Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial

Tisagenlecleucel in Adult Relapsed or Refractory Follicular Lymphoma: The Phase 2 ELARA Trial

Authors: Nathan Hale Fowler[1,2,*], Michael Dickinson[3], Martin Dreyling[4], Joaquin Martinez-Lopez[5], Arne Kolstad[6], Jason Butler[7], Monalisa Ghosh[8], Leslie Popplewell[9], Julio C. Chavez[10], Emmanuel Bachy[11], Koji Kato[12], Hideo Harigae[13], Marie José Kersten[14], Charalambos Andreadis[15], Peter A. Riedell[16], P. Joy Ho[17], José Antonio Pérez-Simón[18], Andy I. Chen[19], Loretta J. Nastoupil[1], Bastian von Tresckow[20,21], Andrés José María Ferreri[22], Takanori Teshima[23], Piers E.M. Patten[24,25], Joseph P. McGuirk[26], Andreas L. Petzer[27], Fritz Offner[28], Andreas Viardot[29], Pier Luigi Zinzani[30,31], Ram Malladi[32], Aiesha Zia[33], Rakesh Awasthi[34], Aisha Masood[35], Oezlem Anak[33], Stephen J. Schuster[36,#], Catherine Thieblemont[37,#]

Affiliations: [1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]BostonGene, Waltham, MA, USA; [3]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia; [4]Medizinische Klinik III, LMU Klinikum, Munich, Germany; [5]Hospital 12 De Octubre, Complutense University, CNIO, Madrid, Spain; [6]Oslo University Hospital, Oslo, Norway; [7]Royal Brisbane Hospital, Herston, Australia; [8]Michigan Medicine University of Michigan, Ann Arbor, MI, USA; [9]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [10]Moffitt Cancer Center, Tampa, FL, USA; [11]Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon, France; [12]Kyushu University Hospital, Fukuoka, Japan; [13]Tohoku University Hospital, Sendai, Japan; [14]Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands; [15]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [16]University of Chicago Medical Center, Chicago, IL, USA; [17]Royal Prince Alfred Hospital and University of Sydney, Camperdown, Australia; [18]Department of Hematology, University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS / CSIC / CIBERONC), Universidad de Sevilla, Sevilla, Spain;

[19]Oregon Health and Science University, Portland, OR, USA; [20]Department I of Internal Medicine, Medical Faculty and University Hospital Cologne, University of Cologne, Cologne, Germany; [21]Department of Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [22]Lymphoma Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; [23]Hokkaido University Hospital, Sapporo, Japan; [24]Comprehensive Cancer Centre, King's College London, UK; [25]Department of Haematology, King's College Hospital, UK; [26]University of Kansas Hospital and Medical Center, Westwood, KS, USA; [27]Internal Medicine I, Ordensklinikum Linz Barmherzige Schwestern-Elisabethinen, Linz, Austria; [28]UZ Gent, Gent, Belgium; [29] Department of Internal Medicine III, University Hospital of Ulm, Ulm, Germany; [30]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istituto di Ematologia "Seràgnoli"; [31]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy, [32]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [33]Novartis Pharma AG, Basel, Switzerland; [34] Novartis Institutes for BioMedical Research, East Hanover, NJ, USA; [35]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [36]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [37]Hôpital Saint-Louis, Paris, France

[#]Dr Schuster and Dr Thieblemont are co-senior authors.

*Correspondence and requests for materials should be addressed to Nathan Hale Fowler, MD; nfowler@mdanderson.org.

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Abstract

Tisagenlecleucel is an autologous anti-CD19 CAR-T cell therapy with clinically meaningful outcomes demonstrated in patients with relapsed/refractory (r/r) B-cell lymphomas. In a prior pilot study of tisagenlecleucel in r/r follicular lymphoma (FL), 71% of patients achieved a complete response (CR). Here we report the primary, prespecified interim analysis of the ELARA phase 2 multinational trial of tisagenlecleucel in adults with r/r FL after ≥2 treatment lines or who relapsed after autologous stem cell transplant (NCT03568461). The primary endpoint was CR rate (CRR). Secondary endpoints included overall response rate (ORR), DOR, progression-free survival, overall survival, pharmacokinetics, and safety. As of March 29, 2021, 97/98 enrolled patients received tisagenlecleucel (median follow-up, 16.59 months; IQR, 13.8–20.21). The primary endpoint was met. In the efficacy set (n=94), CRR was 69.1% (95% CI 58.8–78.3) and ORR 86.2% (95% CI 77.5–92.4). Within 8 weeks of infusion, rates of CRS were 48.5% (grade ≥3, 0%), neurological events were 37.1% (grade ≥3, 3%), and immune effector cell-associated neurotoxicity syndrome were 4.1% (grade ≥3, 1%) in the safety set (n=97) with no treatment-related deaths. Tisagenlecleucel is safe and effective in extensively pretreated r/r FL, including high-risk patients.

Introduction

Follicular lymphoma (FL) is a common non-Hodgkin lymphoma (NHL) that is generally considered indolent, but the disease remains incurable and the majority of patients eventually relapse.[1] Although the median overall survival (OS) has improved with chemo-immunotherapy,[2] approximately 20% of patients with FL experience progression of disease (POD) within 2 years (POD24) of initial chemo-immunotherapy,[3,4] and this subset of patients has a particularly poor prognosis. Patients with relapsed or refractory (r/r) FL will experience progressively shorter duration of response (DOR) to subsequent treatments (second or later lines of therapy)[5] as reflected by progression-free survival (PFS), which has been shown to decrease from 6.6 years after the first-line of therapy to 1.5 years and 10 months after the second- and third-line of therapy, respectively.[6] In the National LymphoCare Study, the 5-year OS rate was 50% for patients with POD24 compared with ≥90% for those with POD 2 years or more after first-line therapy with R-CHOP.[7] Hence, despite improvements in OS following anti-CD20 antibody-containing therapies, lymphoma remains the leading cause of mortality for patients with FL, highlighting an unmet need for patients with r/r disease.[8]

Over the past decade, phosphatidylinositol 3-kinase (PI3K) inhibitors, including idelalisib, copanlisib, duvelisib, and umbralisib, have been approved to treat patients with r/r FL who have relapsed after 2 or more systemic therapies based on single-arm, open-label, phase 2 studies.[9-12] However, PI3K inhibitors have demonstrated modest efficacy in the second-line or later setting, with complete response (CR) rates ranging from 0–14% and overall response rates (ORR) ranging from 41–59%.[9-13] Median DOR of up to 12.5 months and median PFS of 11 months with idelalisib have been reported. Furthermore, treatment interruptions and discontinuations due to toxicities have been common in responding patients.[9,10,13] The immunomodulatory agent lenalidomide in combination with rituximab was approved in 2019 for the treatment of patients with FL treated with more than one line of therapy (based on the phase

