ORIGINAL ARTICLE

Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma

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ABSTRACT

BACKGROUND

Patient outcomes are poor for aggressive B-cell non-Hodgkin's lymphomas not responding to or progressing within 12 months after first-line therapy. Tisagenlecleucel is an anti-CD19 chimeric antigen receptor T-cell therapy approved for diffuse large B-cell lymphoma after at least two treatment lines.

METHODS

We conducted an international phase 3 trial involving patients with aggressive lymphoma that was refractory to or progressing within 12 months after first-line therapy. Patients were randomly assigned to receive tisagenlecleucel with optional bridging therapy (tisagenlecleucel group) or salvage chemotherapy and autologous hematopoietic stem-cell transplantation (HSCT) (standard-care group). The primary end point was event-free survival, defined as the time from randomization to stable or progressive disease at or after the week 12 assessment or death. Crossover to receive tisagenlecleucel was allowed if a defined event occurred at or after the week 12 assessment. Other end points included response and safety.

RESULTS

A total of 322 patients underwent randomization. At baseline, the percentage of patients with high-grade lymphomas was higher in the tisagenlecleucel group than in the standard-care group (24.1% vs. 16.9%), as was the percentage with an International Prognostic Index score (range, 0 to 5, with higher scores indicating a worse prognosis) of 2 or higher (65.4% vs. 57.5%). A total of 95.7% of the patients in the tisagenlecleucel group received tisagenlecleucel; 32.5% of the patients in the standard-care group received autologous HSCT. The median time from leukapheresis to tisagenlecleucel infusion was 52 days. A total of 25.9% of the patients in the tisagenlecleucel group had lymphoma progression at week 6, as compared with 13.8% of those in the standard-care group. The median event-free survival in both groups was 3.0 months (hazard ratio for event or death in the tisagenlecleucel group, 1.07; 95% confidence interval, 0.82 to 1.40; P=0.61). A response occurred in 46.3% of the patients in the tisagenlecleucel group and in 42.5% in the standard-care group. Ten patients in the tisagenlecleucel group and 13 in the standard-care group died from adverse events.

CONCLUSIONS

Tisagenlecleucel was not superior to standard salvage therapy in this trial. Additional studies are needed to assess which patients may obtain the most benefit from each approach. (Funded by Novartis; BELINDA ClinicalTrials.gov number, NCT03570892.)

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This article was published on December 14, 2021, at NEJM.org.

N Engl J Med 2022;386:629-39.
DOI: 10.1056/NEJMoa2116596

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Aggressive non-Hodgkin's lymphomas are common cancers with an estimated annual incidence of 250,000 new cases worldwide.[1] The prognosis is poor for patients with aggressive lymphoma whose disease is refractory to or relapses within 12 months after first-line treatment.[2] Standard-care second-line treatment for suitable patients with relapsed or refractory aggressive lymphoma includes platinum-based immunochemotherapy followed by high-dose chemotherapy and autologous hematopoietic stem-cell transplantation (HSCT) in patients having a response. However, more than half of patients will not receive autologous HSCT owing to the failure of therapy to sufficiently reduce tumor burden.[3-5]

Tisagenlecleucel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved as a third-line therapy for relapsed or refractory aggressive diffuse large B-cell lymphoma.[6-8] In the JULIET trial, a response occurred in 52% of the patients with diffuse large B-cell lymphoma who received tisagenlecleucel, and the 24-month progression-free survival was 33%.[8] BELINDA is an international, randomized, phase 3 trial comparing the efficacy and safety of tisagenlecleucel with those of current standard-care second-line treatment strategies that include salvage chemoimmunotherapy followed by high-dose therapy and autologous HSCT in patients with refractory or early relapsed aggressive lymphoma.

Methods

Trial Design and Patients

We enrolled patients at 65 centers in 18 countries from May 31, 2019, to January 8, 2021. Enrollment was paused from March 31, 2020, to May 11, 2020, owing to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Eligible patients were 18 years of age or older with histologically confirmed aggressive B-cell lymphoma that was refractory (lack of complete response) or relapsed after the receipt of a first-line anti-CD20 antibody and anthracycline-containing regimen within 12 months after the last dose. Patients had to be eligible for autologous HSCT according to the investigator's assessment and have an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher numbers indicating greater disability) and adequate organ function. After providing written informed consent, all screened patients underwent lymphocyte collection by means of leukapheresis for potential tisagenlecleucel manufacture, because the trial allowed for crossover from standard-care therapy to adoptive cellular therapy and starting material for CAR T-cell generation was needed for all the patients.

