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A SPECIAL MEETING REVIEW EDITION

Highlights in CAR T-Cell Therapy From the 62nd American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the All-Virtual 62nd ASH Meeting and Exposition • December 5-8, 2020

Special Reporting on:

- Long-Term Survival and Gradual Recovery of B Cells in Patients With Refractory Large B-Cell Lymphoma Treated With Axicabtagene Ciloleucel
- Lines of Therapy Before Autologous Stem Cell Transplant and CAR-T Infusion Affect Outcomes in Aggressive Non-Hodgkin Lymphoma
- Primary Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma
- CAR T Therapy for Lymphoma With Prophylactic Tocilizumab: Decreased Rates of Severe Cytokine Release Syndrome Without Excessive Neurologic Toxicity
- Retreatment With Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma in ZUMA-5
- ZUMA-19: A Phase 1/2 Multicenter Study of Lenzilumab Use With Axicabtagene Ciloleucel in Patients With Relapsed or Refractory Large B-Cell Lymphoma
- The First Retrospective Commercial Claims–Based Analysis of CAR T–Treated Patients With Relapsed or Refractory Large B-Cell Lymphoma
- Steroid Use, Advanced Stage Disease, and ≥3 Lines of Prior Chemotherapy Are Associated With a Higher Risk of Infection Following CD19 CAR T-Cell Therapy for B-NHL: Real World Data From a Large UK Center
- Interim Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients With High-Risk Large B-Cell Lymphoma
- Results From LUMMICAR-2: A Phase 1b/2 Study of Fully Human B-Cell Maturation Antigen-Specific CAR T Cells (CT053) in Patients With Relapsed and/or Refractory Multiple Myeloma

PLUS Meeting Abstract Summaries

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HIGH-RISK R/R FOLLICULAR LYMPHOMA: IS DANGER LURKING IN THIS "INDOLENT" DISEASE?

Follicular lymphoma (FL) is not always indolent—some patients with relapsed/refractory (r/r) FL are at high risk for reduced PFS, increasingly shorter response duration with each subsequent line of therapy, and shortened survival.[1,2a]

Patients with high-risk r/r FL may be identified by high FLIPI scores, high tumor burden, or early disease progression.[1,2a]

RECOGNIZE THE SIGNS OF HIGH-RISK R/R FL IN YOUR PATIENTS

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[a]Observational study (N=348) of newly diagnosed grade 1, 2, or 3a FL treated at 2 institutions (2001 to 2014). Patients met the GELF criteria for treatment and received chemoimmunotherapy to be included in this study. In patients with high-risk FLIPI scores, the percent of patients with durable response at 5 years was 52%, 21%, and 16% after 1L, 2L, and 3L therapy, respectively. 5-year PFS was 61%, 35%, and 23% in 1L, 2L, and 3L, respectively. 10-year OS: 72% after 1L; 47% after 2L; 5-year OS 20% after 3L.[1]

FLIPI=Follicular Lymphoma International Prognostic Index; GELF=Group d'Etude des Lymphomes Folliculaires; OS=overall survival; PFS=progression-free survival.

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Long-Term Survival and Gradual Recovery of B Cells in Patients With Refractory Large B-Cell Lymphoma Treated With Axicabtagene Ciloleucel

Dr Caron Jacobson and colleagues presented results from the 4-year follow-up analysis of the phase 1/2 ZUMA-1 study, which led to the approval of axicabtagene ciloleucel in adults with relapsed/refractory large B-cell lymphoma (LBCL) following at least 2 prior systemic therapies.[1-3] Eligible trial participants with refractory LBCL underwent leukapheresis at enrollment. They subsequently received conditioning chemotherapy consisting of fludarabine and cyclophosphamide for 3 days followed by a single target dose of 2×10^6 anti-CD19 chimeric antigen receptor (CAR) T cells/kg.[1]

Results for the 2-year and 3-year analyses of the ZUMA-1 study have been previously reported.[2,4] At the 2-year analysis, which was performed at a median follow-up of 27.1 months, the objective response rate (ORR) was 83% and the complete response (CR) rate was 58%.[2] The 3-year analysis, performed at a median follow-up of 39.1 months, revealed a median overall survival (OS) of 25.8 months and an estimated 3-year OS rate of 47%.[4]

The median follow-up was 51.1 months in the 4-year analysis.[1] Among the 111 patients enrolled in ZUMA-1, the median time from enrollment to an objective response and a CR was 1.7 months and 1.9 months, respectively. The investigators observed that these findings emphasize the speed, success, and reliability of manufacturing axicabtagene ciloleucel. Notably, 76% of enrolled patients had an objective response, while 53% had a CR.[1] The median time to administration of the subsequent anticancer therapy was 8.7 months (range, <1-54) after axicabtagene ciloleucel infusion. Two patients who were in remission following treatment with axicabtagene ciloleucel subsequently underwent allogeneic stem cell transplant.

