prespecified salvage regimens was permitted, allowing for enrolment of patients with high-risk aggressive lymphoma. A total of 83% of patients received bridging therapy; 58 (35·8%) received one cycle and 77 (47·5%) received at least two cycles. The median time from leukapheresis to tisagenlecleucel infusion in the tisagenlecleucel group was 52 days (range 31–135) in the overall population. In the tisagenlecleucel group, any-grade and grade 3 or worse cytokine release syndrome occurred in 61% and 5% of patients, respectively, whereas any-grade and grade 3 or worse neurological events occurred in 10% and 2% of patients, respectively.

The efficacy results of TRANSFORM are consistent with those reported by ZUMA-7.[12] TRANSFORM enrolled a broad patient population with poor prognostic features (73% had primary refractory disease and 23% had high-grade B-cell lymphoma with rearrangements of *MYC* and *BCL2*, *BCL6*, or both), including patients with high tumour burden and rapidly progressing disease as demonstrated by the need for bridging therapy in 63% of patients, which is more representative of the real-world patient population.[13,14] The majority of patients were able to receive liso-cel within the per-protocol-specified 29 days after randomisation (±7) time window, which contrasts with the delay in receiving tisagenlecleucel in the BELINDA study.

All three studies (ZUMA-7,[12] BELINDA,[14] and TRANSFORM) had slightly different definitions for event-free survival events, and it is unknown how this difference might have affected the results. In the liso-cel group of TRANSFORM, patients with stable disease were considered to have an event-free survival event rather than waiting for progressive disease. In addition to the low incidence of severe cytokine release syndrome and neurological events, patients in the TRANSFORM study required low use of tocilizumab and steroids to manage those adverse events, with no prophylactic use. One patient had grade 3 cytokine release syndrome and four patients had grade 3 neurological events, including only one patient with grade 3 encephalopathy. The ICU admission rate in TRANSFORM was also low (4% of patients).

A limitation of the prespecified interim study results is the short median follow-up of 6·2 months. The interim and primary analyses were prespecified and are event driven. Although the number of events required to trigger the interim analysis was met, the number required for the primary analysis has not yet been met at the time of this publication. Nevertheless, liso-cel demonstrated a clear treatment effect over standard of care in event-free survival, complete response rate, and progression-free survival. However, the long-term effect of liso-cel on outcome in this patient population, including overall survival, requires longer follow-up. Since event-free survival and progression-free survival events tend to occur early in primary refractory and early relapsed DLBCL,[11,15] and a plateau in the event-free survival and progression-free survival curves began to be observed after 6 months in ZUMA-7,[12] we believe the statistical claims in this analysis are unlikely to change with longer follow-up.

In summary, liso-cel demonstrated superior efficacy compared with standard of care across event-free survival, complete response rate, and progression-free survival, along with a manageable safety profile, as second-line treatment in patients with LBCL that is primary refractory or relapsed within 12 months of first-line therapy. These data support the use of liso-cel as a new second-line treatment option in these patients.

Contributors

MK, SRS, JA, PBJ, BG, VB, SI, SMi, PM, FH-I, KI, and FM contributed to data acquisition. ML, DGM, and JSA contributed to data acquisition and data interpretation. AC, SMo, AP, and KO contributed to study design, data analysis, and data interpretation. LS contributed to study design, data acquisition, and data interpretation. TM contributed to study design and data acquisition. All authors had full access to all study data, which was verified by MK, AC, SM, AP, KO, and LS. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

Declaration of interests

MK is a consultant for ADC Therapeutics, Celgene, a Bristol Myers Squibb (BMS) company, Adaptive Biotechnologies, AbbVie, AstraZeneca, and BeiGene, outside of the submitted work; reports speakers bureau fees for Seagen outside of the submitted work; and reports research funding from TG Therapeutics, Genentech, and Novartis, outside of the submitted work. JA reports honoraria from Juno Therapeutics and BMS, outside of the submitted work. BG is a consultant for BMS, Roche, Kite, and Novartis, outside of the submitted work; reports research funding from Roche and Riemser, outside of the submitted work; reports speakers bureau from Roche outside of the submitted work; and is a current employee of Helios Klinik Berlin-Buch. VB reports membership on Board of Directors or advisory committees for Karyopharm, FATE, and Gamida Cell, outside of the submitted work; and research funding from Incyte, FATE, and Gamida Cell, outside of the submitted work. SI reports divested equity in the past 24 months from Karyopharm Therapeutics outside of the submitted work. SM reports speakers bureaus for Novartis, DNA Prime, and Celgene–BMS, outside of the submitted work; travel support and expert panel from Gilead Kite, outside of the submitted work; and is on the data safety monitoring board for Miltenyi Biotec and Immunicum, outside of the submitted work. PM is a consultant for BMS and received research funding from AstraZeneca, outside of the submitted work. FH-I reports advisory boards from Amgen, Kite, Pharmacyclics, BMS, Celgene, Incyte, Abbvie, Gilead, and Epizyme, outside of the submitted work. KI reports honoraria from Daiichi Sankyo, Eisai, Fuji Film Toyama Chemical, Genmab, Janssen, Kyowa Kirin, Novartis, Ono Pharmaceutical, Symbio, Takeda, Chugai, Celgene, AstraZeneca, Allergan Japan, and AbbVie outside of the submitted work; and research funding from Daiichi Sankyo, Eisai, Genmab, Incyte, Huya Biosciences, Janssen, Kyowa Kirin, Merck Sharpe & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Solasia,

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Data sharing

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html. The study protocol, statistical analysis plan, and patient informed consent form are available in the appendix (pp 51–230).

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