After leukapheresis, patients underwent randomization in a 1:1 ratio, with stratification according to remission duration (disease that was refractory to first-line therapy and relapse <6 months after the last dose of first-line therapy vs. relapse 6 to 12 months after the last dose of first-line therapy), geographic region (North America [all from the United States] vs. rest of the world [non–United States]), and International Prognostic Index (IPI) score (<2 vs. ≥2; scores range from 0 to 5, with higher scores indicating a worse prognosis) at trial entry (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The tisagenlecleucel treatment strategy consisted of optional bridging therapy (investigator's choice of four prespecified platinum-containing combination chemotherapy regimens), lymphodepletion chemotherapy (fludarabine at a dose of 25 mg per square meter of body-surface area per day and cyclophosphamide at a dose of 250 mg per square meter per day for 3 days or, if contraindicated, bendamustine at a dose of 90 mg per square meter per day for 2 days), and a single intravenous infusion of 0.6 to 6.0×10^8 CAR-positive viable T cells. The standard-care treatment strategy consisted of the investigator's choice of four prespecified chemotherapy regimens (same as bridging therapy) followed, in patients having a response, by high-dose chemotherapy and autologous HSCT.

Responses were determined by an independent review committee whose members were unaware of the trial-group assignments. Patients in the standard-care group with an inadequate response to chemotherapy on positron-emission tomography–computed tomography (PET-CT) at week 6 could receive a second chemotherapy regimen, with the aim of having the lowest possible tumor burden before autologous HSCT. Palliative ibrutinib or lenalidomide was used if patients were no longer eligible for autologous HSCT. The rationale for allowing a second chemotherapy regimen in order to achieve a response adequate

for autologous HSCT is supported by published data showing that nearly 30% of the patients who could not proceed to autologous HSCT in the Collaborative Trial in Relapsed Aggressive Lymphoma could still benefit from a second chemotherapy regimen and receive consolidation HSCT, with a significant improvement in long-term survival.[3] Crossover from the standard-care group to receive tisagenlecleucel was allowed after confirmation of stable or progressive disease at or after the week 12 assessment.

ASSESSMENTS AND END POINTS

After randomization, disease assessments were performed at week 6, week 12, and every 3 months thereafter for the first year, every 6 months for the second year, and annually thereafter for up to 5 years. The primary end point was event-free survival, defined as the time from randomization to stable or progressive disease at or after the week 12 assessment by the independent review committee according to the Lugano criteria[9] or death at any time. The rationale for event-free survival to involve efficacy evaluations starting at week 12 was to allow time for the full treatment effect in each group. In the tisagenlecleucel group, the week 6 PET-CT was used to evaluate disease burden before tisagenlecleucel infusion. In the standard-care group, the week 6 PET-CT was used to evaluate response to chemotherapy for eligibility for either autologous HSCT or a second chemotherapy regimen. Therefore, response assessments before week 12 did not represent a failure of the treatment strategy in either group and were not considered for the primary end point. With allowance for a time window around specified assessment dates, any assessment as early as 71 days after randomization was considered to be a week 12 assessment. The secondary end point of overall survival was to be formally tested between the treatment groups only if the results for the primary end point were significant. Other secondary end points included the percentage of patients with a response (based on the best response at or after week 12), safety, and cellular kinetics.

TRIAL OVERSIGHT

The trial was approved by the institutional review board at each participating institution. Data were analyzed and interpreted by the sponsor (Novartis) and the authors. Editorial and writing assistance with earlier versions of the manuscript was provided by a medical writer paid by the sponsor. All the authors reviewed the manuscript. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol, available at NEJM.org.

STATISTICAL ANALYSIS

Efficacy and safety comparisons between treatment groups were based on all the patients who underwent randomization. The primary end point, event-free survival, was compared between treatment groups by means of a stratified log-rank test at a one-sided 2.5% level of significance to reject the null hypothesis of no difference in event-based survival in favor of superior efficacy of the tisagenlecleucel treatment strategy (according to *Journal* guidelines, the one-sided P value was converted to a two-sided P value for this article). Because tisagenlecleucel infusion was anticipated to have occurred by week 6 and owing to similarities of bridging and salvage regimens, no difference between treatment groups was assumed for the first 6 weeks (i.e., hazard ratio for event or death of 1). A hazard ratio of 0.61 in the tisagenlecleucel group was assumed after 6 weeks. Given those assumptions, a total of 200 events were required for the trial to have 92% power to detect a significantly superior effect of the tisagenlecleucel treatment strategy over the standard-care treatment strategy.