3 MAGNIFY and AUGMENT trials), and produced CR rates ranging from 40–51%, and ORR ranging from 69–80% in the overall trial populations.[14-16] However, treatment benefits of lenalidomide plus rituximab are modest for the double-refractory population (defined as failure to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen; median DOR of 20.1 months [95% CI 14.6–not reached]),[16] and the magnitude of the therapeutic effect (CR, 26%; ORR, 50%)[16] did not differ substantially from that observed with idelalisib (CR, 14%, ORR, 56%).[10] Recently, tazemetostat, an EZH2 inhibitor, has shown promising responses in EZH2-mutated disease (ORR 69%), which represents 27% of the overall population,[17] but the CR rate is low (13%), and the median DOR of 10.9 months (95% CI 7.2–not estimable [NE]) appears comparable to data from PI3K inhibitor studies. For patients with wild-type EZH2 disease, ORR was 35% (CR, 4%) and the median DOR was 13 months (5.6–NE).[18]

A key consideration for these approved agents is the need for ongoing treatment until progression, leading to sustained risk of adverse events (AEs) and potential detriment in quality-of-life compared with defined-duration treatments. Furthermore, a shorter response duration at each relapse[5] and durable responses being observed only in a small proportion of patients indicate a high unmet need for an effective therapy for the r/r patient population.

Tisagenlecleucel is an autologous anti-CD19 chimeric antigen receptor (CAR)-T cell therapy that is approved in the US for the treatment of patients up to 25 years of age with r/r B-cell precursor acute lymphoblastic leukemia (B-ALL), and adult patients with r/r diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma, and DLBCL arising from FL.[19,20] The recent approval of axicabtagene ciloleucel (axi-cel) has established the feasibility of CAR-T cell therapy in r/r FL.[21] In a prior pilot study of tisagenlecleucel in 14 patients with r/r FL, 10 (71%) patients achieved a CR with the median DOR not reached at a median follow-up of over 5 years, and the probability of sustaining response for 5 years was 60% (95% CI 25–83).[22,23] Here, we present

the primary, pre-specified interim analysis of safety and efficacy data from ELARA, a phase 2 trial of tisagenlecleucel after two or more lines of therapy in adult patients with r/r FL.

RESULTS

Patients and Study Design

Between November 26, 2018, and January 17, 2020, a total of 119 patients were screened, of which 21 (17.6%) patients did not complete the screening, including 19 (16.0%) patients who failed screening (ie, did not meet at least one inclusion/exclusion criterion; Fig. 1). Patients included in the ELARA study were ≥18 years of age with r/r FL grade 1, 2, or 3A. Patients were excluded if they had evidence of histologic transformation, FL grade 3B, prior anti-CD19 therapy or allogeneic hematopoietic stem cell transplantation (HSCT; See Methods section for further details). As of the March 29, 2021, data cutoff date, 98 patients were enrolled and 97 received a tisagenlecleucel infusion; one patient discontinued before receiving an infusion due to investigator discretion based on CR to antineoplastic bridging therapy prior to tisagenlecleucel infusion. At study entry, 63.9% of patients had bulky disease, 85.6% had stage III-IV disease, and 78.4% were refractory to the last prior treatment.

Tisagenlecleucel was administered in the outpatient setting in 18% of patients. Most patients (93/97, 95.9%) received the protocol-specified dose range of 0.6 to 6 $\times$ 10^8 CAR-positive viable T cells; four patients received a lower dose of 0.1 to 0.46 × 10^8 CAR-T cells. In addition, two patients received out of specification (product that does not meet the release criteria approved by the FDA) CAR-T cells, one due to low cell viability and the other due to high cell count, both patients were infused with doses within the protocol-specified dose range of 0.8 $\times$ 10^8 and 6.0 $\times$ 10^8 CAR+ cells, respectively. The median CAR-T cell dose was 2.06 $\times$ 10^8 cells (IQR, 1.40–2.67 $\times$ 10^8). The median time from enrolment to infusion was 46 days (IQR, 38–57). The median follow-up time from infusion to data cutoff was 16.59 months (IQR, 13.8–20.21) for the infused patients. Ninety-four (96%) patients were evaluable for efficacy (median follow-up, 16.85 months; IQR, 13.80–20.21).

Patient demographics and baseline characteristics of all 97 infused patients are summarized in Table 1. Prior to infusion, 44 patients (45%) received optional antineoplastic bridging chemotherapy for stabilization. The most commonly used agents (in ≥5% of patients) were rituximab (22%), dexamethasone (11%), gemcitabine (10%), oxaliplatin (7%), prednisolone (7%), etoposide (6%), cyclophosphamide (5%), and vincristine (5%). One patient received bendamustine and two patients received radiotherapy alone.

The primary endpoint was CRR based on best response determined by an IRC per the Lugano 2014 classification response criteria.[24] Secondary endpoints included ORR, DOR, PFS, OS, safety, cellular kinetics analyses, and patient reported outcomes (not reported) for all infused patients. The full efficacy analysis set (EAS) and safety set included all patients who received an infusion of tisagenlecleucel. The EAS included all patients who received infusion of tisagenlecleucel and had measurable disease pre-infusion per IRC review. The per-protocol set (PPS) consisted of a subset of patients in the EAS with none of the following protocol deviations: diagnosis of disease other than FL at baseline, missing or incomplete documentation of disease at baseline, and receiving less than the recommended dose of 0.6×10^8 CAR-positive viable T cells.