The median OS was 25.8 months, and the 4-year OS rate was 44% among the patients who received an infusion of axicabtagene ciloleucel (Figure 1).[1] Similarly, the median OS was 17.4 months, and the 4-year OS rate was 41% among the entire enrolled study population.

Among the patients enrolled in ZUMA-1, 66 (59%) have died since study initiation.[1] The primary cause of death was progressive disease (52 patients). Since publication of the 2-year data,[2] there were 8 additional deaths: 5 from progressive disease, 1 from cardiac arrest, 1 from myelodysplastic syndrome deemed to be unrelated to axicabtagene ciloleucel, and 1 from an unknown cause. No new adverse events (AEs) related to axicabtagene ciloleucel were reported. There were no cases of secondary malignancies related to axicabtagene

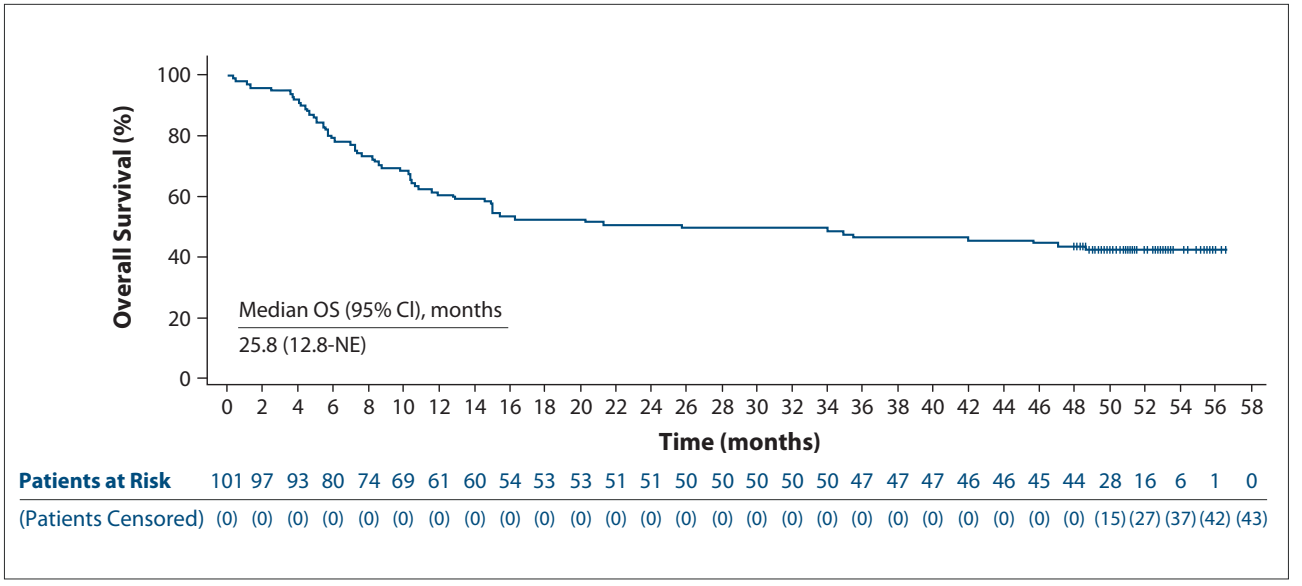

Figure 1. Overall survival at 4 years among the modified intention-to-treat population in the phase 1/2 ZUMA-1 study, which led to the approval of axicabtagene ciloleucel for adults with relapsed/refractory large B-cell lymphoma following at least 2 prior systemic therapies. NE, not estimable; OS, overall survival. Adapted from Jacobson C et al. ASH abstract 1187. *Blood.* 2020;136(suppl 1).[1]