Unadjusted Cox regression, stratified according to randomization stratification factors, was used in the primary analysis to estimate the hazard ratio and 95% confidence interval for event or death between treatment groups. As a supportive analysis to assess treatment effect with adjustment for potential imbalances in patient characteristics, an adjusted Cox regression was performed with prespecified covariates of age, sex, race, ECOG performance-status score, histologic subgroup, disease stage, and disease subtype. The only statistical test performed was for the primary end point, event-free survival. All secondary and exploratory analyses are presented without adjustment for multiplicity; as such, no inference regarding statistical significance can be drawn from the confidence intervals presented.

The prespecified definitions of event-free survival and overall response rate assumed that the week 12 assessment would measure the effect of tisagenlecleucel and standard-care treatment strat-

egies and, therefore, considered all disease assessments from day 71 onward until stable disease, progressive disease, or the start of new therapy. However, some patients in both groups had delayed infusion or a delayed response. A systematic post hoc exploratory analysis approach was used to understand trial results in the tisagenlecleucel group for patients who received tisagenlecleucel. To account for infusion delays, only assessments after tisagenlecleucel were considered in post hoc analyses of modified event-free survival and modified best overall response. Furthermore, to account for possible delayed responses, stable or progressive disease was not considered to be an event if there was a later response of complete or partial response without further anticancer therapies. Further details of the post hoc exploratory methods are provided in the Supplementary Appendix.

RESULTS

PATIENTS

As of May 6, 2021, a total of 322 patients had undergone randomization, 162 to the tisagenlecleucel group and 160 to the standard-care group (Figs. 1 and S2). Patient characteristics at baseline are described in Table 1 and are representative of the worldwide population of patients with aggressive lymphoma (Table S1); as expected, the majority of patients (68.9%) were younger than 65 years of age owing to the transplantation eligibility requirement of the protocol. There were some between-group differences in patient characteristics (high-grade B-cell lymphoma [24.1% in the tisagenlecleucel group vs. 16.9% in the standard-care group] and an IPI score of ≥2 [65.4% vs. 57.5%]); 29.5% of the patients were enrolled in the United States. The difference in IPI score between the two groups was due to incorrect entry of patient prognostic factors into the interactive response technology system at the time of randomization, which caused randomization of a small number of patients to the wrong stratum. This error was noted and subsequently corrected; the IPI scores shown in Table 1 are accurate as confirmed by the investigator. In both groups, the median time from progression after first-line therapy to randomization was less than 1.5 months; 66.5% of the patients had disease that was refractory to first-line therapy, and 19.3% had had a relapse less than 6 months after first-line therapy.

In the tisagenlecleucel group, 27 patients (16.7%; includes 1 patient who had a protocol deviation and discontinued the trial) did not receive bridging therapy, 58 (35.8%) received one cycle, and 77 (47.5%) received at least two cycles or regimens (Figs. 1 and S3 and Table S2). Patients who did not receive bridging therapy were generally older (≥65 years of age; 44%), had refractory disease (70%), had an IPI score of less than 2 (56%), and had histologic subtypes other than high-grade B-cell lymphoma (93%) (Table S3). The number of bridging-therapy cycles was higher in non-U.S. patients than in U.S. patients (no bridging therapy, 9% vs. 35%; one cycle, 32% vs. 44%; and at least two cycles or regimens, 59% vs. 21%).

The in-specification manufacturing success rate was 97% for both the patients in the tisagenlecleucel group and the patients who crossed over. The median time from leukapheresis to tisagenlecleucel infusion in the tisagenlecleucel group was 52 days (range, 31 to 135) in the overall population, 41 days (range, 31 to 91) in U.S. patients, and 57 days (range, 38 to 135) in non-U.S. patients; the values were 44 days (range, 34 to 76) in patients who received no bridging therapy, 47 days (range, 31 to 79) in those who received one cycle, and 58 days (range, 37 to 135) in those who received at least two cycles or regimens (Fig. S4 and Table S4). The median time from randomization to receipt of leukapheresis at the manufacturing facility was 6 days (range, 2 to 12) in the United States and 10 days (range, 3 to 27) in non-U.S. countries. The median time from leukapheresis receipt at the manufacturing facility to tisagenlecleucel shipment was 23.5 days (range, 22 to 34) in the United States and 28 days (range, 22 to 115) in non-U.S. countries. The median time from shipment to infusion was 11 days (range, 4 to 63) in the United States and 15 days (range, 2 to 91) in non-U.S. countries.