Primary and Secondary Efficacy Endpoints

The primary endpoint of this study was met at the interim analysis with a median follow-up of 9.9 months (N=52; complete response rate [CRR], 65.4% [99.5% CI 45.1–82.4]; p<0.0001; the null hypothesis of CRR 15% or less by independent review committee [IRC] was rejected). At the primary analysis (a pre-specified interim analysis), 94 patients were evaluable for efficacy. The CRR was 69.1% (65/94; 95% CI 58.8–78.3) in the EAS population, and ORR was 86.2% (81/94; 95% CI 77.5–92.4) per IRC assessment. A high concordance (86%) was observed between IRC

and local assessments of response. Among 31 patients who had achieved partial response (PR) initially at 3 months, 15 patients converted to CR. Of these 15 patients, in 11 CR was achieved at the next planned disease assessment at month 6. At the last assessment before the data cutoff date, 65 patients (69.1%) had ongoing response per IRC. In the PPS population, the CRR was 72.9% (62/85; 95% CI 62.2–82.0) and ORR was 87.1% (74/85; 95% CI 78.0–93.4; Table 2). Two of the four patients who received a lower dose of tisagenlecleucel were responders; one of the two patients attained PR and eventually progressed (DOR, 70 days) and the other patient was in CR and eventually progressed (DOR, 476 days). The CRR was comparable across key prognostic subgroups including high-risk disease characteristics such as histological grade, prior HSCT, and bulky disease (Fig. 2). Patients with POD24 had a lower CRR (59.0%; 95% CI 45.7–71.4) versus those without POD24 (87.9%; 95% CI 71.8–96.6). Median DOR, PFS, OS, and time to next anti-lymphoma treatment were not reached (Fig. 3). Among patients who achieved CR, the estimated DOR rate at 9 months was 86.5% (95% CI 74.7–93.1), and estimated PFS rate at 12 months was 85.5% (95%CI 74.0-92.2). The PFS rate for the overall population at 12 months was 67% (95% CI 56–76).

Safety

Of 97 patients evaluable for safety, 99% experienced any-grade AEs, and 78.4% experienced at least one grade 3 or higher AE during the study, most commonly neutropenia (42.3%). Treatment-related AEs of any-grade were reported in 78.4% of patients and grade 3 or higher in 46% of patients. Within 8 weeks after infusion, 96.9% had at least one AE; 71% had grade 3 or 4 events, respectively.

CRS occurred in 49% of 97 patients (grade 3 or higher, 0%; per Lee scale[25]; Table 3) and in 57% of the 62 patients with bulky disease (no patients with bulky disease experienced grade 3 or higher CRS), within 8 weeks post infusion. Median time to onset and resolution of CRS was 4 days (IQR, 2–7 and 3–6 days, respectively) each. Among the 47 patients with CRS, 34% of

patients received tocilizumab and 6.4% received steroids (Extended Data Fig. 1). Patients with CRS received supportive care including intravenous fluids and/or vasopressors for hypotension (n=19; 40.4%), oxygen supplementation (n=9; 19%), a low dose of a single vasopressor was used in 3 patients (6.4%), and total parenteral nutrition (n=3; 6.4%); four patients with CRS were admitted to the intensive care unit (ICU) and needed supportive care requiring vasopressors and close monitoring.

Any-grade and grade 3 or higher hematological disorders including cytopenias were observed in 75.3% and 69.1% of patients, respectively, within 8 weeks post infusion. Ten patients (10%) had grade ≥3 febrile neutropenia. Based on laboratory data, 20% of patients had prolonged grade ≥3 lymphopenia and 7.7% had prolonged grade ≥3 leukopenia at 12 months (Extended Data Fig. 2). None of the patients had prolonged grade ≥3 neutropenia, and prolonged thrombocytopenia was not estimable at 12 months. At the time of study entry, 25 patients (25.8%) had hypogammaglobulinemia. Sixteen patients (16.5%) had AEs of prolonged depletion of normal B cells/agammaglobulinemia post-tisagenlecleucel infusion; in 10 patients (10.3%) the AE was suspected to be treatment-related. One patient had a grade 3 AE. No grade 4 AEs were reported. These AEs were ongoing in 10 patients at the time of the data cutoff date. Prophylactic intravenous immunoglobulins were administered to 33 patients (34.0%). Intravenous immunoglobulins were also administered to 3 patients (3.1%) for treatment of infections and 8 patients (8.2%) for other reasons.

Any-grade neurological events occurred in 37.1% and immune effector cell-associated neurotoxicity syndrome in 4.1% of patients within 8 weeks post infusion. Three patients developed grade ≥3 neurological events and one patient developed grade 4 immune effector cell-associated neurotoxicity syndrome (ICANS) on day 10 related to tisagenlecleucel concurrent with possible HHV6 encephalitis (Extended Data Fig. 3). The patient required ventilation and fully recovered after receiving high-dose methylprednisolone and ganciclovir.

Median time to onset of serious neurological events was 9 days (IQR, 5–35 days), with median time to resolution being 2 days (IQR, 1–4 days). Among 17 patients who received tisagenlecleucel in the outpatient setting, 11 (65%) patients had an inpatient hospitalization for post-infusion AE management. Median length of stay for hospitalization was 4 days, and none of the patients infused in the outpatient setting needed ICU stay.

Any-grade infections occurred in 18.6% of patients 8 weeks post infusion; 5.2% had grade ≥3 events. Majority of patients had B-cell levels below the limit of quantification of 0.2 cells/µL prior to infusion and continued to demonstrate levels below the normal range of 80-616 cells/µL post infusion. The median time to B-cell recovery for responding patients was not estimable at a median follow-up of 9 months. A total of seven patients died in the study. Five patients died because of progressive lymphoma, one patient died because of CRS, and another patient died because of general disorders and administration site conditions. All deaths occurred >30 days post infusion and none were treatment-related.

Pharmacokinetics

Cellular kinetic analyses were performed for all patients as a secondary endpoint. In the 97 patients evaluable, median time to maximal expansion based on transgene testing was similar between responders and non-responders (9.92 days [IQR, 8.88–13.8] vs. 13.0 days [IQR, 9.86–14.8], respectively, Extended Data Fig. 4); transgene persistence was detected up to 558 days and 366 days, respectively. Higher mean expansion (geometric mean maximum expansion [C_{max}] in copies/µg, geometric mean %CV; n) was observed in patients with grade 1 and 2 CRS (10100 copies/µg, 381%; n=40) relative to patients with no CRS (2990 copies/µg, 282%; n=35). The geometric mean C_{max} was slightly lower in non-responders than in responders (3000 vs. 6280 copies/µg, respectively). The mean area under the concentration-time curve from day 0 to

day 28 ($AUC_{0–28d}$) and to day 84 ($AUC_{0–84d}$) were comparable among responders and non-responders. Linear regression analyses showed no relationship between dose and cellular kinetic parameters (C_{max} and AUC). Favorable responses were observed across all the dose ranges investigated and the probability of achieving response was comparable across dose quartiles. There was no impact of dose on the best overall response. The incidence of CRS within 8 weeks of infusion in patients who received tisagenlecleucel doses below approximately 1×10^8 CAR-positive viable T cells was 27% (n=11) and in patients who received more than or equal to 1×10^8 CAR-positive viable T cells was 51% (n=86).