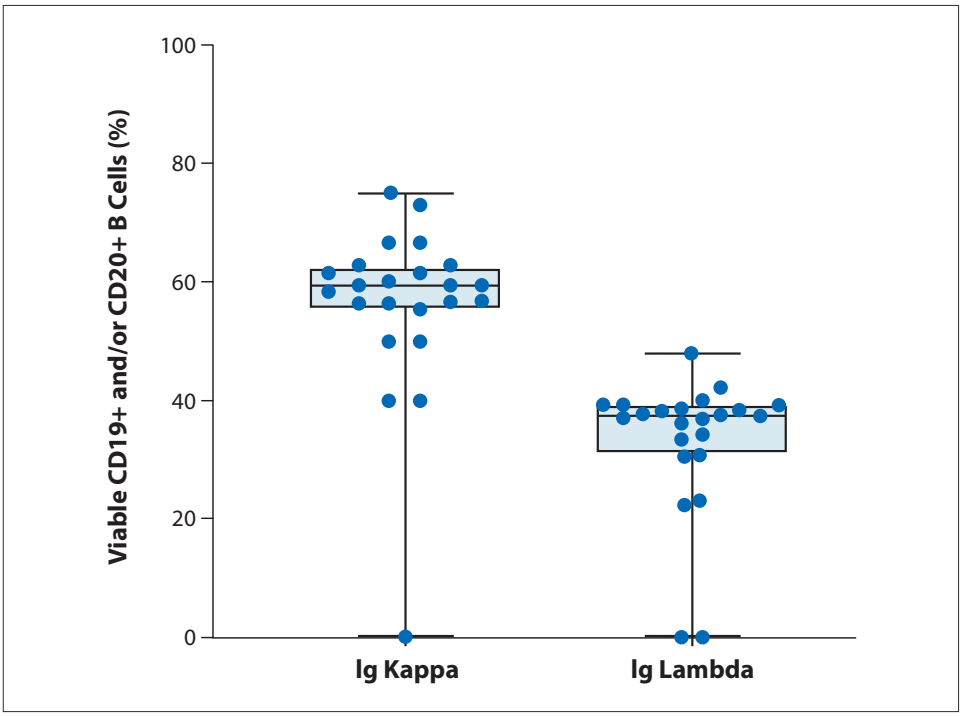

Figure 2. B-cell recovery at 4 years in the phase 1/2 ZUMA-1 study of patients treated with axicabtagene ciloleucel. Among 23 patients, 21 demonstrated recovery of polyclonal B cells. Ig, immunoglobulin. Adapted from Jacobson C et al. ASH abstract 1187. *Blood.* 2020;136(suppl 1).[1]

ciloleucel or confirmed cases of replication-competent retrovirus as of the 4-year data update.

Blood samples from patients in ongoing response 3 years after the infusion of axicabtagene ciloleucel were used to quantify levels of CAR T cells and to phenotype B cells.[1] At 3 years, all 21 patients had detectable B cells in the blood (Figure 2), whereas 14 patients (67%) had detectable CAR gene-marked cells and polyclonal B cells. Most patients (21 of 23) with evaluable B cells who had an ongoing response at the 3-year follow-up demonstrated polyclonal B-cell recovery as measured by the presence of both κ and λ light chains on nonmalignant CD19-positive and/or CD20-positive B cells. Most patients demonstrated polyclonal B-cell diversity, which implies reconstitution of the B-cell repertoire.

In summary, this updated analysis revealed deep and durable responses to axicabtagene ciloleucel, with a 4-year OS rate of 44%. Patients with ongoing responses 3 years after treatment showed evidence of polyclonal B-cell restoration and clearance of functional CAR T cells, a key component of the long-term safety of CAR T-cell therapies. Together, these long-term findings support the hypothesis that persistence of functional CAR T cells is not essential for deep and durable remission.

ABSTRACT SUMMARY Long-Term Outcomes Following Donor-Derived Anti-CD19 CAR-T Cell Therapy for B-Cell Acute Lymphoblastic Leukemia Patients Relapsed After Allogenic Stem Cell Transplantation

Zhang and colleagues presented key findings from 10 adult patients with B-cell acute lymphoblastic leukemia who received donor-derived anti-CD19 CAR T-cell therapy following relapse after allogeneic stem cell transplant (Abstract 500). Donor T cells were obtained from peripheral blood and infected with lentivirus carrying CD19 CAR plasmid. Recipients were pretreated with fludarabine, cyclophosphamide, and cytarabine before CAR T-cell infusion (median, 1.82 × 106 cells/kg). Peak expansion of CAR T cells was achieved after 7 to 14 days and decreased to a low level within 1 month of infusion. Peak serum levels of IL-6 and IL-2R were observed 5 to 7 days after CAR T-cell infusion. All patients experienced CRS events, which were mostly grade 1 or 2. No patients developed acute or new-onset graft-vs-host disease. After a median follow-up of 20.6 months, the 30-month OS was 51% and leukemia-free survival was 48%. Six patients were alive, and 1 patient required a second stem cell transplant.