Among 162 patients assigned to the tisagenlecleucel group, 155 (95.7%) received tisagenlecleucel at a median dose of 2.9×10^8 cells (range, 0.4 to 5.9). A total of 155 patients (96.9%) in the standard-care group received at least two chemotherapy cycles, including 86 (53.8%) who received at least two regimens (Figs. 1 and S3 and Table S2). A total of 52 patients (32.5%) in the standard-care group received autologous HSCT; 16 of these patients (31%) received two different

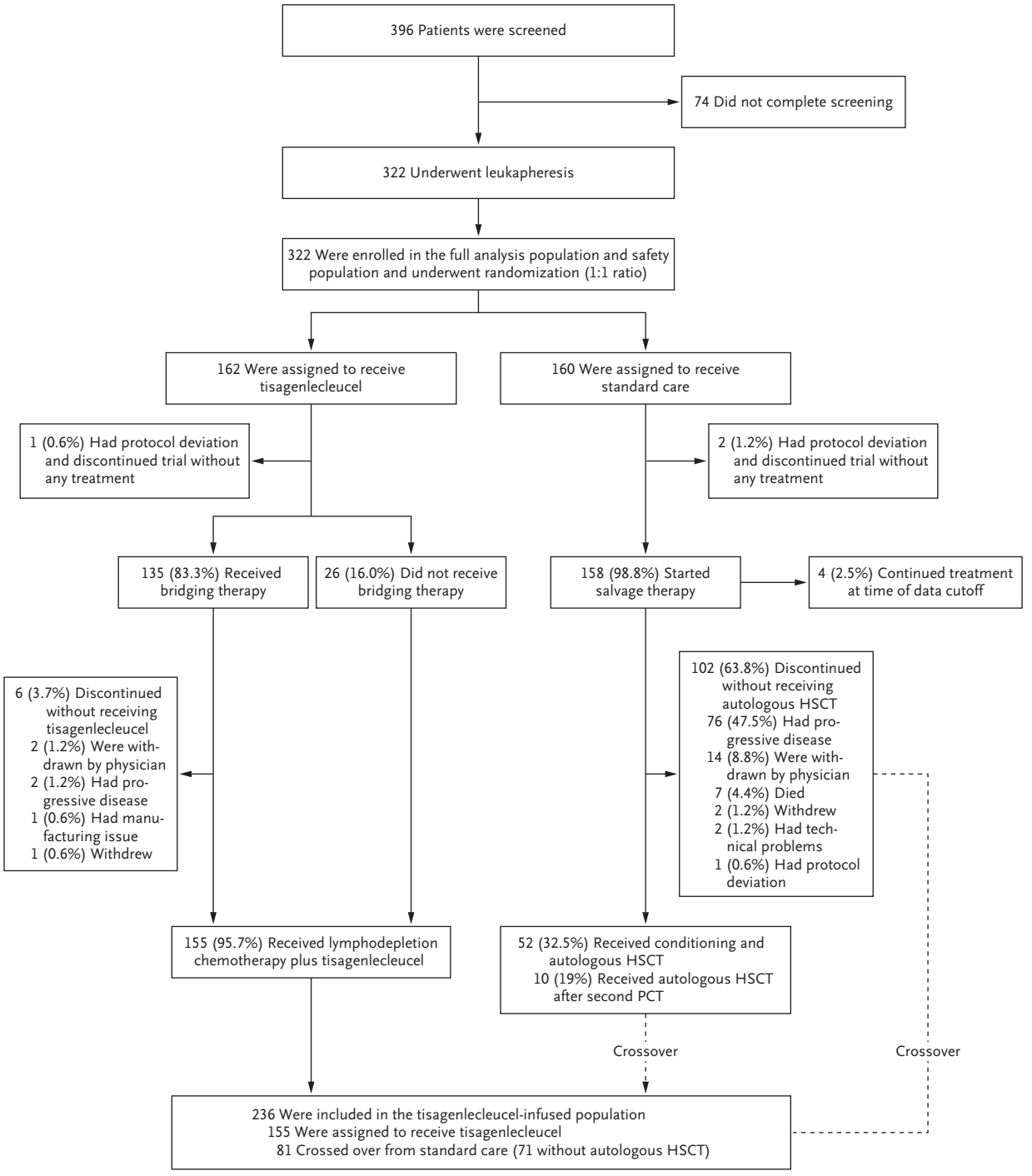


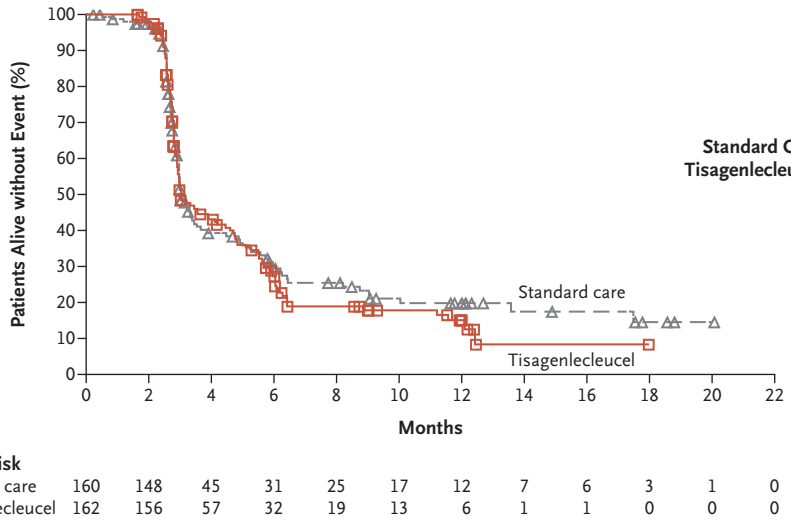
Figure 1. Randomization and Treatment.