For the 15 patients whose response changed from PR to CR following tisagenlecleucel infusion, the cellular kinetic profile and B-cell kinetics were investigated with respect to change in the kinetics relative to the time of change in response (PR to CR as per the IRC assessment). The mean C_{max} by quantitative polymerase chain reaction (qPCR) was similar between the 14 evaluable patients (with reportable C_{max} values) and the rest of the patients. Likewise, the time to maximal expansion (T_{max}) was similar between the 2 groups (patients with response change from PR to CR, C_{max}, n=14, 5372 copies/µg, median T_{max} = 12 days [range: 8.8 to 28 days]; rest of the patients, C_{max}, 5645 copies/µg, median T_{max} = 10 days [range: 2.6 to 20 days]). All patients, except for one, showed a decline in the transgene levels after maximal expansion with no obvious re-expansion corresponding to the time of change in response from PR to CR. One patient with a change in response from PR to CR demonstrated a slight increase in transgene levels. Similarly, 10 patients exhibited B-cell aplasia at all timepoints post infusion. Only one patient showed B-cell recovery to normal range at month 12.

DISCUSSION

The primary analysis results from ELARA demonstrate that tisagenlecleucel is an effective therapy with a manageable safety profile for r/r FL patient population after two or more lines of therapy with limited treatment options and an unfavorable prognosis. Antitumor activity was

seen independently of established risk factors for progression and across subgroups of patients, including heavily pre-treated patients (median number of prior therapies was four [IQR, 3–5]), disease refractory to more than two lines of therapies (78% were refractory to last treatment), POD24 (63%), bulky disease (64%), advanced disease (86% had stage 3/4 disease), and high FLIPI score (60%). The majority of patients were PI3K-, lenalidomide-, and lenalidomide + rituximab-naïve. With a median follow-up of approximately 17 months among efficacy-evaluable patients, high CRR (69%) and ORR (86%) were observed, and median DOR, PFS, and OS were not reached. Complete response is one of the key predictors of long-term benefits in patients with FL and other B-cell lymphomas in both frontline and relapsed settings.[26]

The cellular kinetic analyses showed no impact of dose on cellular kinetic parameters (C_{max} and AUC), probability of CRS or neurological events, or median DOR. Overall exposure in the ELARA study population was comparable to that observed in patients with DLBCL.[23] The higher tisagenlecleucel expansion with higher severity of CRS is consistent with data from pediatric B-ALL and DLBCL.[27,28] Despite the C_{max} observed in responders being slightly higher, strong conclusions cannot be driven due to the limited number of non-responding patients and the associated variability. Longer follow-up will be required to fully understand the clinical significance of tisagenlecleucel persistence in this patient population.

Among trials of PI3K inhibitors in the third-line setting, the reported median DOR of less than a year[9-13] may not have been reliably estimated using the Kaplan-Meier method due to discontinuations related to toxicities, which were common with these agents,[9,10,13] and censoring at the time of start of a new anticancer therapy. In comparison, a higher response rate was observed with tisagenlecleucel in ELARA; however, longer follow-up is needed to evaluate the impact on DOR and PFS. In addition, as tisagenlecleucel is a single infusion treatment, the lack of a need for sustained therapy in treated patients provides a logistical and safety benefit relative to most PI3K or EZH2 inhibitors requiring ongoing treatment until progression.

The primary analysis results from the phase 2 ZUMA-5 trial of axi-cel in patients with r/r indolent NHL were reported in 146 efficacy-evaluable patients, of whom 68% were refractory to last prior treatment.[29] Although differences in the patient populations and study designs preclude direct comparisons between trials, patients in the ZUMA-5 study did not receive bridging therapy, were less heavily pre-treated than ELARA (median three lines of prior treatment vs. four), and the timing of initial efficacy assessments differed between the two studies (28 days in ZUMA-5 vs. 3 months in ELARA). Among 81 evaluable patients with FL who received axi-cel in ZUMA-5, the best ORR was 91% and CR rate was 60%.[21] In 124 patients with FL evaluable for safety, 6% of patients had grade 3 or higher CRS compared to no cases of high-grade CRS in ELARA. Fifteen percent of patients in ZUMA-5 had grade 3 or higher neurological events, while 3.1% of patients in ELARA had high-grade neurological events within 8 weeks of infusion and one patient with a grade 4 ICANS event who recovered fully. One patient had multisystem organ failure leading to death related to axi-cel treatment (occurring in the context of CRS). Together, the safety profile of tisagenlecleucel compared favorably to that of axi-cel. The higher rates of severe CRS and neurological events, along with the higher use of tocilizumab and corticosteroids reported in the ZUMA-5 study suggest that administration of axi-cel in an outpatient setting may be less feasible compared with tisagenlecleucel as administered in the ELARA study. One third of patients infused in the outpatient setting (n=17) in ELARA required no hospitalization for AE management, and none of the patients required ICU assistance. Five deaths in the ELARA study were due to progressive disease, and two additional deaths were due to CRS and to general disorders and administration site conditions. None of the deaths were treatment-related. Further research is needed to identify the patients most likely to benefit from CAR-T cell therapy in an outpatient setting. In addition, emerging data for bispecific antibodies have shown promising results for the treatment of patients with multiple types of r/r NHL, including r/r FL and DLBCL,[30-32] and further studies are required to understand their long-

term clinical effects and to help determine the most effective sequencing of therapies for patients with r/r FL.

Along with the possibility of outpatient treatment with tisagenlecleucel, the efficacy and safety data from the ELARA study in heavily pretreated patients with r/r FL, including those with high-risk disease characteristics are promising and will need to be evaluated for potential long-term benefits through studies with longer follow-up.

METHODS

Study Design

ELARA is a multinational, multicentre study conducted at 30 sites in 12 countries across the United States, Europe, Japan, and Australia (ClinicalTrials.gov: NCT03568461). Please see the redacted study protocol and redacted statistical analysis plan (SAP; available in the Supplementary Information) for additional details regarding study design and primary and secondary endpoints of the ELARA trial reported here. No independent data safety monitoring board was utilized for ELARA. The Novartis safety team and steering committee were involved in all safety reviews for each planned analysis. Before initiating the trial, the investigator/institution obtained approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, patient recruitment procedures (eg, advertisements) and any other written information to be provided to patients. Prior to enrollment, all patients were required to sign a written informed consent form.

