Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study

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Summary

Background Lisocabtagene maraleucel (liso-cel) is an autologous, CD19-directed, chimeric antigen receptor (CAR) T-cell product. We aimed to assess the activity and safety of liso-cel in patients with relapsed or refractory large B-cell lymphomas.

Methods We did a seamless design study at 14 cancer centres in the USA. We enrolled adult patients (aged ≥18 years) with relapsed or refractory large B-cell lymphomas. Eligible histological subgroups included diffuse large B-cell lymphoma, high-grade B-cell lymphoma with rearrangements of *MYC* and either *BCL2*, *BCL6*, or both (double-hit or triple-hit lymphoma), diffuse large B-cell lymphoma transformed from any indolent lymphoma, primary mediastinal B-cell lymphoma, and follicular lymphoma grade 3B. Patients were assigned to one of three target dose levels of liso-cel as they were sequentially tested in the trial (50×10^6 CAR$^+$ T cells [one or two doses], 100×10^6 CAR$^+$ T cells, and 150×10^6 CAR$^+$ T cells), which were administered as a sequential infusion of two components (CD8$^+$ and CD4$^+$ CAR$^+$ T cells) at equal target doses. Primary endpoints were adverse events, dose-limiting toxicities, and the objective response rate (assessed per Lugano criteria); endpoints were assessed by an independent review committee in the efficacy-evaluable set (comprising all patients who had confirmed PET-positive disease and received at least one dose of liso-cel). This trial is registered with ClinicalTrials.gov, NCT02631044.

Findings Between Jan 11, 2016, and July 5, 2019, 344 patients underwent leukapheresis for manufacture of CAR$^+$ T cells (liso-cel), of whom 269 patients received at least one dose of liso-cel. Patients had received a median of three (range 1–8) previous lines of systemic treatment, with 260 (97%) patients having had at least two lines. 112 (42%) patients were aged 65 years or older, 181 (67%) had chemotherapy-refractory disease, and seven (3%) had secondary CNS involvement. Median follow-up for overall survival for all 344 patients who had leukapheresis was 18·8 months (95% CI 15·0–19·3). Overall safety and activity of liso-cel did not differ by dose level. The recommended target dose was 100×10^6 CAR$^+$ T cells (50×10^6 CD8$^+$ and 50×10^6 CD4$^+$ CAR$^+$ T cells). Of 256 patients included in the efficacy-evaluable set, an objective response was achieved by 186 (73%, 95% CI 66·8–78·0) patients and a complete response by 136 (53%, 46·8–59·4). The most common grade 3 or worse adverse events were neutropenia in 161 (60%) patients, anaemia in 101 (37%), and thrombocytopenia in 72 (27%). Cytokine release syndrome and neurological events occurred in 113 (42%) and 80 (30%) patients, respectively; grade 3 or worse cytokine release syndrome and neurological events occurred in six (2%) and 27 (10%) patients, respectively. Nine (6%) patients had a dose-limiting toxicity, including one patient who died from diffuse alveolar damage following a dose of 50×10^6 CAR$^+$ T cells.

Interpretation Use of liso-cel resulted in a high objective response rate, with a low incidence of grade 3 or worse cytokine release syndrome and neurological events in patients with relapsed or refractory large B-cell lymphomas, including those with diverse histological subtypes and high-risk features. Liso-cel is under further evaluation at first relapse in large B-cell lymphomas and as a treatment for other relapsed or refractory B-cell malignancies.

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Introduction

Fewer than 50% of patients with relapsed or refractory large B-cell lymphomas achieve a response to subsequent treatment after a standard second-line salvage regimen, and few are cured.[1–4] Outcomes are worse in patients with chemotherapy-refractory disease, with 7% achieving a complete response to conventional treatment and overall survival of 6 months.[5] Older age (>65 years), CNS involvement,[6,7] and comorbidities[8] further portend adverse outcomes.

CD19-directed chimeric antigen receptor (CAR) T-cell treatments have shown high response rates and durable remission in patients with relapsed or refractory diffuse large B-cell lymphoma, diffuse large B-cell lymphoma

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Research in context

Evidence before this study

We searched PubMed on April 9, 2020, with the terms "CD19" AND "chimeric antigen receptor T-cell therapy" AND "lymphoma". We restricted our search to clinical trials but did not restrict by date or language. Search results were subsequently restricted to reports of interventional clinical trials. Patients with large B-cell lymphomas whose disease has progressed after two or more lines of systemic treatment are unlikely to benefit from other existing treatments. However, since 2017, the treatment landscape for third-line or later large B-cell lymphomas has changed, with approval of two CD19-directed chimeric antigen receptor (CAR) T-cell products, axicabtagene ciloleucel (in 2017) and tisagenlecleucel (in 2018). Both these CAR T-cell treatments have shown high response rates and durable remission in patients with relapsed or refractory large B-cell lymphomas. However, severe CAR T-cell-related toxicities, including cytokine release syndrome and neurological events, have challenged clinical management of these patients. Additionally, eligibility criteria for the ZUMA-1 and JULIET trials, which led to regulatory approval of axicabtagene ciloleucel and tisagenlecleucel by the US Food and Drug Administration, respectively, resulted in limited treatment experience in some patient subgroups.

Added value of this study

Lisocabtagene maraleucel (liso-cel) is a novel CD19-directed CAR T-cell with a 4-1BB co-stimulatory domain administered as sequential infusions of equal target doses of $CD8^+$ and $CD4^+$ CAR^+ T cells. The TRANSCEND NHL 001 study of liso-cel enrolled a broad range of patients with relapsed or refractory large B-cell lymphomas, compared with study populations of the previous ZUMA-1 and JULIET trials, including B-cell lymphomas with diverse histological features and patients with low creatinine clearance or poor cardiac function, and high-risk features such as CNS involvement. Additionally, patients could receive bridging therapy during the liso-cel manufacturing process.

Implications of all the available evidence

TRANSCEND NHL 001 data build on those from previous studies of CAR T-cell treatment in large B-cell lymphomas. Clinically meaningful activity was noted with liso-cel across various patient subgroups, with low rates of grade 3 or worse cytokine release syndrome and neurological events. These data support use of CAR T-cell treatment in patients with multiple subtypes of large B-cell lymphoma, who have high-risk features, including older patients (aged ≥65 years) and those who have moderate comorbidities.

transformed from follicular lymphoma, primary mediastinal B-cell lymphoma, and high-grade B-cell lymphoma.[9–12] However, data for other subtypes of large B-cell lymphomas and high-risk populations, such as older patients (aged ≥65 years) and those with comorbidities or CNS involvement, remain scarce. Furthermore, severe CAR T-cell-related toxicities, including cytokine release syndrome and neurological events, continue to represent a challenge in the clinical management of these patients.[13,14]

Lisocabtagene maraleucel (liso-cel) is an investigational, autologous, CD19-directed CAR T-cell product with a 4-1BB co-stimulatory domain,[15] which is administered as a sequential infusion of two components ($CD8^+$ and $CD4^+$ CAR^+ T cells) at equal target doses.[16] Each of the $CD8^+$ and $CD4^+$ CAR T-cell target doses is required to meet quality specifications. In animal models, a 1:1 ratio of $CD8^+$:$CD4^+$ CAR T cells showed improved expansion and activity over treatment with either T-cell component alone.[17] During liso-cel manufacturing, $CD8^+$ and $CD4^+$ T cells are selected from leukapheresis material and then independently activated, transduced, and expanded.[18] The manufacturing process results in a clonally diverse, less differentiated pure T-cell product with predominant memory T-cell composition and $CD19^+$ cells below the level of quantitation.[18]

In the seamless design TRANSCEND NHL 001 study (TRANSCEND), we aimed to assess the safety and activity of liso-cel in a broad population of patients with relapsed or refractory large B-cell lymphomas, including lymphomas with diverse histological features and patients with aggressive disease and high-risk features. Preliminary data from the dose-finding portion of the study showed a promising risk:benefit ratio after liso-cel infusion.[19] Therefore, additional expansion cohorts were enrolled via seamless design. Here, we report results from the entire cohort with large B-cell lymphoma in TRANSCEND.

See Online for appendix

Methods

Study design and patients

TRANSCEND is a multicentre, multicohort, seamless design study at 14 cancer centres in the USA (appendix p 1). Eligible patients (aged ≥18 years) had PET-positive relapsed or refractory diffuse large B-cell lymphoma (de novo or transformed from any indolent lymphoma), high-grade B-cell lymphoma with rearrangements in *MYC* and either *BCL2*, *BCL6*, or both (double-hit or triple-hit lymphoma), primary mediastinal B-cell lymphoma, or follicular lymphoma grade 3B.[20] Patients must have received two or more previous lines of systemic treatment (including previous chemoimmunotherapy containing anti-CD20 and anthracycline) with subsequent relapse, and they could have received a previous autologous or allogeneic haematopoietic stem-cell transplant. Patients with moderate comorbidities of renal (creatinine clearance >30 to <60 mL/min) and cardiac (left-ventricular ejection fraction ≥40% to <50%) dysfunction, low absolute lymphocyte count (no minimum count required), and

secondary CNS involvement were eligible. Full eligibility criteria are provided in the appendix (pp 10–11).