The full analysis population and the safety population were used to compare efficacy and safety between the two treatment strategies. The tisagenlecleucel-infused population was used to assess the efficacy and safety of tisagenlecleucel as second-line therapy (tisagenlecleucel group) and third-line therapy (crossover). More details on randomization and treatment are provided in Figure S2 in the Supplementary Appendix. HSCT denotes hematopoietic stem-cell transplantation, and PCT platinum-based immunochemotherapy.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Tisagenlecleucel Group (N=162)	Standard-Care Group (N=160)
Median age (range) — yr	59.5 (19–79)	58 (19–77)
Age ≥65 yr — no. (%)	54 (33.3)	46 (28.8)
Male sex — no. (%)	103 (63.6)	98 (61.2)
Race — no. (%)†		
White	128 (79.0)	128 (80.0)
Asian	20 (12.3)	22 (13.8)
Black	8 (4.9)	3 (1.9)
Other or unknown	6 (3.7)	7 (4.4)
Hispanic or Latino ethnic group — no. (%)†	12 (7.4)	13 (8.1)
Geographic region — no. (%)		
United States‡	48 (29.6)	47 (29.4)
Non–United States	114 (70.4)	113 (70.6)
ECOG performance-status score of 1 — no. (%)§	70 (43.2)	65 (40.6)
IPI score ≥2 — no. (%)¶	106 (65.4)	92 (57.5)
Disease subtype — no. (%)		
Diffuse large B-cell lymphoma, not otherwise specified	101 (62.3)	112 (70.0)
Germinal center B-cell–like	46 (28.4)	63 (39.4)
Activated B-cell–like	52 (32.1)	42 (26.2)
Unclassified or missing	3 (1.9)	7 (4.4)
High-grade B-cell lymphoma with *MYC* rearrangement plus rearrangement of *BCL2*, *BCL6*, or both	32 (19.8)	19 (11.9)
Primary mediastinal B-cell lymphoma	12 (7.4)	13 (8.1)
High-grade B-cell lymphoma, not otherwise specified	7 (4.3)	8 (5.0)
Follicular lymphoma grade 3B	5 (3.1)	1 (0.6)
Other	5 (3.1)	7 (4.4)
Transformation from previous lymphoma — no. (%)	27 (16.7)	22 (13.8)
Remission duration — no. (%)‖		
Disease that was refractory to first-line therapy	107 (66.0)	107 (66.9)
Relapse <6 mo after last dose of first-line therapy	30 (18.5)	32 (20.0)
Relapse 6–12 mo after last dose of first-line therapy	25 (15.4)	21 (13.1)
Median time since initial diagnosis (IQR) — mo	8.4 (6.8–11.1)	8.2 (5.9–11.4)
Median time since most recent relapse or progressive disease (IQR) — mo	1.4 (0.9–2.2)	1.1 (0.8–1.8)
One previous line of therapy for current lymphoma — no. (%)**	160 (98.8)	158 (98.8)
Disease stage at time of trial entry — no. (%)		
I or IE	19 (11.7)	22 (13.8)
II, IIE, or II bulky	36 (22.2)	40 (25.0)
III	29 (17.9)	24 (15.0)
IV	78 (48.1)	74 (46.2)

* Percentages may not total 100 because of rounding. IQR denotes interquartile range.
† Race and ethnic group were reported by the patient.
‡ North America was a stratification factor, and all enrolled patients in this group were from the United States.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ International Prognostic Index (IPI) scores range from 0 to 5, with higher scores indicting a worse prognosis. The difference in scores between the two groups, despite the IPI score being a stratification factor, was due to incorrect entry of patient prognostic factors into the interactive response technology system at the time of randomization, which was noted and subsequently corrected. Therefore, the IPI scores shown in the table are accurate as confirmed by the investigator.
‖ Refractory disease was defined as a lack of complete response to first-line therapy for current lymphoma. Relapse after the last dose of first-line therapy was defined as a complete response to first-line therapy with subsequent relapse.
** Four patients had not received previous treatment for current lymphoma. Three patients received first-line treatment for a previous aggressive non-Hodgkin's lymphoma that then transformed into the current lymphoma. One patient did not meet inclusion criteria and discontinued the trial after randomization.