Patients included in the ELARA study were ≥18 years of age and histologically confirmed by central pathology review to have FL (grade 1, 2, 3A). Eligible patients were required to meet one of the following criteria: (1) refractory to a second or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent) or relapsed within 6 months after completion of a second or later line of systemic therapy, (2) relapsed during anti-CD20 antibody maintenance (following ≥2 lines of therapies as above) or within 6 months after maintenance completion, (3) relapsed after autologous HSCT. Radiographically measurable disease (ie, at least one nodal lesion >20 mm in the long axis, regardless of the length of the short axis and/or extranodal lesions [outside lymph node or nodal mass, including liver and spleen] >10 mm in the long and short axis) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at screening were required. Patients were required to meet the following laboratory values

without transfusion at screening: absolute neutrophil count (ANC) ≥1000/mm^3 (≥1×10^9/L), absolute lymphocyte count (ALC) >300/mm^3 (>0.3×10^9/L), absolute number of CD3+ T cells >150/mm^3 (>0.15×109/L), platelets ≥50000/mm^3 (≥50×10^9/L), hemoglobin ≥8.0 g/dL (≥4.9 mmol/L), a serum creatinine of ≤1.5 times ULN or eGFR ≥60 mL/min/1.73 m^2, ALT/AST ≤5 times the ULN, and total bilirubin ≤1.5 times ULN (with the exception of patients with Gilbert's syndrome). Patients with Gilbert's syndrome could be included if their total bilirubin was ≤3.0 times ULN and direct bilirubin ≤1.5 times ULN. Patients were required to have adequate pulmonary function (ie, no or mild dyspnea [grade ≤1] and oxygen saturation measured by pulse oximetry of >90% on room air). Lastly, a leukapheresis product of non-mobilized cells accepted for manufacturing was required for all eligible patients.

Patients were excluded from the ELARA study if they had evidence of histologic transformation; FL grade 3B; prior anti-CD19 therapy; prior gene therapy; prior adoptive T-cell therapy; prior allogeneic HSCT; active CNS involvement by malignancy; active neurological autoimmune or inflammatory disorders (eg, Guillain-Barre syndrome, amyotrophic lateral sclerosis); received investigational drugs within the last 30 days or five half-lives (whichever is longer) prior to screening; presence of active or prior hepatitis B or C as indicated by serology; presence of HIV antibody; or uncontrolled acute life-threatening bacterial, viral, or fungal infection. Patients were excluded who had cardiac or cardiac repolarization abnormalities, including history of myocardial infarction, angina pectoris, coronary artery bypass graft within 6 months prior to infusion, clinically significant cardiac arrhythmias, left ventricular ejection fraction <45% (as determined by ECHO or MRA or MUGA), or NYHA functional class III or IV.[33] Patients with a previous or concurrent malignancy were excluded with the following exceptions: adequately treated basal cell or squamous cell carcinoma (adequate wound healing was required prior to enrollment); in situ carcinoma of the cervix or breast, treated curatively and without evidence of recurrence for ≥3 years prior to enrollment; or a primary malignancy that was completely

resected and in complete remission for ≥3 years at the time of enrollment. Women who were pregnant or nursing (lactating) or of child-bearing potential (ie, all women physiologically capable of becoming pregnant, unless they were using highly effective methods of contraception ≥12 months after infusion and until CAR-T cells were no longer present by qPCR on two consecutive tests) were also excluded. Sexually active males were required to use a condom during intercourse for ≥12 months after the tisagenlecleucel infusion and until CAR-T cells were no longer present by qPCR on two consecutive tests. In addition, male participants were not allowed to donate sperm for the time period specified above. Lastly, patients who did not tolerate the excipients of the tisagenlecleucel cell product were excluded from the study.

Central histologic confirmation of the diagnosis was performed at study entry. Bulky disease was defined as one nodal or extranodal tumor mass more than 7 cm in diameter or involvement of three or more nodal sites, each with a diameter more than 3 cm. After providing written informed consent, all patients underwent leukapheresis; enrolment was complete when the cryopreserved material was received by the manufacturing facility and clinical eligibility was confirmed. Bridging therapy, when needed, was allowed at the investigator's discretion and disease status was reassessed prior to tisagenlecleucel infusion in all patients to establish a new baseline. One week prior to infusion, all patients received one cycle of lymphodepleting chemotherapy. For lymphodepletion, patients could receive either fludarabine (25 mg/m^2) and cyclophosphamide (250 mg/m^2) daily for 3 days or bendamustine (90 mg/m^2) daily for 2 days.

Tisagenlecleucel was manufactured in multiple sites worldwide, including Morris Plains, New Jersey; FBRI, Japan; Les Ulis, France; and Stein, Switzerland. Tisagenlecleucel was administered as a single intravenous infusion at the protocol-specified dose of 0.6-6 $\times$ 10^8 CAR-positive viable T cells on day 1. Tisagenlecleucel could be administered in either an inpatient or outpatient setting per local policies and at the investigator's discretion. After infusion, the first response assessment (per Lugano classification[24]) was performed 3 months post infusion and

then every 3 months for the first year post infusion, and every 6 months during the second year and through the end of the study (month 24). Response was defined as CR or PR and non-responders were defined as patients with progressive disease, stable disease, or unknown disease status.

Endpoints

The primary endpoint was CRR based on best response determined by an IRC per the Lugano 2014 classification response criteria.[24] Secondary endpoints included ORR, DOR, PFS, OS, safety, and cellular kinetics analyses for all infused patients. AEs were reported based on MedDRA and CTCAE v4.03. CRS was graded per the Lee scale,[25] and neurological events were graded according to CTCAE v4.03 and American Society of Transplantation and Cellular Therapy ICANS consensus grading.

Statistical Analysis

Data collection was performed using the Novartis Rave EDC Platform. Based on the null hypothesis of CRR 15% or less and assuming an underlying CRR of 30% for tisagenlecleucel, 90 patients in the primary analysis were required to provide at least 90% cumulative power to demonstrate statistical significance, using a two-look Lan-DeMets group sequential design with O'Brien-Fleming type boundary and an exact CI at one-sided cumulative 0.025 level of significance. The primary analysis occurred after 90 patients had reached 6 months follow-up post infusion or had discontinued early. The full efficacy analysis set (EAS) and safety set included all patients who received an infusion of tisagenlecleucel. The EAS included all patients who received infusion of tisagenlecleucel and had measurable disease pre-infusion per IRC review. The PPS consisted of a subset of patients in the EAS with none of the following protocol deviations: diagnosis of disease other than FL at baseline, missing or incomplete documentation of disease at baseline, and receiving less than the recommended dose of 0.6×10^8 CAR-

positive viable T cells. All data analyses were performed, and outputs were generated utilizing the SAS version 9.4. DOR, PFS, and OS were estimated using the Kaplan-Meier method. Cellular kinetics were measured in the peripheral blood of evaluable patients by qPCR. Please see the associated SAP for additional details related to data analysis.