The study was done in accordance with the Declaration of Helsinki, International Conference on Harmonization 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.

Procedures

Patients underwent leukapheresis to collect autologous peripheral blood mononuclear cells via venous catheter for manufacture of liso-cel (appendix pp 14–15). Leukapheresis material was used to immunomagnetically select $CD8^+$ and $CD4^+$ T cells, which were then independently activated, transduced, and expanded. Bridging chemotherapy after leukapheresis was allowed at the discretion of the treating clinician during the liso-cel manufacturing process but required reconfirmation of PET-positive disease before lymphodepleting chemotherapy (appendix p 16). Systemic therapy, radiation therapy, or both were allowed for bridging therapy. Lymphodepleting chemotherapy comprising fludarabine (30 mg/m²) and cyclophosphamide (300 mg/m²) was administered intravenously daily for 3 days once the liso-cel product was available and the patient was confirmed to be eligible for infusion (appendix p 16). The median time from leukapheresis to when liso-cel was available for shipment to the study site was 24 days (range 17–51). The median time from leukapheresis to infusion was 37 days (range 27–224). 2–7 days after lymphodepleting chemotherapy, we administered liso-cel as two sequential infusions of $CD8^+$ and $CD4^+$ CAR^+ T cells, at one of three target dose levels: 50×10^6 CAR^+ T cells (dose level 1), 100×10^6 CAR^+ T cells (dose level 2), and 150×10^6 CAR^+ T cells (dose level 3); a two-dose schedule at dose level 1 was also investigated (dose level 1D; appendix p 12). TRANSCEND followed the seamless design principle, consisting of dose-finding, dose-expansion, and dose-confirmation phases.[21,22] All dose levels were assessed for dose-limiting toxicities and activity based on complete response in the dose-finding and dose-expansion phases. One recommended regimen (dose level 2) was tested during dose confirmation. Patients who achieved a complete response after liso-cel infusion and subsequently relapsed could receive retreatment. Outpatient administration and monitoring was allowed at the investigator's discretion.

Neurological events were defined as investigator-identified neurological adverse events related to liso-cel and were graded using the National Cancer Institute's common terminology criteria for adverse events, version 4.03.[23] The appendix (pp 13–14) includes additional information on examinations done. Cytokine release syndrome was graded according to the 2014 Lee criteria.[24] Activity was assessed by investigators and an independent review committee according to the Lugano criteria.[25] Additional information about study design, treatment (including lymphodepleting chemotherapy and bridging therapy), safety assessments (including definition of dose-limiting toxicities), and cellular kinetics is available in the appendix (pp 12–15).

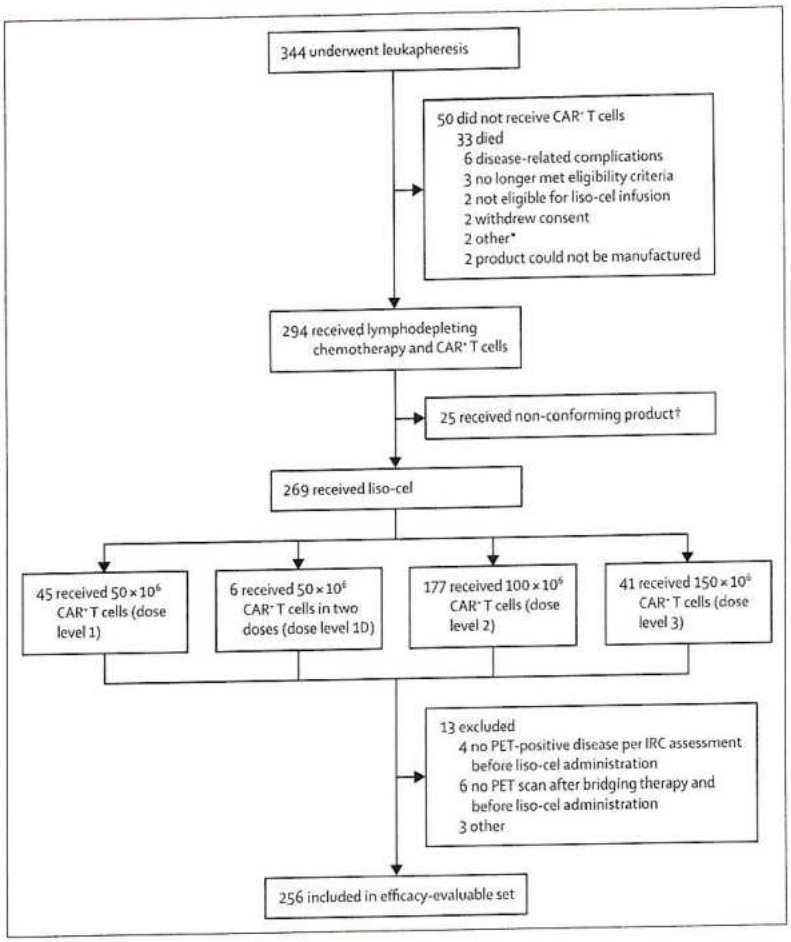


Figure 1: **Flow of patients through the study**
CAR=chimeric antigen receptor. IRC=independent review committee. liso-cel=lisocabtagene maraleucel. *One patient was admitted to hospice care with rapid clinical deterioration, and one patient decided to pursue another treatment. †One of the CD8 or CD4 cell components did not meet one of the requirements to be considered liso-cel.

Outcomes

Primary endpoints were the incidence of adverse events, the probability of dose-limiting toxicities, and the objective response rate, defined as the proportion of patients who achieved a best overall response of complete response or partial response, based on assessment by the independent review committee per Lugano criteria.[25] Secondary endpoints were the proportion of patients achieving a complete response, the duration of response, progression-free survival, overall survival, and cellular kinetic variables (appendix p 14). Duration of response was defined as the time from first complete response or partial response to

disease progression or death. Progression-free survival was defined as the time from first infusion of liso-cel to progression of disease or death. Overall survival was defined as the time from first infusion of liso-cel to the date of death.

	Patients (n=269)
Gender	
Male	174 (65%)
Female	95 (35%)
Age, years	63 (54–70)
≥65	112 (42%)
≥75	27 (10%)
Diffuse large B-cell lymphoma, not otherwise specified	137 (51%)
Diffuse large B-cell lymphoma transformed from indolent lymphomas	78 (29%)
Transformed from follicular lymphoma	60 (22%)
Transformed from other indolent non-Hodgkin lymphoma subtypes*	18 (7%)
High-grade B-cell lymphoma with gene rearrangments in *MYC* and either *BCL2*, *BCL6*, or both†	36 (13%)
Primary mediastinal B-cell lymphoma	15 (6%)
Follicular lymphoma grade 3B	3 (1%)
ECOG performance status at screening	
0	110 (41%)
1	155 (58%)
2	4 (1%)
Before lymphodepleting chemotherapy	
Sum of product diameter, cm^2	22·5 (8·5–57·9)
Sum of product diameter ≥50 cm^2‡	73 (28%)
Lactate dehydrogenase, U/L	266·0 (112·0–11 933·0)
Lactate dehydrogenase ≥500 U/L	58 (22%)
Creatinine clearance >30 to <60 mL/min§	51 (19%)
Baseline C-reactive protein, mg/L	27·6 (7·9–81·6)
Left-ventricular ejection fraction ≥40% and <50%¶	13 (5%)
Previous lines of systemic therapy‖	3 (2–4)
1	9 (3%)
2	121 (45%)
3	68 (25%)
≥4	71 (26%)
Chemotherapy refractory**	181 (67%)
Received previous HSCT	94 (35%)
Autologous HSCT	90 (33%)
Allogeneic HSCT	9 (3%)
Never achieved complete response with previous therapy††	119 (44%)
Received bridging therapy	159 (59%)
Secondary CNS lymphoma	7 (3%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. HSCT=haematopoietic stem-cell transplant. liso-cel=lisocabtagene maraleucel. *Transformed from marginal zone lymphoma (n=10), chronic lymphocytic leukaemia or small lymphocytic lymphoma (n=5), Waldenström macroglobulinaemia (n=2), and 50% follicular and 50% Epstein-Barr virus-positive (n=1). †Patients with diffuse large B-cell lymphoma transformed from indolent lymphomas with gene rearrangements in *MYC* and either *BCL2*, *BCL6*, or both were not included as high-grade B-cell lymphoma. ‡Not all patients were evaluable for sum of product diameter (n=256). Sum of product diameter was calculated per central review assessment before lymphodepleting chemotherapy. §Creatinine clearance had to be >30 mL/min per eligibility criteria. ¶Left-ventricular ejection fraction had to be ≥40% per eligibility criteria. ‖The original study protocol enrolled patients with at least two previous lines of treatment, including nine patients who had received one line of systemic treatment plus consolidation with HSCT or radiation. The protocol was amended to require at least two previous lines of systemic treatment. **No response to or progressive disease after last chemotherapy-containing regimen, or relapse <12 months after autologous HSCT. ††Not only primary refractory but also refractory to subsequent lines of treatment.