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Lines of Therapy Before Autologous Stem Cell Transplant and CAR-T Infusion Affect Outcomes in Aggressive Non-Hodgkin Lymphoma

The number of autologous stem cell transplants (ASCTs) performed among patients with aggressive NHL has decreased since the approval of CAR T-cell therapies, particularly among patients with a partial response to salvage chemotherapy.[1] In some cases, patients who are refractory to second-line chemotherapy can receive a third-line therapy before moving to ASCT if they exhibit sensitivity to chemotherapy. Because these patients have aggressive disease—and sufficient time is required to manufacture CAR T cells—the timing of referral is crucial to avoid additional treatments and their complications.

Dr Arushi Khurana and colleagues evaluated the impact of prior lines of therapy on the efficacy of CAR T-cell therapy and ASCT, to support the case for early referral.[2] In this retrospective analysis, the investigators reviewed data for patients treated with axicabtagene ciloleucel or ASCT for relapsed/refractory aggressive non-Hodgkin lymphoma (NHL) at the Mayo Clinic (Rochester) between June 2016 and March 2020. Response to all lymphoma-directed therapy was evaluated using 2014 Lugano criteria.

In all, 105 patients had undergone ASCT: 87 after 2 lines of chemotherapy and 18 after 3 lines of chemotherapy. The baseline characteristics were comparable between these 2 subgroups, except for response to first-line chemotherapy. The rate of CR was 78% in patients previously treated with 2 lines of chemotherapy vs 39% in those treated with 3 prior lines (P<.001). Progressive disease was reported in 21% vs 44%, respectively (P<.001).

The median follow-up after ASCT was 19.7 months. Event-free survival (EFS), defined as time from transplant to disease progression, was greater in patients who had undergone ASCT after 2 vs 3 prior lines of chemotherapy. The 1-year EFS rate was 67% for ASCT administered after 2 prior lines of chemotherapy vs 44% for ASCT given after 3 prior lines of chemotherapy (P=.015; Figure 3). In contrast, there was no significant difference in the 1-year OS rates observed in these