Role of the funding source

The funders participated in the study design, data collection, statistical analysis, and interpretation, and provided funding for medical writing and editorial support. All authors had unrestricted access to the study data and were responsible for submission for publication.

DATA AVAILABILITY

The authors declare that all data supporting the findings of this analysis are available within the article and its appendix. Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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AUTHOR CONTRIBUTIONS

N.H.F., M.D., S.J.S., and C.T. contributed to the study design. N.H.F., M. Dickinson, M. Dreyling, J.M.-L., A.K., J.B., M.G., L.P., J.C.C., E.B., K.K., H.H., M.J.K., C.A., P.A.R., P.J.H., J.A.P.-S., A.C., L.J.N., B.v.T., A.J.M.F., T.T., P.E.M.P., J.P.M., A.L.P., F.O., A.V., P.L.Z., R.M., S.J.S., and C.T. enrolled and treated patients, and gathered data. Data were analyzed and interpreted by all authors. All authors participated in the writing and review of this manuscript, and approved the final submitted version.

COMPETING INTERESTS

N.H.F. is an advisor or consultant for Roche/Genentech, TG Therapeutics, Verastem, Bayer, Celgene, and Novartis; reports research support from Roche, Celgene, Gilead Sciences, TG Therapeutics, Novartis, AbbVie, and BeiGene. M. Dickinson is an advisor or consultant for Novartis, Bristol-Myers Squibb, Gilead Sciences, Roche, and Janssen; has received honoraria from Roche, Amgen, MSD, Janssen, Bristol-Myers Squibb, Novartis; has participated in speaker

bureau for Novartis; and reports research support from Novartis, Roche, Takeda, Celgene, and MSD. M. Dreyling is an advisor or consultant for AstraZeneca, Bayer/Vital, BeiGene, Celgene/Jazz, Genmab, Gilead Sciences, Incyte, Janssen-Cilag, Novartis, and Roche; has participated in speaker bureau for Amgen, AstraZeneca, Bayer Health, Celgene, Gilead Sciences, Janssen-Cilag, and Roche Pharma AG; reports research support from AbbVie, Bayer, Celgene, Janssen-Cilag, and Roche Pharma AG; and travel support from Celgene, Janssen-Cilag, and Roche Pharma AG. J.M.L. is an advisor or consultant for Janssen, Novartis, BMS, Incyte, Astellas, and GlaxoSmithKline; reports research support from Bristol-Myers Squibb and Roche; has participated in speaker bureau for Janssen, Novartis, BMS, Incyte, Astellas, and GlaxoSmithKline; and owns stock in Altum Sequencing. A.K. is an advisor or consultant for Nordic Nanovector; reports research support from Merck and Nordic Nanovector; and travel support from Nordic Nanovector. J.B. is an advisor or consultant for Novartis; and has participated in speaker bureau for Novartis. M.G. declares no competing interests. L.P. reports honoraria from Pfizer and Roche; and travel support from Novartis. J.C.C. is a consultant for Kite/Gilead, Novartis, Karyopharm Therapeutics, MorphoSys, TeneBio, AbbVie, ADC Therapeutics, Janssen; has participated in speaker bureau for AstraZeneca, BMS, BeiGene, MorphoSys; and reports research support from Merck, AstraZeneca, ADC Therapeutics (Inst.). E.B. is an advisor or consultant for Roche and Incyte; reports research support from Takeda, and Amgen; reports financial support from Roche, Janssen, Celgene, Novartis, and Gilead; and non-financial support from Roche, BeiGene, Celgene, and AbbVie. K.K. is an advisor or consultant for AbbVie, AstraZeneca, Celgene, Chugai, Eisai, Janssen, and Novartis; has received honoraria from Celgene, Chugai, Janssen, Kyowa Kirin, Merck, Mundi, Novartis, Ono, Sumitomo Dainippon, and Takeda; and reports research support from AbbVie, Celgene, Chugai, Eisai, Janssen, Kyowa Kirin, Ono, Novartis, and Takeda. H.H. has received honoraria from BMS, Novartis, Chugai, and Janssen; and reports research support from Astellas. M.J.K. is an advisor or consultant for, and has received honoraria and travel support from Amgen, Bristol-

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TABLES

Table 1: Baseline demographic and disease characteristics of all treated patients

	Infused patients N=97
Median age (IQR), years	57.0 (49–64)
≥65 years, n (%)	24 (24.7)
Male, n (%)	64 (66.0)
Female, n (%)	33 (34)
ECOG PS ≥1 prior to infusion, n (%)	41 (43.3)
Stage at study entry III-IV, n (%)	83 (85.6)
Bone marrow involvement at study entry, n (%)	37 (38.1)
Bulky disease at baseline, n (%)	62 (63.9)
FLIPI high (≥3) at study entry, n (%)	58 (59.8)
Median no. of prior therapies (range)	4 (2-13)
>4, n (%)	27 (27.8)
POD24 from first anti-CD20 mAb containing therapy, n (%)	61 (62.9)
Prior anti-neoplastic therapy, n (%)	
Anti-CD20 mAb	97 (100)
Alkylating agents	97 (100)
Anti-CD20 mAb + alkylating agent (same or different regimen)	97 (100)
PI3K inhibitors	20 (20.6)
Lenalidomide	21 (21.6)
Lenalidomide + rituximab	16 (16.5)
Prior therapy to which the disease was refractory,[a] n (%)	
Anti-CD20 mAb	84 (86.6)
Alkylating agents	69 (71.1)
Anti-CD20 mAb + alkylating agent combination (same regimen)	61 (62.9)
Anthracyclines	43 (44.3)
Lenalidomide	18 (18.6)
Lenalidomide + anti-CD20 mAb (same regimen)	18 (18.6)
PI3K inhibitors	14 (14.4)
Refractory disease to last line of therapy, n (%)	76 (78.4)
Best response SD/PD	54 (55.7)
Relapse within 6 months	22 (22.7)
Prior autologous HSCT, n (%)	35 (36.1)
Relapsed ≤12 months after HSCT, n (%)	15 (15.5)
Refractory[a] to ≥2 regimens, n (%)	69 (71.1)
Double refractory,[b] n (%)	66 (68.0)

[a]Refractory is defined as failure to respond to previous treatment (SD/PD as best response) OR PD within 6 months of prior therapy completion.