	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

Figure 2. Kaplan–Meier Plot of Event-free Survival.

An event was defined as progressive disease or stable disease on or after day 71 or death at any time (i.e., event-free survival at a given time point represents the estimated percentage of patients who had a complete or partial response at this time point among all randomly assigned patients). Responses were determined by an independent review committee whose members were unaware of the trial-group assignments. The triangles (standard-care group) and squares (tisagenlecleucel group) indicate censoring times.

chemotherapy regimens before HSCT. The median time from randomization to autologous HSCT was 3.0 months (range, 2.0 to 5.2). A total of 25 patients (15.6%) became ineligible for autologous HSCT during the treatment period for reasons other than inadequate response, mainly a decline in performance status or unacceptable side effects from chemotherapy (8.8%) or the failure of stem-cell collection (1.9%). Eleven patients (6.9%) received ibrutinib- or lenalidomide-based therapies as palliative therapy. By data cutoff, 81 patients (50.6%) in the standard-care group had crossed over and received tisagenlecleucel; 10 crossed over after autologous HSCT. The median time from randomization to crossover infusion was 4.3 months (range, 2.5 to 10.8).

EFFICACY

Event-free survival did not differ significantly between the treatment groups (stratified unadjusted hazard ratio for event or death [tisagenlecleucel vs. standard care], 1.07; 95% confidence interval [CI], 0.82 to 1.40; two-sided P=0.61 by stratified log-rank test). The median event-free survival in both groups was 3.0 months (Fig. 2). The stratified adjusted hazard ratio for event or death was 0.95 (95% CI, 0.72 to 1.25) (Table S5). The median time from randomization to data cutoff was 10.0 months (range, 2.9 to 23.2). Data on overall survival were immature at data cutoff (Fig. S5); the stratified unadjusted hazard ratio for death was 1.24 (95% CI, 0.83 to 1.85), and the stratified adjusted hazard ratio was 0.99 (95% CI, 0.64 to 1.52). In both groups, event-free and overall survival were shorter among patients with high-grade B-cell lymphoma than among those with primary mediastinal B-cell lymphoma or diffuse large B-cell lymphoma (Fig. S6). No substantial difference in the hazard ratio for event or death between the two groups was observed for any disease histologic type, but the trial was not powered for subgroup analyses (Fig. S7). Comparison of event-free survival between treatment groups on the basis of the randomization stratification factor of geographic region showed similar median event-free survival with regard to regions and treatment strategies (non-U.S. countries, 3.3 months in the tisagenlecleucel group and 3.0 months in the standard-care group; United States, 2.9 months and 3.1 months, respectively), yielding an adjusted hazard ratio for event or death of 0.82 (95% CI, 0.59 to 1.15) in non-U.S. countries and an adjusted hazard ratio of 1.19 (95% CI, 0.64 to 2.19) in the United States.

Table 2. Overall Response at Week 6 Assessment and Best Overall Response.*

Response	Week 6 Assessment†		Best Overall Response at or after Week 12 Assessment‡	
	Tisagenlecleucel Group (N=162)	Standard-Care Group (N=160)	Tisagenlecleucel Group (N=162)	Standard-Care Group (N=160)
Best overall response — no. (%)				
Complete response	18 (11.1)	31 (19.4)	46 (28.4)	44 (27.5)
Partial response	44 (27.2)	55 (34.4)	29 (17.9)	24 (15.0)
Stable disease	48 (29.6)	46 (28.8)	19 (11.7)	22 (13.8)
Progressive disease	42 (25.9)	22 (13.8)	50 (30.9)	46 (28.8)
Unknown§	10 (6.2)	6 (3.8)	18 (11.1)	24 (15.0)
Complete or partial response				
No. of patients	62	86	75	68
Percent (95% CI)¶	38.3 (30.8–46.2)	53.8 (45.7–61.7)	46.3 (38.4–54.3)	42.5 (34.7–50.6)

* Responses were determined by an independent review committee whose members were unaware of the trial-group assignments. Percentages may not total 100 because of rounding.
† The week 6 assessment was considered to be the earliest assessment on or after day 29 and on or before the earliest of day 70 or the date of new anticancer therapy and, according to the protocol, reflected the last disease assessment before infusion in the tisagenlecleucel group and disease status after the first regimen to assess eligibility for transplantation in the standard-care group.
‡ Best overall response reflects efficacy assessments on or after day 71 and until stable disease or progressive disease or the start of new therapy.
§ Patients with unknown response were either assessed as having unknown response or had no available disease assessments owing to death, discontinuation of the trial, or the start of new anticancer therapy.
¶ The 95% confidence intervals for overall response (complete or partial response) are exact Clopper–Pearson confidence intervals. The confidence intervals were not adjusted for multiplicity, and no inference can be made on the statistical significance of the results.