Table 1: **Baseline characteristics of patients who received liso-cel**

Statistical analysis

Dose escalation was guided by modified Bayesian continuous reassessment methodology.[26] A recommended regimen was further assessed during dose confirmation (appendix p 17). Safety analyses were done in all patients with large B-cell lymphomas who received liso-cel. Activity was assessed in three patient populations: the efficacy-evaluable set (which consisted of all patients who received at least one dose of liso-cel and who had confirmed PET-positive disease before liso-cel administration based on independent review committee assessment), the primary analysis set (a subset of efficacy-evaluable patients who were treated at dose level 2), and the intention-to-treat set (all patients who underwent leukapheresis; appendix p 14).

The one-sided significance level for the interim analysis was 0·01, and for the primary analysis it was 0·021, using the interpolated spending function. An interim analysis was not done based on discussions with regulatory agencies; thus, the entire α of 0·025 was used for the primary analysis, which was done in the primary analysis set. We calculated the objective response rate and corresponding two-sided Clopper-Pearson 95% CIs. Kaplan-Meier methodology was used to estimate the medians and 95% CIs for duration of response, progression-free survival, and overall survival; follow-up times were calculated using the reverse Kaplan-Meier method.

This trial is registered with ClinicalTrials.gov, NCT02631044.

Role of the funding source

The funder had a role in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all study data. The corresponding author had final responsibility for the decision to submit for publication.

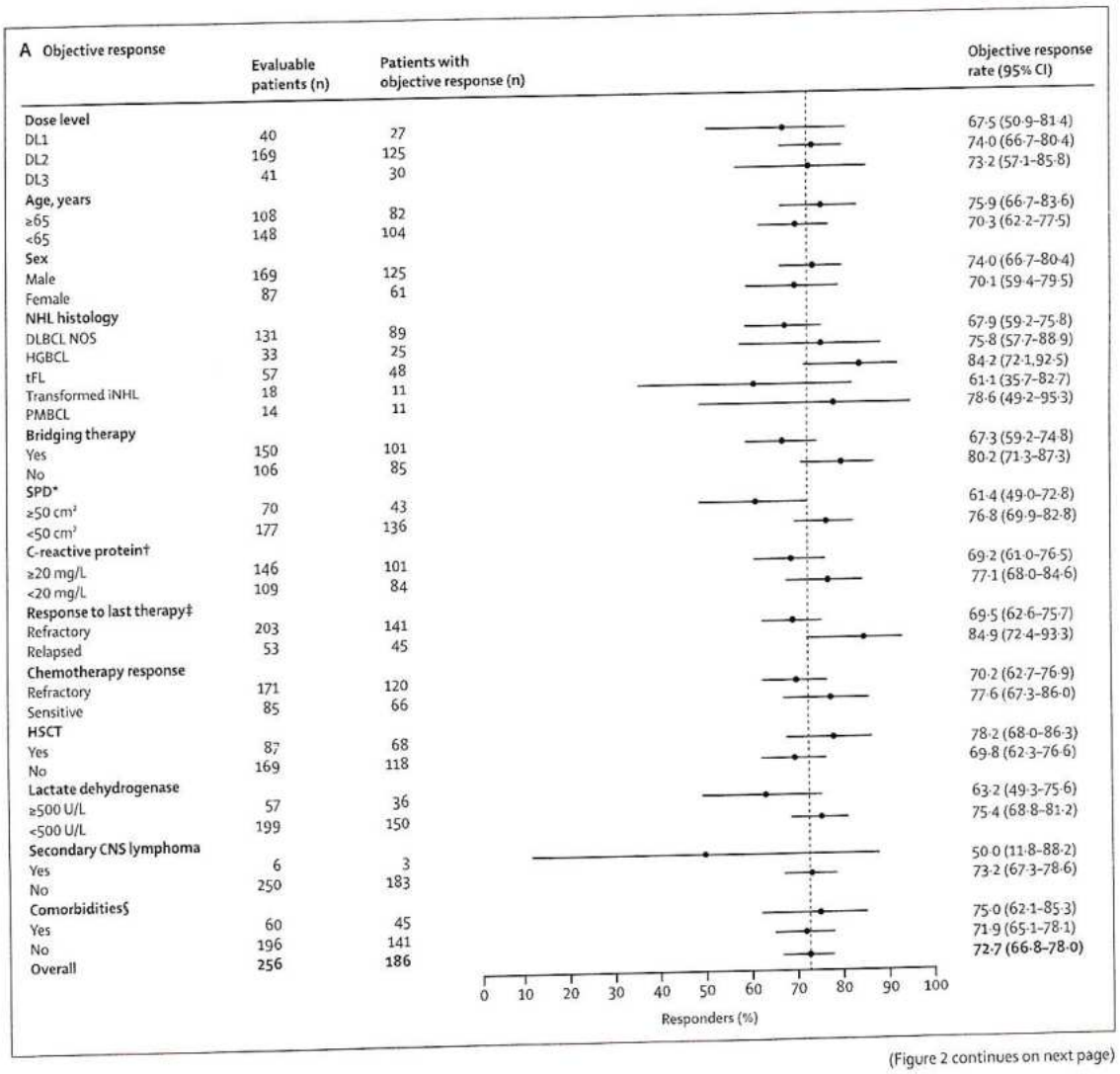
Results

Between Jan 11, 2016, and July 5, 2019, 344 patients underwent leukapheresis for manufacture of CAR$^+$ T cells. Median follow-up for overall survival for all patients who had leukapheresis was 18·8 months (95% CI 15·0–19·3). Data cutoff for this analysis was on Aug 12, 2019. Follow-up is ongoing.

Of 344 patients with large B-cell lymphoma who underwent leukapheresis, 294 received CAR T cells a median of 3 days (IQR 3–4) after lymphodepleting chemotherapy. Product could not be manufactured for two patients, and 48 patients had lymphoma complications or died before infusion (figure 1). Of 294 patients who received CAR T cells across all dose levels, 269 received liso-cel and 25 received a non-conforming CAR T-cell product (ie, one component did not meet release criteria but was considered safe for infusion). Of the 269 patients

who received liso-cel, 45 received 50×10^6 CAR$^+$ T cells (dose level 1), six received 50×10^6 CAR$^+$ T cells in two doses (dose level 1D), 177 received 100×10^6 CAR$^+$ T cells (dose level 2), and 41 received 150×10^6 CAR$^+$ T cells (dose level 3; appendix p 17). Patients received a median of 91×10^6 CAR$^+$ T cells (range 44–156×10^6). 25 patients at five different study sites received liso-cel in the outpatient setting.

Table 1 shows characteristics at baseline of the 269 patients who received liso-cel. Median age was 63 years (IQR 54–70; range 18–86); 112 (42%) patients were aged 65 years or older. Patients were heavily pretreated, with a median of three (IQR 2–4) previous lines of systemic therapy; 181 (67%) patients had chemotherapy-refractory disease (defined as no response to or progressive disease after their last chemotherapy-containing regimen, or relapse <12 months after autologous stem-cell transplant) and 119 (44%) had never achieved a complete response with previous treatment. Bridging therapy was administered in 159 (59%) patients at the investigator's discretion (appendix p 16). Bridging therapy did not result in a lower tumour burden in most patients (appendix p 2). The most common histological subgroups were diffuse large B-cell lymphoma not otherwise specified in 137 (51%) patients, diffuse large B-cell lymphoma transformed from indolent lymphomas in 78 (29%) patients, and high-grade B-cell lymphoma with gene rearrangements of *MYC* and either *BCL2*, *BCL6*, or both (double-hit or triple-hit lymphoma) in 36 (13%) patients. Of 78 patients with diffuse large B-cell lymphoma transformed from indolent lymphomas, 60 (22%) were transformed from follicular lymphoma, ten (4%) from marginal zone lymphoma, five (2%) from chronic lymphocytic leukaemia or small lymphocytic lymphoma, and



(Figure 2 continues on next page)

three (1%) from other subtypes (table 1). Seven patients (3%) had secondary CNS involvement.