[b]Double refractory is defined as failure to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen.
ECOG=Eastern Cooperative Oncology Group; FLIPI=Follicular Lymphoma International Prognostic Index; HSCT=hematopoietic stem cell transplant; IQR= interquartile range; OR=overall response; PD=progressive disease; POD24=progression of disease within 2 years; PS=performance score; SD=stable disease. Column titles are bolded for clarity.

Table 2. Best overall response in the efficacy analysis set and per-protocol population[a]

	Per-Protocol set n=85		Efficacy Analysis Set n=94	
	Local assessment	**IRC assessment**	**Local assessment**	**IRC assessment**
Best overall response, n (%)				
CR	64 (75.3) 95% CI 64.7–84.0	62 (72.9) 95% CI 62.2–82.0	68 (72.3) 95% CI 62.2–81.1	65 (69.1) 95% CI 58.5–78.3
PR	14 (16.5)	12 (14.1)	17 (18.1)	16 (17.0)
SD	2 (2.4)	3 (3.5)	3 (3.2)	3 (3.2)
PD	5 (5.9)	8 (9.4)	6 (6.4)	9 (9.6)
UNK				1 (1.1)
Overall response rate (CR + PR), n (%)	78 (91.8) 95% CI 83.8–96.6	74 (87.1) 95% CI 78.0–93.4	85 (90.4) 95% CI 82.6–95.5	81 (86.2) 95% CI 77.5–92.4

[a]The per-protocol set is a subset of the patients in the primary analysis efficacy set with no major protocol deviations.

CI=confidence interval; CR=complete response; IRC=independent review committee; PD= progressive disease; PR=partial response; SD=stable disease; UNK=unknown. Column titles are bolded for clarity.

Table 3: Overall safety profile

	Treated patients N=97
Any AE of special interest within 8 weeks post infusion	88 (90.7)
AESIs occurring in patients 8 weeks post infusion (regardless of study drug relationship)	
Cytokine release syndrome	47 (48.5)
Grade ≥3	0
Hematologic events	
Hypogammaglobulinemia	9 (9.3)
Grade ≥3	0
Neutropenia	32 (33.0)
Grade ≥3	31 (32.0)
Anemia	24 (24.7)
Grade ≥3	13 (13.4)
White blood cell count decreased	17 (17.5)
Grade ≥3	12 (12.4)
Thrombocytopenia	16 (16.5)
Grade ≥3	9 (9.3)
Platelet count decreased	5 (5.2)
Grade ≥3	3 (3.1)
Neutrophil count decreased	15 (15.5)
Grade ≥3	15 (15.5)
Febrile neutropenia	10 (10.3)
Grade ≥3	10 (10.3)
Leukopenia	4 (4.1)
Grade ≥3	4 (4.1)
Lymphocyte count decreased	6 (6.2)
Grade ≥3	5 (5.2)
Infections	18 (18.6)
Grade ≥3	5 (5.2)
Neurological events	36 (37.1)
Grade ≥3	3 (3.1)
Headache	23 (23.7)
Grade ≥3	1 (1)
Dizziness	6 (6.2)
Grade ≥3	0
Immune effector cell-associated neurotoxicity syndrome	4 (4.1)
Grade ≥3	1 (1.0)
Cardiac disorders	5 (5.2)
Grade ≥3	0
Gastrointestinal disorders	40 (41.2)
Grade ≥3	4 (4.1)
Diarrhea	17 (17.5)
Grade ≥3	1 (1)
Constipation	13 (13.4)
Grade ≥3	0

Nausea	12 (12.4)
Grade ≥3	2 (2.1)
Vomiting	7 (7.2)
Grade ≥3	0
Abdominal pain	6 (6.2)
Grade ≥3	1(1)
General disorders	35 (36.1)
Grade ≥3	4 (4.1)
Fatigue	15 (15.5)
Grade ≥3	3 (3.1)
Pyrexia	11 (11.3)
Grade ≥3	1 (1)
Asthenia	5 (5.2)
Grade ≥3	0
Chills	5 (5.2)
Grade ≥3	0
Metabolism and nutrition disorders	29 (29.9)
Grade ≥3	4 (4.1)
Hypokalemia	7 (7.2)
Grade ≥3	0
Hypomagnesemia	7 (7.2)
Grade ≥3	0
Hypophosphatemia	6 (6.2)
Grade ≥3	3 (3.1)
Decreased appetite	5 (5.2)
Grade ≥3	0
Musculoskeletal and connective tissue disorders	27 (27.8)
Grade ≥3	1 (1)
Muscle spasms	6 (6.2)
Grade ≥3	0
Myalgia	6 (6.2)
Grade ≥3	0
Arthralgia	5 (5.2)
Grade ≥3	0
Psychiatric disorders	7 (7.2)
Grade ≥3	0
Insomnia	5 (5.2)
Grade ≥3	0
Respiratory, thoracic and mediastinal disorders	12 (12.4)
Grade ≥3	0
Skin and subcutaneous tissue disorders	16 (16.5)
Grade ≥3	0
Vascular disorders	12 (12.4)
Grade ≥3	1 (1)
Hypotension	6 (6.2)
Grade ≥3	0
SAE (within 8 weeks post-infusion)	27 (27.8)

Suspected to be study drug related	23 (23.7)
Grade 3/4 AE (within 8 weeks post-infusion)	69 (71.1)
Suspected to be study drug related	39 (40.2)

AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event.
Column titles are bolded for clarity.

FIGURE LEGENDS

Fig. 1: CONSORT diagram for ELARA. Flowchart of participants disposition for the ELARA study.

Fig. 2: Best response of complete remission according to subgroup (EAS population). Forest plot summary of treatment effect of tisagenlecleucel across major demographic and prognostic subgroups.

*Denotes key findings across major demographic and prognostic subgroups in relation to CRR. [a]Patients primarily refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb-containing treatment. CI, confidence interval; CRR, complete response rate; EAS, efficacy analysis set; FLIPI, Follicular Lymphoma International Prognostic Index; HSCT, hematopoietic stem-cell transplantation; LDH, lactate dehydrogenase; PI3K, phosphoinositide 3-kinase; R2, lenalidomide + rituximab.

Fig. 3: Kaplan-Meier curves for patients with r/r FL who received tisagenlecleucel infusion. (a) duration of response, (b) progression-free survival, (c) overall survival, and (d) and time to next anti-lymphoma treatment.