At week 6, a response occurred in 38.3% of the patients in the tisagenlecleucel group and in 53.8% of those in the standard-care group, and progressive disease was noted in 25.9% and 13.8%, respectively. In the tisagenlecleucel group, a response occurred before CAR T-cell infusion in 26.1% of U.S. patients and in 43.1% of non-U.S patients. A response occurred at or after the week 12 assessment in 46.3% of the patients in the tisagenlecleucel group and in 42.5% of those in the standard-care group (Table 2).

In the tisagenlecleucel group, 6 patients had a response to the infusion but were recorded as having an event owing to stable or progressive disease before or soon after infusion. Exploratory post hoc model-based analyses in the tisagenlecleucel group showed a hazard ratio of 2.30 (95% CI, 1.44 to 3.66) for the modified event-free survival among patients with stable or progressive disease before infusion as compared with those with a complete or partial response before infusion (Table S6). A potential dose–response relationship in patients with stable or progressive disease before infusion was observed in the model-based exploratory analyses (Tables S6 and S7 and Fig. S8).

SAFETY

Nearly all the patients (98.8% in each group) had an adverse event during the safety comparison period (Table S8). A total of 136 patients (84.0%) in the tisagenlecleucel group and 144 (90.0%) in the standard-care group had an adverse event of grade 3 or higher; 121 (74.7%) and 137 (85.6%), respectively, had grade 3 or higher events that were considered by the investigators to be treatment-related. In the tisagenlecleucel group, 95 of the 155 patients (61.3%) who received an infusion had cytokine release syndrome; 8 patients (5.2%) had cytokine release syndrome of grade 3 or higher (Table S9). The median time from the infusion to the onset of cytokine release syndrome was 4 days (range, 1 to 27); the median time to resolution was 5 days (95% CI, 4 to 5). A total of 16 patients (10.3%) in the tisagenlecleucel group had neurologic events after infusion; 3 patients (1.9%) had a neurologic event of grade 3 or higher. The median time from the

infusion to the onset of a neurologic event was 5 days (range, 3 to 93); the median time to resolution was 9 days (95% CI, 3 to 14). Except for cytokine release syndrome in the tisagenlecleucel group, the most common adverse events in both groups were anemia, neutropenia, thrombocytopenia, and nausea (Table S10). A total of 52 patients (32.1%) in the tisagenlecleucel group and 45 (28.1%) in the standard-care group died during the trial, including 42 (25.9%) and 32 (20.0%), respectively, who died due to disease progression. Ten patients in the tisagenlecleucel group and 13 in the standard-care group died from adverse events, including 2 patients in each group who died of SARS-CoV-2–related complications (Table S11).

CELLULAR KINETICS OF TISAGENLECLEUCEL EXPANSION AND PERSISTENCE

The geometric mean in vivo peak expansion was twice as high in patients who had a response as in those who did not have a response, with a similar median time to maximal expansion (Fig. S9). Four months after randomization, tisagenlecleucel transgene was detected in 53 of the 54 samples (98%) that could be evaluated. Longer event-free survival was observed among patients with higher-than-median peak expansion (Fig. S10). Of the 38 patients who had a relapse after having had a response to tisagenlecleucel infusion, 18 had quantifiable CAR transgene levels in peripheral blood (levels above the limit of quantification of 50 copies per microgram) at or close to the time of relapse, whereas in 16 patients, the CAR transgene levels either were not detected or were below the limit of quantification at or close to the time of relapse (cellular kinetic data were not sufficient in the remaining 4 patients).

DISCUSSION

Management of aggressive lymphoma that does not respond to or that progresses shortly after first-line therapy remains a substantial clinical challenge. Our trial was designed with the expectation that the tisagenlecleucel treatment strategy would provide a superior outcome as compared with current standard-care treatment in the context of second-line therapy, particularly in patients whose disease was refractory to chemotherapy. However, we observed no difference in event-free survival between the two treatment strategies.

At the time of the trial design, the patients' disease status at the time of infusion was not expected to influence postinfusion outcomes for CAR T-cell therapies, although growing evidence suggests the importance of disease burden before infusion on long-term outcomes.[10] A higher percentage of patients was observed with progressive disease at week 6 (preinfusion) in the tisagenlecleucel group than in the standard-care group (25.9% vs. 13.8%), which was attributed to a lower number of chemotherapy cycles than in the standard-care group. Our exploratory post hoc model-based analyses also indicated the relevance of disease status before infusion of tisagenlecleucel.