Accrual and estimated probabilities of dose-limiting toxicities and complete responses for the dose-finding phase are shown in the appendix (p 17). Among 139 patients evaluable for dose-limiting toxicities in the dose-finding (n=59) and dose-expansion (n=80) phases, nine (6%) had dose-limiting toxicities, including one patient who died of diffuse alveolar damage at dose level 1 (appendix p 18). No maximum-tolerated dose was identified. Patients' demographics and baseline characteristics were similar across dose levels (appendix pp 19–20). No dose relationship was noted for overall safety and activity across all dose levels. An increased rate of grade 1–2 cytokine release syndrome at dose level 3 (appendix p 21) and a numerically higher objective response rate at dose level 2 and dose level 3 (figure 2; appendix p 22) supported the selection of dose level 2 (100×10^6 CAR$^+$ T cells) for the dose-confirmation phase.

Data across all dose levels were combined because of the absence of a clear dose-related toxicity relationship. In the safety analysis, among 269 patients treated with liso-cel, the most frequent treatment-emergent adverse events were neutropenia in 169 (63%) patients, anaemia in

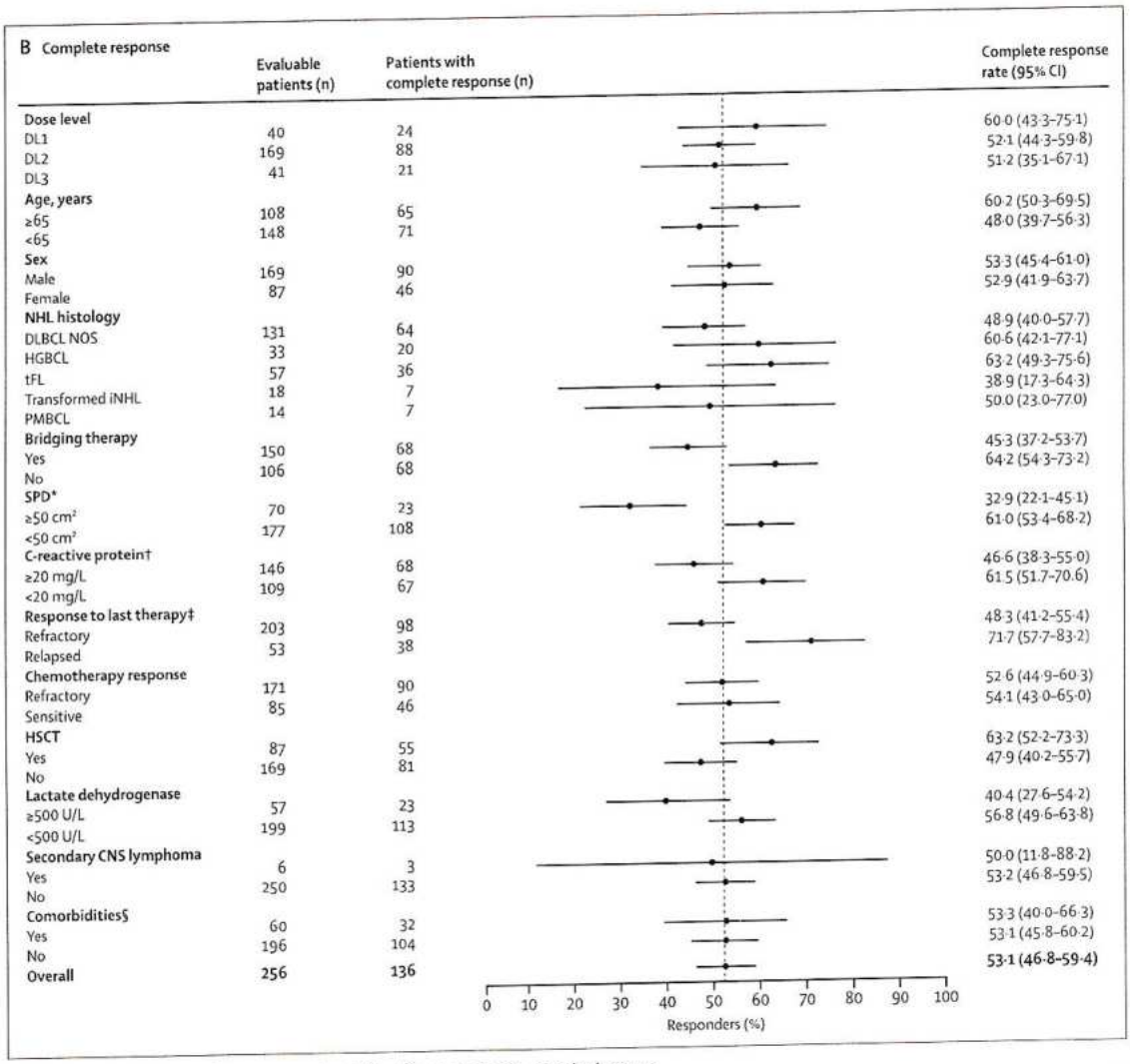


Figure 2: **Objective and complete response rates in the efficacy-evaluable set and subgroups**
Forest plots showing objective response (A) and complete response (B) rates. DL1=50×10^6 CAR$^+$ T cells (one or two doses). DL2=100×10^6 CAR$^+$ T cells. DL3=150×10^6 CAR$^+$ T cells. NHL=non-Hodgkin lymphoma. DLBCL NOS=diffuse large B-cell lymphoma not otherwise specified. HGBCL=high-grade B-cell lymphoma with gene rearrangements in *MYC* and either *BCL2*, *BCL6*, or both. tFL=transformed from follicular lymphoma. iNHL=DLBCL transformed from indolent non-Hodgkin lymphomas other than follicular lymphoma. PMBCL=primary mediastinal large B-cell lymphoma. SPD=sum of product diameter. HSCT=haematopoietic stem-cell transplant. *SPD assessed before lymphodepleting chemotherapy. †C-reactive protein was assessed at baseline. ‡Relapsed versus refractory is defined as best response of complete response versus best response of partial response, stable disease, or progressive disease to last systemic or transplant treatment with curative intent. §Comorbidities included patients with creatinine clearance <60 mL/min and left-ventricular ejection fraction <50%.

129 (48%), fatigue in 119 (44%), cytokine release syndrome in 113 (42%), and nausea in 90 (33%; table 2). The most common grade 3 or worse treatment-emergent adverse events were neutropenia in 161 (60%) patients, anaemia in 101 (37%), and thrombocytopenia in 72 (27%; appendix pp 23–25). Febrile neutropenia was recorded in 25 (9%) patients and grade 3 or worse febrile neutropenia in 24 (9%) patients. Seven (3%) patients with treatment-emergent adverse events died. Causes were (n=1 for each) diffuse alveolar damage (dose-limiting toxicity), pulmonary haemorrhage, multiple organ dysfunction syndrome, cardiomyopathy, leukoencephalopathy, septic shock, and progressive multifocal leukoencephalopathy. Diffuse alveolar damage, pulmonary haemorrhage, multiple organ dysfunction syndrome, and cardiomyopathy were considered related to both liso-cel and lymphodepleting chemotherapy by the investigator. Fludarabine-associated leukoencephalopathy and septic shock were considered related to lymphodepleting chemotherapy by the investigator. Progressive multifocal leukoencephalopathy was considered unrelated to both liso-cel and lymphodepleting chemotherapy by the investigator.

Among 269 patients in the safety population, 127 (47%) developed cytokine release syndrome, neurological events, or both (table 3). Cytokine release syndrome of any grade was reported in 113 (42%) patients, with a median onset of 5 days (range 1–14). Grade 3 or worse cytokine release syndrome was reported in six (2%) patients. The most common symptoms of cytokine release syndrome were fever (reported in 107 patients, 40% of patients overall and 95% of patients with cytokine release syndrome) and hypotension (reported in 55 patients, 20% of patients overall and 49% of patients with cytokine release syndrome; appendix p 26). No patients died from cytokine release syndrome; however, two patients died with ongoing cytokine release syndrome, one from septic shock and one from pulmonary haemorrhage. Cytokine release syndrome was managed with tocilizumab, corticosteroids, or both in 53 (20%) patients; 27 (10%) received tocilizumab alone (table 3). The 48 patients who received tocilizumab (with or without corticosteroids) for cytokine release syndrome had a median of one dose (range 1–4), with median time from cytokine release syndrome onset to receipt of tocilizumab of 1·5 days (range 0–8). Other interventions for cytokine release syndrome included vasopressors for seven (3%) patients and both siltuximab and anakinra for grade 4 cytokine release syndrome for one (<1%) patient. Four (1%) patients underwent dialysis and five (2%) were intubated.