REFERENCES

1 Swerdlow, S. H. *et al.* The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* **127**, 2375-2390 (2016).

2 Marcus, R. *et al.* Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med* **377**, 1331-1344 (2017).

3 Lansigan, F. *et al.* The prognostic significance of PFS24 in follicular lymphoma following firstline immunotherapy: A combined analysis of 3 CALGB trials. *Cancer Med* **8**, 165-173, doi:10.1002/cam4.1918 (2019).

4 Salles, G. *et al.* Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* **377**, 42-51, doi:10.1016/S0140-6736(10)62175-7 (2011).

5 Rivas-Delgado, A. *et al.* Response duration and survival shorten after each relapse in patients with follicular lymphoma treated in the rituximab era. *Br J Haematol* **184**, 753-759 (2019).

6 Link, B. K. *et al.* Second-line and subsequent therapy and outcomes for follicular lymphoma in the United States: data from the observational National LymphoCare Study. *Br J Haematol* **184**, 660-663, doi:10.1111/bjh.15149 (2019).

7 Casulo, C. *et al.* Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol* **33**, 2516 (2015).

8 Sarkozy, C. *et al.* Cause of death in follicular lymphoma in the first decade of the rituximab era: a pooled analysis of French and US cohorts. *J Clin Oncol* **37**, 144 (2019).

9 Gopal, A. K. *et al.* PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med* **370**, 1008-1018 (2014).

10 Salles, G. *et al.* Efficacy and safety of idelalisib in patients with relapsed, rituximab-and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. *Haematologica* **102**, e156-e159 (2017).

11 Dreyling, M. *et al.* Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol* **35**, 3898-3905 (2017).

12 Zinzani, P. L. *et al.* DYNAMO: A phase 2 study demonstrating the clinical activity of duvelisib in patients with double-refractory follicular lymphoma. *Haematologica* **102**, 315. Abstract S777 (2017).

13 Ukoniq [package insert]. Edison, NJ: TG Therapeutics, Inc; 2021.

14 US Food and Drug Administration. FDA approves lenalidomide for follicular and marginal zone lymphoma. May 2019. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lenalidomide-follicular-and-marginal-zone-lymphoma#:~:text=On%20May%2028%2C%202019%2C%20the,marginal%20zone%20lymphoma%20(MZL). Accessed April, 14, 2021.

15 Leonard, J. P. *et al.* AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol* **37**, 1188 (2019).

16 Rummel, M. J. *et al.* MAGNIFY: phase IIIb interim analysis of induction lenalidomide + rituximab (R2) followed by maintenance in relapsed/refractory indolent non-Hodgkin lymphoma. Presented at: 25th Congress of the European Hematology Association (EHA); June 11-14, 2020. Poster EP1161.

17 Bodor, C. *et al.* EZH2 mutations are frequent and represent an early event in follicular lymphoma. *Blood* **122**, 3165-3168, doi:10.1182/blood-2013-04-496893 (2013).

18 Morschhauser, F. *et al.* Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol* **21**, 1433-1442 (2020).

19 Maude, S. L. *et al.* Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med* **378**, 439-448, doi:10.1056/NEJMoa1709866 (2018).

20 Schuster, S. J. *et al.* Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med* **380**, 45-56, doi:10.1056/NEJMoa1804980 (2019).

21 US Food and Drug Administration. FDA grants accelerated approval to axicabtagene ciloleucel for relapsed or refractory follicular lymphoma. March 2021. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-axicabtagene-ciloleucel-relapsed-or-refractory-follicular-lymphoma. Accessed May 3, 2021.

22 Chong, E. A. *et al.* CD19-directed CAR T cell therapy (CTL019) for relapsed/refractory diffuse large B-cell and follicular lymphomas: four year outcomes. Presented at: 15th International Conference on Malignant Lymphoma; June 18-22, 2019; Lugano, Switzerland. Abstract 090.

23 Chong, E. A., Ruella, M., Schuster, S. J. & Lymphoma Program Investigators at the University of Pennsylvania. Five-year outcomes for refractory B-cell lymphomas with CAR T-cell therapy. *N Engl J Med* **384**, 673-674, doi:10.1056/NEJMc2030164 (2021).

24 Cheson, B. D. *et al.* Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* **32**, 3059-3068, doi:10.1200/JCO.2013.54.8800 (2014).

25 Lee, D. W. *et al.* Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* **124**, 188-195 (2014).

26 Bruna, R. *et al.* Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial. *Haematologica* **104**, 2241-2248, doi:10.3324/haematol.2018.209932 (2019).

27 Awasthi, R. *et al.* Tisagenlecleucel cellular kinetics, dose, and immunogenicity in relation to clinical factors in relapsed/refractory DLBCL. *Blood Adv* **4**, 560-572, doi:10.1182/bloodadvances.2019000525 (2020).

28 Mueller, K. T. *et al.* Cellular kinetics of CTL019 in relapsed/refractory B-cell acute lymphoblastic leukemia and chronic lymphocytic leukemia. *Blood* **130**, 2317-2325, doi:10.1182/blood-2017-06-786129 (2017).

29 Jacobson, C. *et al.* Primary analysis of ZUMA-5: a phase 2 study of axicabtagene ciloleucel (axi-cel) in patients with relapsed/refractory indolent non-Hodgkin lymphoma. Presented at: 62nd ASH Annual Meeting and Exposition; December 5-8, 2020. Abstract 700.

30 Assouline, S. E. *et al.* Mosunetuzumab shows promising efficacy in patients with multiply relapsed follicular lymphoma: updated clinical experience from a phase I dose-escalation trial. Presented at: 62nd ASH Annual Meeting and Exposition; December 5-8, 2020. Abstract 702.

31 Hutchings, M. *et al.* Glofitamab, a novel, bivalent CD20-targeting T-cell-engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. *J Clin Oncol*, JCO2003175, doi:10.1200/JCO.20.03175 (2021).

32 Schuster, S. J. *et al.* Mosunetuzumab induces complete remissions in poor prognosis non-Hodgkin lymphoma patients, including those who are resistant to or relapsing after chimeric antigen receptor T-cell (CAR-T) therapies, and is active in treatment through multiple lines. *Blood* **134**, 6 (2019).

33 Chavey, W. E., 2nd *et al.* Guideline for the management of heart failure caused by systolic dysfunction: Part I. Guideline development, etiology and diagnosis. *Am Fam Physician* **64**, 769-774 (2001).