Bridging therapy is frequently used to stabilize rapidly proliferative disease and was allowed in this trial owing to the enrollment of patients with high-risk aggressive lymphoma and the expected time to infusion.[11-14] Although the reasons for use of bridging therapy were not collected, an IPI score of 2 or higher and a diagnosis of high-grade B-cell lymphoma were more frequent in patients who received bridging therapy. In addition, the difference in the number of cycles between U.S. sites and non-U.S. sites may be due to differences in the expected time to product availability (shorter in U.S. sites) and possible regional preferences, with a tendency among non-U.S. investigators to administer more chemotherapy before CAR T-cell infusion. More non-U.S. patients than U.S. patients received at least two cycles or regimens of bridging therapy (59% vs. 21%), and less progressive disease before tisagenlecleucel infusion was observed in non-U.S. patients than in U.S. patients despite a longer time to infusion.

A longer time to infusion and delayed response confounded the original definition of event-free survival in both groups, because some events at the week 12 assessment were observed before the onset of treatment response. Some patients had a response at later time points in the absence of new anticancer therapies. The reasons for a longer time to infusion included logistic challenges affecting the time before receipt of leukapheresis material at the manufacturing facility and after tisagenlecleucel shipment, patients not meeting preinfusion criteria at the time of product availability, the need to delay infusion for washout after bridging-therapy cycles, and the SARS-CoV-2 pandemic. In particular, for patients

who did not have a response to bridging chemotherapy, a substantially shorter time to infusion may be required in order to benefit from CAR T-cell therapy; however, identification of these patients a priori is currently difficult.

Additional trial design considerations included the option for patients in the standard-care group to receive a second chemotherapy regimen, an intervention that improved efficacy. In the standard-care group, 86 patients (53.8%) received at least two regimens of salvage chemotherapy, of which only 16 (19%) were able to proceed to autologous HSCT, a finding that is indicative of the aggressive disease characteristics in this population. However, these 16 patients contributed to improved outcomes in the standard-care group, in which approximately 1 of 3 recipients of autologous HSCT had received at least two chemotherapy regimens.

Furthermore, although responses to tisagenlecleucel were observed across the whole dose range, exploratory modeling suggests that in this population with aggressive lymphoma, patients with stable or progressive disease before infusion had an increasing probability of response with increasing dose. In patients with stable or progressive disease before infusion, for whom a lower CAR T-cell dose was manufactured because of technical and patient-related challenges, an attempt to reduce tumor burden before infusion may be beneficial. The tisagenlecleucel dose–exposure relationship is influenced by factors such as T-cell function at the time of leukapheresis, tisagenlecleucel product phenotype, disease burden, and previous therapies.[15,16] Hence, these findings suggest the need for further research on the underlying effect of disease burden, cell dose, T-cell function in patients with lymphoma, and expansion on disease response. Our data suggest the importance of disease control with more effective bridging therapy before CAR T-cell infusion and a shorter time to infusion may be needed for this population of patients with disease refractory to chemotherapy.

Supported by Novartis.

Disclosure forms are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the members of the data monitoring committee associated with the conduct of this trial, and Miranda Bader-Goodman of the Healthcare Consultancy Group for editorial and writing assistance with earlier versions of the manuscript.

APPENDIX

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REFERENCES

1. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med 2021;384:842-58.
2. Costa LJ, Maddocks K, Epperla N, et al. Diffuse large B-cell lymphoma with primary treatment failure: ultra-high risk features and benchmarking for experimental therapies. Am J Hematol 2017;92:161-70.
3. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the international CORAL study. Bone Marrow Transplant 2016;51:51-7.
4. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD Study. J Clin Oncol 2017;35:544-51.
5. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol 2014;32:3490-6.
6. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. N Engl J Med 2018;378:439-48.
7. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56.
8. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2021;22:1403-15.
9. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.
10. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv 2020;4:4898-911.
11. Pinnix CC, Gunther JR, Dabaja BS, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. Blood Adv 2020;4:2871-83.
12. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. J Clin Oncol 2020;38:3095-106.
13. Yang JC, Plastaras JP. Navigating the narrow bridge to CAR T-cell therapy. Blood Adv 2020;4:2884-5.
14. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. J Clin Oncol 2020;38:3119-28.
15. Dasyam N, George P, Weinkove R. Chimeric antigen receptor T-cell therapies: optimising the dose. Br J Clin Pharmacol 2020;86:1678-89.
16. Frey NV, Gill S, Hexner EO, et al. Long-term outcomes from a randomized dose optimization study of chimeric antigen receptor modified T cells in relapsed chronic lymphocytic leukemia. J Clin Oncol 2020;38:2862-71.