Neurological events of any grade occurred in 80 (30%) patients, with a median time to onset of 9 days (range 1–66; table 3). Neurological events occurred during or after cytokine release syndrome in 58 (73%) patients. Grade 3 or worse neurological events occurred in 27 (10%) patients (table 3). Among seven patients with secondary CNS lymphoma, two (29%) had neurological events (both were grade 3). No patients died from neurological events; however, the seven patients who died from other causes had ongoing neurological events. The most common neurological events of any grade were encephalopathy (reported in 57 patients, 21% of patients overall and 71% of patients with neurological events), tremor and aphasia (each reported in 26 patients, 10% of patients overall and 33% of patients with neurological events), and delirium (reported in 16 patients, 6% of patients overall and 20% of patients with neurological events; table 4). Treatment-emergent adverse events reported as CNS disorders (regardless of attribution to

	Any grade	Grade ≥3
Patients with treatment-emergent adverse events	267 (99%)	213 (79%)
Neutropenia	169 (63%)	161 (60%)
Anaemia	129 (48%)	101 (37%)
Fatigue	119 (44%)	4 (1%)
Cytokine release syndrome	113 (42%)	6 (2%)
Nausea	90 (33%)	4 (1%)
Thrombocytopenia	84 (31%)	72 (27%)
Headache	80 (30%)	3 (1%)
Decreased appetite	76 (28%)	7 (3%)
Diarrhoea	71 (26%)	1 (<1%)
Constipation	62 (23%)	0
Dizziness	60 (22%)	1 (<1%)
Hypotension	60 (22%)	8 (3%)
Cough	57 (21%)	0
Vomiting	56 (21%)	1 (<1%)
Hypokalaemia	52 (19%)	6 (2%)
Hypomagnesaemia	50 (19%)	0
Pyrexia	45 (17%)	0
Leucopenia	44 (16%)	39 (14%)
Abdominal pain	44 (16%)	5 (2%)
Peripheral oedema	42 (16%)	1 (<1%)
Sinus tachycardia	42 (16%)	0
Tremor	41 (15%)	0
Confusional state	39 (14%)	2 (1%)
Hypogammaglobulinaemia	37 (14%)	0
Hypertension	37 (14%)	12 (5%)
Dyspnoea	36 (13%)	2 (1%)
Insomnia	36 (13%)	1 (<1%)
Back pain	33 (12%)	3 (1%)
Chills	31 (12%)	0
Hypophosphataemia	27 (10%)	16 (6%)
Anxiety	27 (10%)	0
Arthralgia	26 (10%)	2 (1%)

Table shows treatment-emergent adverse events in ≥10% of patients and all corresponding grade ≥3 treatment-emergent adverse events.
liso-cel=lisocabtagene maraleucel.

Table 2: **Treatment-emergent adverse events in liso-cel-treated patients (n=269)**

	Patients (n=269)
Cytokine release syndrome, neurological events, or both	127 (47%)
Cytokine release syndrome*	
Any grade	113 (42%)
Grade 3	4 (1%)
Grade 4	2 (1%)
Time to onset, days	5 (1–14)
Time to resolution, days	5 (1–17)
Neurological events†	
Any grade	80 (30%)
Grade 3	23 (9%)
Grade 4	4 (1%)
Time to onset, days	9 (1–66)
Time to resolution, days	11 (1–86)
Tocilizumab, corticosteroids, or both for cytokine release syndrome‡	53 (20%)
Tocilizumab only	27 (10%)
Tocilizumab and corticosteroids	21 (8%)
Corticosteroids only	5 (2%)
Grade of cytokine release syndrome at first use of tocilizumab	
Grade 1	20 (7%)
Grade 2	25 (9%)
Grade 3	2 (1%)
Grade 4	1 (<1%)
Other drugs for treatment of cytokine release syndrome	
Vasopressors	7 (3%)
Anakinra	1 (<1%)
Siltuximab	1 (<1%)
Prolonged cytopenias§	100 (37%)
Hypogammaglobulinaemia	37 (14%)
Grade ≥3 infections¶	33 (12%)
Tumour lysis syndrome	2 (1%)
Infusion-related reactions	3 (1%)‖

Data are n (%) or median (range). No deaths from cytokine release syndrome or neurological events occurred. liso-cel=lisocabtagene maraleucel. *Cytokine release syndrome was graded according to Lee criteria.[24] †Defined as investigator-identified neurological adverse events related to liso-cel. ‡Patients with concurrent cytokine release syndrome and neurological events might have received tocilizumab or corticosteroids for both events. §Prolonged cytopenia included grade ≥3 neutropenia, thrombocytopenia, or anaemia not resolved at the day 29 study visit based on laboratory assessments. ¶Grade ≥3 bacterial infections occurred in 11 (4%) patients, fungal infections in two (1%), and viral infections in four (1%). ‖All infusion-related reactions were grade 1–2 and patients were able to receive both the CD8 and CD4 components of liso-cel.

Table 3: **Treatment-emergent adverse events of special interest in liso-cel-treated patients (n=269)**

	Any grade	Grade 3 or 4
Encephalopathy	57 (21%)	18 (7%)
Confusional state	30 (11%)	2 (1%)
Encephalopathy	17 (6%)	11 (4%)
Mental status changes	10 (4%)	4 (1%)
Somnolence	6 (2%)	1 (<1%)
Lethargy	5 (2%)	0
Other*	17 (6%)	2 (1%)
Aphasia	26 (10%)	5 (2%)
Aphasia	22 (8%)	3 (1%)
Dysarthria	5 (2%)	2 (1%)
Other†	4 (1%)	0
Tremor	26 (10%)	0
Tremor	25 (9%)	0
Essential tremor	1 (<1%)	0
Delirium	16 (6%)	4 (1%)
Agitation	9 (3%)	3 (1%)
Other‡	10 (4%)	2 (1%)
Dizziness	11 (4%)	2 (1%)
Dizziness	11 (4%)	1 (<1%)
Syncope	1 (<1%)	1 (<1%)
Headache	9 (3%)	2 (1%)
Headache	9 (3%)	2 (1%)
Migraine	1 (<1%)	0
Ataxia or gait disturbance	8 (3%)	1 (<1%)
Ataxia	6 (2%)	1 (<1%)
Gait disturbance	2 (1%)	0
Cerebellar	6 (2%)	0
Other§	6 (2%)	0

Neurological events were defined as investigator-assessed neurological adverse events related to liso-cel and were graded using National Cancer Institute common terminology criteria for adverse events version 4.03.[23] Patients could have more than one event. liso-cel=lisocabtagene maraleucel. *Other events occurred in four or fewer patients and included amnesia, cognitive disorder, depressed level of consciousness, memory impairment, flat affect, depersonalisation or derealisation disorder, disturbance in attention, incoherent, and hypersomnia. †Other events occurred in four or fewer patients and included dysphemia, dysphonia, slow speech, and speech disorder. ‡Other events occurred in four or fewer patients and included delirium, disorientation, delusion, hallucination, visual hallucination, and irritability. §Other events occurred in four or fewer patients and included cerebellar syndrome, dysmetria, balance disorder, dyskinesia, and impaired hand–eye coordination.

Table 4: **Treatment-emergent neurological events in five or more patients by group term in liso-cel-treated patients (n=269)**

liso-cel) occurred in 179 (67%) patients, including headache in 80 (30%) patients, dizziness in 60 (22%), and tremor in 41 (15%).

Other treatment-emergent adverse events of special interest included prolonged cytopenias at day 29 in 100 (37%) patients, hypogammaglobulinaemia in 37 (14%) patients, and grade 3 or worse infections in 33 (12%) patients (table 3). Of 100 patients with prolonged cytopenias who had haematology laboratory results after day 29, recovery to grade 2 or lower anaemia, neutropenia, and thrombocytopenia, respectively, occurred in nine (82%) of 11, 36 (84%) of 43, and 36 (62%) of 58 patients by day 90, in ten (91%) of 11, 40 (93%) of 43, and 43 (74%) of 58 patients by day 180, and in ten (91%) of 11, 41 (95%) of 43, and 47 (81%) of 58 patients by the end of the study. 19 (7%) patients were admitted to the intensive care unit (ICU) during initial hospitalisation after liso-cel infusion, with 12 (4%)

admissions for cytokine release syndrome, neurological events, or both.

Safety outcomes, including cytokine release syndrome and neurological events, across subgroups, including age, presence of comorbidities, secondary CNS lymphoma, and outpatient infusion or monitoring, are shown in the appendix (p 27). Patients with high tumour burden or increased inflammatory markers and those who received bridging therapy had a higher incidence of cytokine release syndrome, neurological events, or both of any grade. Of 25 patients treated in the outpatient setting, 18 (72%) were hospitalised for adverse events after receiving liso-cel, including ten with cytokine release syndrome, neurological events, or both. Median time from liso-cel infusion to hospitalisation was 5 days (range 3–22). One outpatient was admitted to the ICU.

256 patients were included in the efficacy-evaluable set, which included patients who received at least one dose of liso-cel and had PET-positive disease per independent review committee assessment. An objective response was achieved by 186 (73%, 95% CI 66·8–78·0) patients (one-sided p<0·0001; figure 2A) and a complete response by 136 (53%, 46·8–59·4) patients (one-sided p<0·0001; figure 2B, table 5). The primary endpoint of objective response rate was met in the primary analysis set (which comprised patients in the efficacy-evaluable set who received dose level 2), with 99 (74%, 95% CI 66·2–81·6) of 133 patients achieving an objective response (one-sided p<0·0001); a complete response was achieved by 72 (54%, 95% CI 45·3–62·8) patients (one-sided p<0·0001). In the intention-to-treat set (comprising 344 patients who underwent leukapheresis), an objective response was achieved by 208 (61%, 95% CI 55·1–65·7) patients (one-sided p<0·0001) and a complete response by 150 (44%, 38·3–49·0) patients (one-sided p<0·0001; appendix p 28). 16 patients who achieved a complete response after liso-cel treatment but later progressed received retreatment with liso-cel.

Median time to first complete response or partial response was 1·0 months (range 0·7–8·9; table 5); time to first complete response was 1·0 months (0·8–12·5). Although most patients achieved their best response at 1·0 months, 28 patients with an initial response of partial response later achieved a complete response at a median of 3·0 months (range 1·8–12·5), and seven patients with an initial response of stable disease achieved either a complete response or a partial response at a median of 3·0 months (1·7–8·9).

The median duration of response was not reached (95% CI 8·6–not reached; figure 3A, table 5) at median follow-up for duration of response of 12·0 months (95% CI 11·2–16·7). The estimated duration of response rate at 1 year was 55% (95% CI 46·7–62·0) for the total population, and 65% (56·2–72·8) among those who achieved a complete response (appendix p 29). Median progression-free survival was 6·8 months (95% CI 3·3–14·1) after median follow-up for progression-free survival of 12·3 months (95% CI 12·0–17·5; figure 3B, table 5); among patients who achieved a complete response, median progression-free survival was not reached. Progression-free survival at 1 year was 44% (95% CI 37·3–50·7) for the total population and 65% (56·1–72·7) among patients who had complete response (appendix p 29). Median overall survival was 21·1 months (95% CI 13·3–not reached; figure 3C, table 5), with median follow-up for overall survival of 17·5 months (95% CI 12·9–17·8). Estimated 12-month overall survival was 58% (95% CI 51·3–63·8) for the total population. Among patients who achieved a complete response, median overall survival was not reached, and overall survival was 86% (95% CI 78·2–90·5) at 1 year. Estimated probabilities for duration of response, progression-free survival, and overall survival at additional timepoints are shown in the appendix (p 29). Activity of liso-cel was similar across dose levels (figure 2), with no difference noted between individual dose levels for objective response rate (p=0·68), progression-free survival (p=0·46), or duration of response (p=0·76), or between analysis sets (appendix p 28).

Based on the investigator's assessment, retreatment with liso-cel in 16 patients relapsing after initial complete response resulted in a low objective response rate (three [19%] patients achieved an objective response, two complete responses and one partial response; appendix p 30). The two patients with a complete response had a duration of response of 3 months and 8 months, and the

	Patients (n=256)
Objective response rate	186 (73%, 66·8–78·0)
Complete response	136 (53%, 46·8–59·4)
Partial response	50 (20%, 14·9–24·9)
Stable disease*	32 (13%)
Progressive disease	28 (11%)
Not evaluable	10 (4%)
Median (range) time to first complete response or partial response, months	1·0 (0·7–8·9)
Median (95% CI) duration of response, months	NR (8·6–NR)
Duration of response (95% CI) at 6 months, %	60·4% (52·6–67·3)
Duration of response (95% CI) at 12 months, %	54·7% (46·7–62·0)
Median (95% CI) progression-free survival, months	6·8 (3·3–14·1)
Progression-free survival (95% CI) at 6 months, %	51·4% (44·6–57·7)
Progression-free survival (95% CI) at 12 months, %	44·1% (37·3–50·7)
Median (95% CI) overall survival, months	21·1 (13·3–NR)
Overall survival (95% CI) at 6 months, %	74·7% (68·9–79·6)
Overall survival (95% CI) at 12 months, %	57·9% (51·3–63·8)

Data are n (%, 95% CI) or n (%), unless otherwise specified. The efficacy-evaluable set included all patients who received at least one dose of liso-cel and had confirmed PET-positive disease before liso-cel administration, based on IRC assessment. IRC=independent review committee. liso-cel=lisocabtagene maraleucel. NR=not reached. *Includes patients with IRC-assessed best overall response of stable disease and non-progressive disease. Non-progressive disease could be assigned as a best overall response by the IRC when PET was not evaluable or not done for all the post-baseline assessment timepoints and the best response based on a CT-staging evaluation was complete response, partial response, or stable disease.

Table 5: **Summary of efficacy endpoints in the efficacy-evaluable set (n=256)**

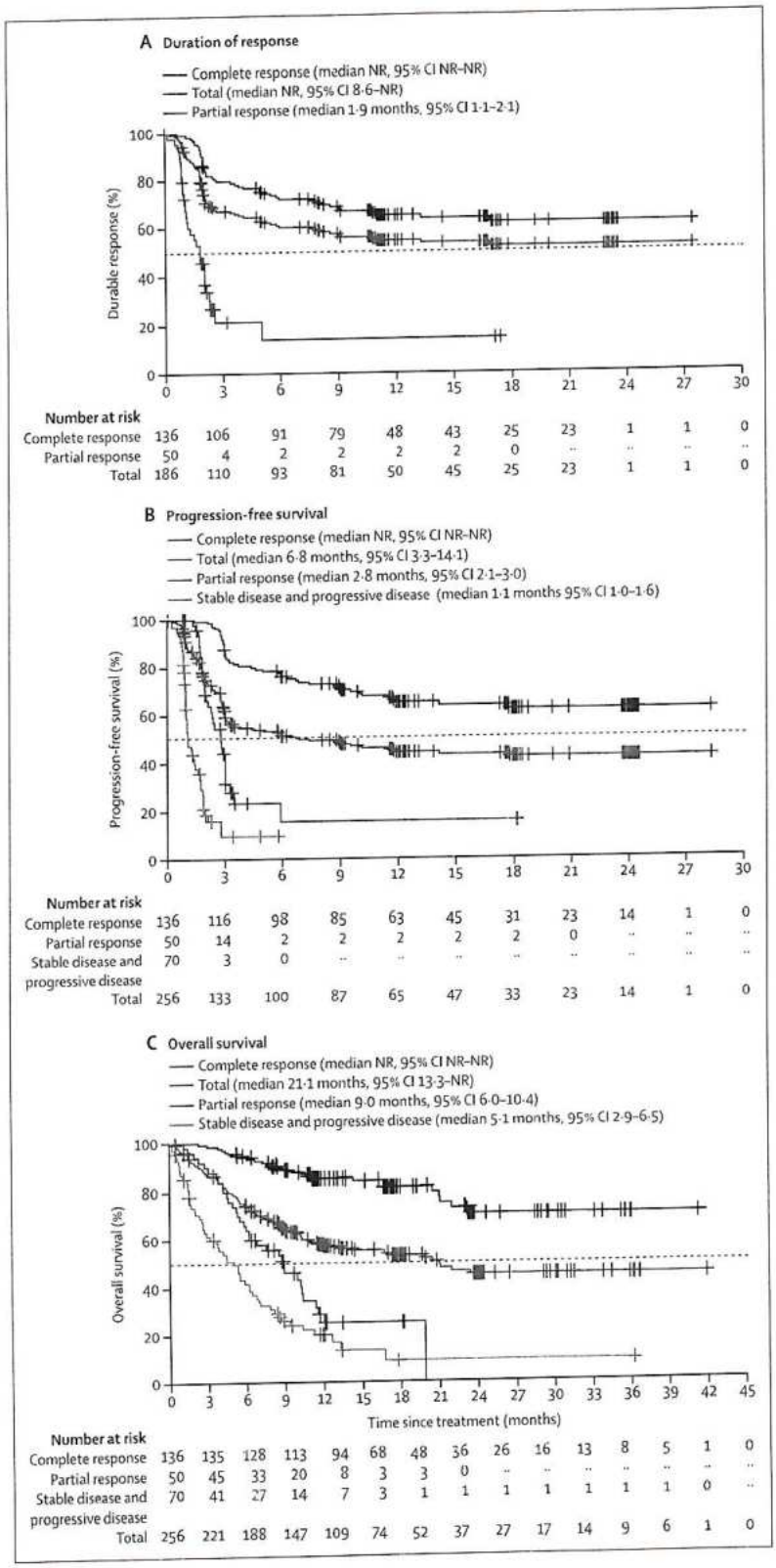


Figure 3: **Kaplan-Meier analyses of response and survival outcomes in the efficacy-evaluable set, by best overall response**
Kaplan-Meier analysis of duration of response (A), progression-free survival (B), and overall survival (C). NR=not reached.

patient with partial response had a duration of response of less than 1 month. Activity among 25 patients who received non-conforming product was similar to that recorded among patients who received liso-cel (appendix p 30).

Objective responses were achieved across all subgroups, including in patients with high-risk features such as high-grade B-cell lymphoma, those aged 65 years or older, patients with chemotherapy-refractory disease, and patients receiving bridging therapy (figure 2). Three of six patients in the efficacy-evaluable set with secondary CNS lymphoma achieved a complete response. Durable responses (based on independent review committee assessment) were seen across B-cell lymphoma subtypes (appendix p 9). Duration of response and progression-free survival in patients with primary mediastinal B-cell lymphoma and diffuse large B-cell lymphoma transformed from follicular lymphoma were longer than for other subtypes (appendix p 9). Both patients with follicular lymphoma grade 3B who received liso-cel remain in complete response after 1 year. Median overall survival has not yet been reached for patients with high grade B-cell lymphoma, transformed follicular lymphoma, follicular lymphoma grade 3B, or primary mediastinal B-cell lymphoma (appendix p 9). Durable responses were also seen in patients aged 65 years or older, those with chemotherapy-refractory disease, patients with a high tumour burden (ie, sum of product diameter ≥50 cm^2), those with moderate comorbidities, and patients who received bridging therapy. Median duration of response, progression-free survival, and overall survival did not differ between these subgroups (appendix pp 3–8, 31).

Among 245 patients evaluable for cellular kinetic analyses, median time to CAR T-cell peak expansion across all dose levels was 12 days (IQR 10–14), median maximum expansion (C_{max}) was 23928·2 copies per µg, and median area under the curve from 0–28 days post-infusion (AUC_{0-28d}) was 213730·1 day×copies per µg. Expansion was similar across all dose levels (appendix p 32). Among 179 people with either a complete or partial response, median C_{max} (3·55-fold; p<0·0001) and AUC_{0-28d} (2·72-fold; p<0·0001) were higher than in 53 non-responders. Higher median C_{max} was also associated with higher baseline tumour burden (2·46-fold; p=0·0097), any grade cytokine release syndrome (2·29-fold; p=0·0003), any grade neurological events (3·34-fold; p<0·0001), and grade 3 or worse neurological events (5·04-fold; p=0·0002; appendix p 33). CAR T cells showed long-term persistence at 1 year in 35 (52%) of 67 patients (appendix p 34). Among all evaluable patients, 51 (73%) of 70 had persistent B-cell aplasia at 1 year (appendix p 35). Notably, 241 (92%) of 262 patients had B-cell aplasia at baseline.

Discussion

TRANSCEND is the largest clinical study reported to date of CD19-directed CAR T-cell treatment for patients with relapsed or refractory large B-cell lymphomas. Of 344 patients who underwent leukapheresis, 50 (15%) did not receive CAR T cells, primarily because of death from progression (n=33), which shows the aggressiveness of this disease in a high-risk patient population. Of the remaining 294 patients, 25 received non-conforming CAR$^-$ T cells. Among 256 patients in the efficacy-evaluable set who received at least one dose of liso-cel and had PET-positive disease per independent review committee assessment, an objective response was achieved by 186 (73%), and 136 (53%) achieved a complete response. Responses were durable, with an estimated duration of response at 1 year of 55% among patients who had a complete or partial response and 65% among those who achieved a complete response. Progression-free survival and overall survival at 1 year were 44% and 58%, respectively. Responses were seen across all histological subtypes and high-risk features. Response was associated with increased CAR T-cell expansion in vivo, and CAR T cells persisted long term after liso-cel infusion, with circulating CAR T cells detected at 1 year in most patients. Liso-cel was associated with a low incidence of grade 3 or 4 cytokine release syndrome (in six [2%] patients) and neurological events (in 27 [10%] patients).

Two CD19-directed CAR T-cell therapies, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, are currently approved for treatment of relapsed or refractory aggressive B-cell lymphomas. In the ZUMA-1 study,[10,27] a complete response with axi-cel was achieved by 58% of patients, with 39% in durable remission at median follow-up of 27·1 months. At the 1-year analysis of the ZUMA-1 study, median progression-free survival was 5·8 months (95% CI 3·3–not estimable) and median overall survival was not reached (95% CI 12·0–not estimable).[10] Axi-cel was associated with cytokine release syndrome and neurological events in 93% and 64% of patients, respectively.[10] Grade 3 or worse cytokine release syndrome (per Lee criteria)[24] and neurological events occurred in 13% and 28%, respectively.[27] In the JULIET study, tisagenlecleucel resulted in overall and complete response rates of 52% and 40%, respectively, with approximately a third of patients progression-free at 1 year.[11] Cytokine release syndrome and neurological events occurred in 58% and 21% of patients, respectively. Grade 3 or worse cytokine release syndrome (Penn grading criteria)[28] and neurological events were reported in 22% and 12% of patients, respectively.[11] Notably, the Penn grading system for cytokine release syndrome results in higher rates of severe cytokine release syndrome relative to the Lee criteria used in TRANSCEND and ZUMA-1.[28–30]

The broad eligibility criteria in TRANSCEND aligns with recommendations for clinical trials of CAR T-cell therapies to maximise generalisability of results.[31] JULIET and ZUMA-1 enrolled patients with diffuse large B-cell lymphoma, high-grade B-cell lymphoma, and transformed follicular lymphoma,[11] and patients with primary mediastinal B-cell lymphoma were also enrolled in ZUMA-1. TRANSCEND data expand current knowledge about CAR T-cell treatment in aggressive B-cell non-Hodgkin lymphoma by including additional populations with a high unmet need for novel treatments and who are under-represented in clinical trials.[31,32] Although excluded from pivotal studies, post-marketing registry studies indicate that outcomes with tisagenlecleucel and axi-cel could be similar in real-world settings with patient populations closely similar to those in TRANSCEND, supporting the safety and activity of CAR T cells in these populations.[33,34]

TRANSCEND enrolled a large population of older patients (112 [42%] of 269 patients were aged ≥65 years) and provides data for understudied subtypes important for real-world care of patients with large B-cell lymphomas. Safety and activity outcomes of liso-cel among patients aged 65 years or older were comparable with those in patients younger than 65 years. Patients with moderate comorbidities had objective response and complete response rates and safety outcomes comparable with those of people without comorbidities. Although patients with secondary CNS lymphoma were excluded from JULIET and ZUMA-1,[10,11] independent-investigator retrospective studies have shown activity and manageable toxicity in these patients after tisagenlecleucel[35] or axi-cel[36–38] treatment. Of six evaluable patients with secondary CNS lymphoma in TRANSCEND, three (50%) achieved a complete response, no patients had severe cytokine release syndrome, and two (33%) patients had grade 3 neurological events. Additional studies on the management of these patients receiving CAR T-cell treatment, particularly regarding neurological events, are warranted. Our data also showed notable duration of response in patients with diffuse large B-cell lymphoma transformed from follicular lymphoma and patients with primary mediastinal B-cell lymphoma. Similar results have been reported in other studies.[10] Although the reasons for these findings are not clear, both histological subtypes are biologically distinct diseases that arise in different demographic groups and are treated with distinct lines of treatment, all of which could contribute to different outcomes when compared with other histological subgroups.

Bridging therapy was associated with a higher incidence of cytokine release syndrome and neurological events and poorer efficacy outcomes among patients in our study (appendix p 26). Importantly, patients receiving bridging therapy are likely to have more aggressive disease and, therefore, are more likely to have other risk factors for increased rates of cytokine release syndrome, neurological events, or both (eg, increased amounts of lactate dehydrogenase, sum of product diameter, or both, before lymphodepleting chemotherapy, and baseline C-reactive

protein). Data regarding bridging therapy and incidence of cytokine release syndrome, neurological events, or both should be considered in that context. In a large multicentre cohort of patients receiving axi-cel, bridging therapy was associated with lower overall survival.[39] Bridging therapy was used in 159 (59%) of 269 patients in TRANSCEND and 92% of patients in JULIET,[11] but it was prohibited in ZUMA-1,[10] although most patients treated with axi-cel in real-world settings have needed bridging therapy.[29] Patients needing bridging therapy for disease control during the CAR T-cell manufacturing process generally have a higher tumour burden and more rapidly progressive symptomatic disease than do patients who can be observed without active treatment while CAR T cells are manufactured,[40] which could account for the poorer outcomes seen for these patients. Despite the large percentage of patients in TRANSCEND who needed bridging therapy, outcomes including duration of response, progression-free survival, and overall survival were encouraging and in line with what has been reported in ZUMA-1, in which bridging therapy was not permitted. The unique characteristics of liso-cel, including its defined composition and consistent total and relative dose of $CD4^+$:$CD8^+$ CAR T cells, could have a role in these observed results and might be a possible explanation.

127 (47%) of 269 patients in TRANSCEND developed cytokine release syndrome, neurological events, or both. Importantly, the incidence of grade 3 or worse cytokine release syndrome and neurological events was low (2% and 10%, respectively) and no patients died from these adverse events. Several factors might have contributed to this outcome. The 4-1BB co-stimulatory domain in the liso-cel construct has been associated with lower incidence of cytokine release syndrome and neurological events than have CD28-containing constructs.[41] Liso-cel comprises purified $CD8^+$ and $CD4^+$ T cells that are activated, transduced, and expanded separately in vitro, resulting in clonally diverse and less differentiated T-cell populations in the final CAR^+ T-cell product.[16,18] As a result, there is low variability in the administered total and $CD8^+$ CAR^+ T-cell doses, factors that have been associated with increased toxicity in previous studies.[10,12,42,43] Since most patients did not experience cytokine release syndrome or neurological events, in addition to the low incidence of grade 3 or worse cytokine release syndrome and neurological events, and the late median onset, additional clinical studies are investigating which patients can receive liso-cel and be safely monitored in the outpatient setting.[44]

Study limitations include the open-label single-arm design, since this study is non-comparative, and the relatively short follow-up period for patients who were enrolled later during the study. However, plateauing on the duration of response and progression-free survival curves suggests substantial durability. In view of the broad population included in our study, the number of patients in some subsets of interest (eg, follicular lymphoma grade 3B, diffuse large B-cell lymphoma transformed from indolent lymphomas other than follicular lymphoma, and patients with secondary CNS lymphoma) are small, meaning that to draw definitive conclusions in these subsets is difficult.

In summary, findings of the TRANSCEND trial show that liso-cel can lead to rapid and durable remission, with low incidence of all-grade and severe cytokine release syndrome and neurological events among patients with high-risk aggressive relapsed or refractory large B-cell lymphomas. Clinically meaningful activity was noted across populations with unmet medical need, including uncommon histological subtypes and patients with characteristics of poor prognosis.

Contributors

JSA, MLP, MW, JA, AS, NG, AK, and TS contributed to data acquisition, data analysis, and data interpretation. LIG, MAL, AM, EP, KN, MM, KO, and YK contributed to data analysis and data interpretation. DGM, TMA, DL, and JG contributed to study design, data acquisition, data interpretation, and data analysis. CA and SRS contributed to data acquisition and data interpretation. JSA and TMA wrote the report with contributions and critical revisions from all authors. All authors approved the final version to be published and agree to be accountable for all aspects of the work.

Declaration of interests

JSA is an advisor or consultant for AbbVie, Allogene, Amgen, AstraZeneca, Bayer, BeiGene, Celgene, C4 Therapeutics, EMD Serono, Genentech, Gilead Sciences, Incyte, Janssen, Juno Therapeutics, a Bristol-Myers Squibb Company, Karyopharm, Kite Pharma, Morphosys, Merck, Novartis, Seattle Genetics, and Verastem, outside of the submitted work; and has received speaker honoraria from Celgene, outside of the submitted work. MLP has held consulting or advisory roles for Kite Pharma, Novartis, Merck, and Pharmacyclics, outside of the submitted work; a family member has received honoraria from Amgen, Evelo, Flagship Pioneering, Jazz Pharmaceuticals, Merck, Novartis, Seres Therapeutics, and Therakos; and a family member holds stock in Seres Therapeutics and patents or other intellectual property for Juno Therapeutics, a Bristol-Myers Squibb Company, and Seres Therapeutics. LIG is a consultant or advisor for Bayer, Gilead Sciences, Juno Therapeutics, a Bristol-Myers Squibb Company, and Kite Pharma outside of the submitted work; and has patents or intellectual property with Zylem (no royalties). MAL has received funding as a consultant or advisor from AbbVie, Acotech, ADC Therapeutics, AstraZeneca, Bayer, BeiGene, Bristol-Myers Squibb, Celgene, Gilead Sciences, Janssen, Pharmacyclics, Kite Pharma, Karyopharm, Legend, Novartis, Portola, Seattle Genetics, Spectrum, TG Therapeutics, and Verastem outside of the submitted work; and personal fees from DAVA, OncLive, and Vanium outside of the submitted work. MW reports grants from MD Anderson, during the conduct of the study; stock ownership and participation in advisory boards for MoreHealth, outside of the submitted work; research funding from Beigene, BioInvent, Eli Lilly, Juno Therapeutics, a Bristol-Myers Squibb Company, Kite Pharma, Loxo Oncology, Novartis, Pharmacyclics, VelosBio, and Verastem, outside of the submitted work; is an advisor or consultant for AstraZeneca, Acerta Pharma, Celgene, Guidepoint Global, Janssen, Kite Pharma, Loxo Oncology, Pharmacyclics, and Pulse Biosciences, outside of the submitted work; reports honoraria or travel support from AstraZeneca, Acerta Pharma, Celgene, Janssen, OMI, Pharmacyclics, and Targeted Oncology, outside of the submitted work; and provided expert testimony for AstraZeneca and Acerta Pharma, outside of the submitted work. JA reports grants from Juno Therapeutics, a Bristol-Myers Squibb Company, during the conduct of the study; and is a consultant or advisor for Juno Therapeutics, a Bristol-Myers Squibb Company, and Regeneron. AM reports grants from Juno Therapeutics, a Bristol-Myers Squibb Company, during the conduct of the study; grants from Incyte, Fortyseven, Takeda, Affimed, Merck, Genentech, Astex, Bristol-Myers Squibb, TG Therapeutics, Miragen, Rhizen, and ADC Therapeutics, outside of the submitted work; grants and

personal fees from Celgene, Gilead, Seattle Genetics, Kite Pharma, and Pharmacyclics, outside of the submitted work; and personal fees from AstraZeneca, Incyte, Morphosys, and TG Therapeutics, outside of the submitted work. EP was affiliated with the University of Colorado during the conduct of the study but is currently an employee of Genentech. DGM has received grants to his institution and honoraria from Juno Therapeutics, a Bristol-Myers Squibb Company, and Celgene, during the conduct of the study; grants to his institution from Kite Pharma, outside of the submitted work; has participated in advisory board meetings and honoraria for Amgen, Bioline RX, Genentech, Gilead Sciences, Kite Pharma, MorphoSys, Novartis, and Pharmacyclics, outside of the submitted work; has a patent pending with Juno Therapeutics, a Bristol-Myers Squibb Company; and is a member of the A2 Biotherapeutics Scientific Advisory Board and has stock options. CA reports research funding from Amgen, Celgene, Juno Therapeutics, a Bristol-Myers Squibb Company, Merck, and Novartis, outside of the submitted work; has acted as an advisor to Astellas Pharma, Jazz Pharmaceuticals, Kite Pharma, Gilead, and Seattle Genetics, outside of the submitted work; and reports a family member with employment and stock in Genentech, outside of the submitted work. AS reports funding for clinical trials from Celgene and Juno Therapeutics, a Bristol-Myers Squibb Company, during the conduct of the study; and research funding from Celgene, Juno Therapeutics, a Bristol-Myers Squibb Company, Kite Pharma, Gilead, and Merck, outside of the submitted work. NG received research funding from Celgene, Fortyseven, Genentech, Pharmacyclics, and TG Therapeutics, outside of the submitted work; has participated in speaker bureaus for AbbVie, AstraZeneca, Celgene, Gilead Sciences, Janssen, Pharmacyclics, and Seattle Genetics, outside of the submitted work; and has provided consulting for Bristol-Myers Squibb, Celgene, Genmab, Gilead Sciences, Incyte, Janssen, Karyopharm, Pharmacyclics, Seattle Genetics, and TG Therapeutics, outside of the submitted work. TMA, JG, AK, MM, YK, and DL are employees of Juno Therapeutics, a Bristol-Myers Squibb Company, and hold stock in Bristol-Myers Squibb. KO and KN are employees of and hold stock in Bristol-Myers Squibb. TS is an advisor for AstraZeneca, BeiGene, Celgene, Juno Therapeutics, a Bristol-Myers Squibb Company, and Kite Pharma, outside of the submitted work; and has participated in speaker bureaus for AstraZeneca, Janssen, Pharmacyclics, and Seattle Genetics, outside of the submitted work. SRS declares no competing interests.

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