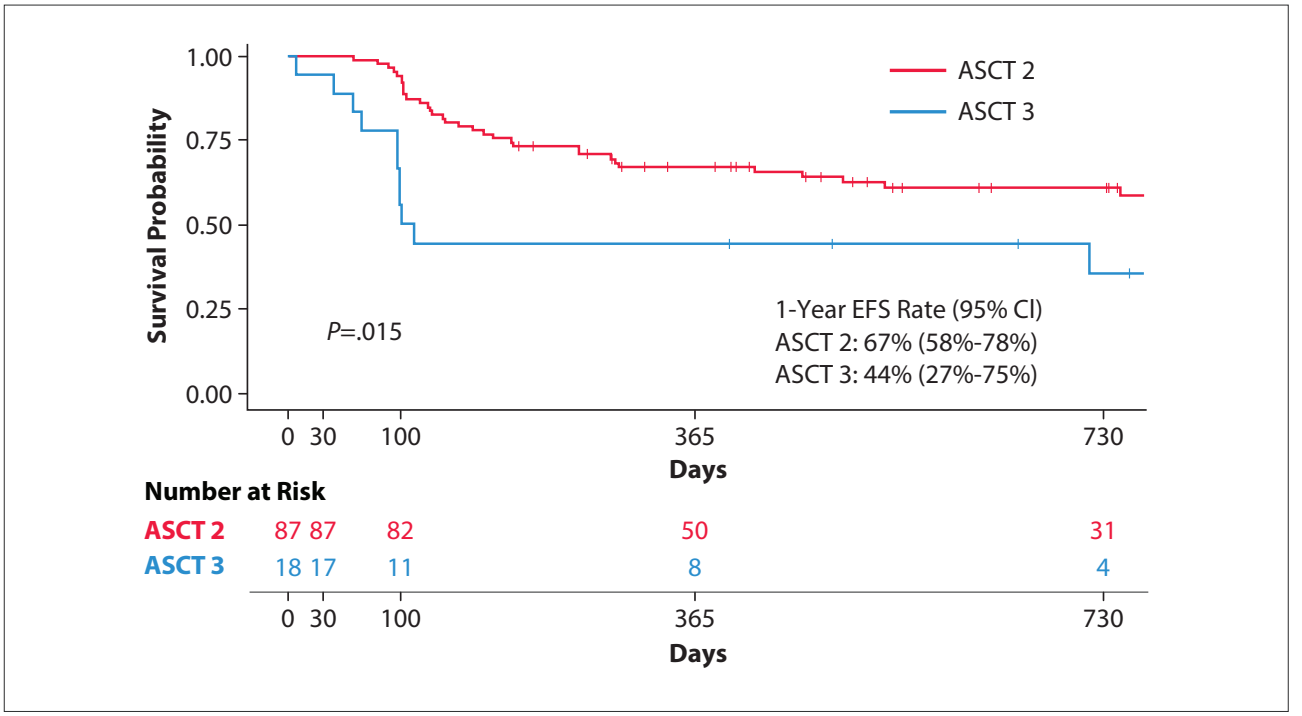

Figure 3. Survival probability among patients who had undergone ASCT after 2 vs 3 prior lines of chemotherapy. ASCT, autologous stem cell transplant; EFS, event-free survival. Adapted from Khurana A et al. ASH abstract 737. *Blood.* 2020;136(suppl 1).[2]

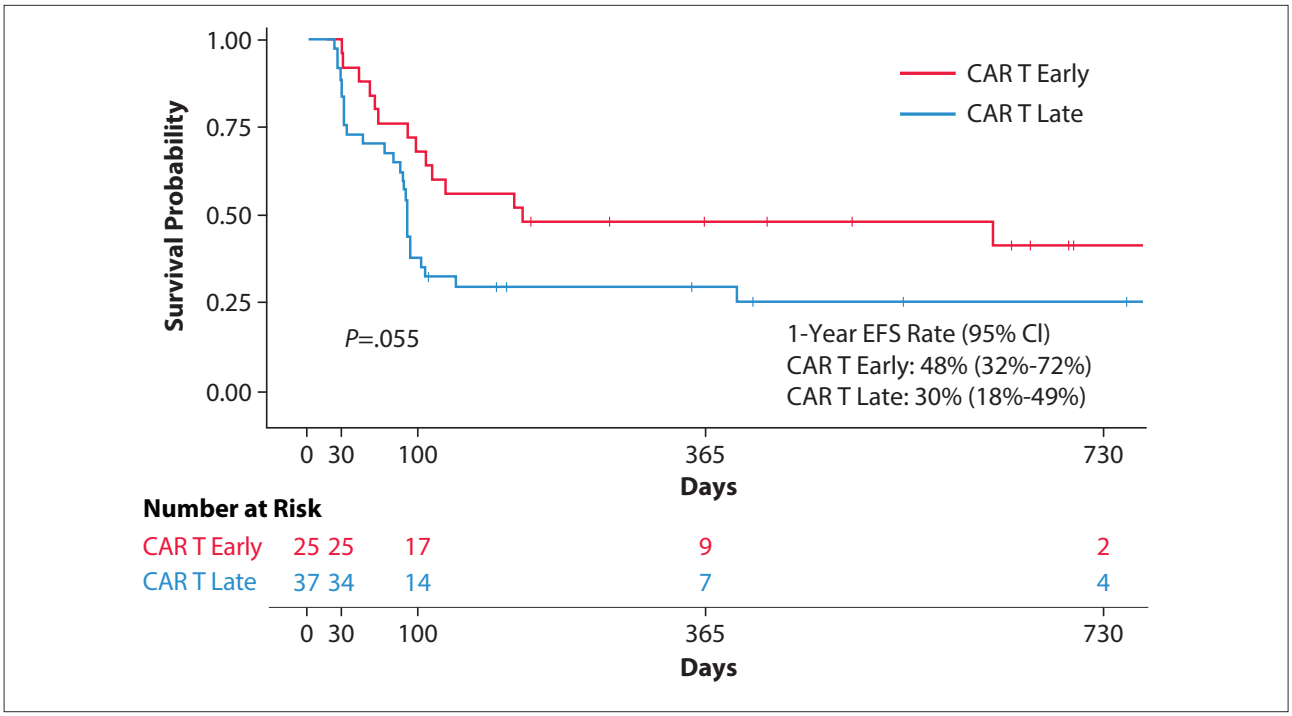

Figure 4. Event-free survival among patients who received CAR T-cell therapy early or late. The early group received CAR T-cell therapy after 2 lines of chemotherapy or after ASCT that followed 2 lines of chemotherapy. Patients in the late group received CAR T-cell therapy after at least 3 lines of chemotherapy or had received additional treatment after ASCT. ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor therapy; EFS, event-free survival. Adapted from Khurana A et al. ASH abstract 737. *Blood.* 2020;136(suppl 1).[2]

subgroups (89% vs 69%; *P*=.13).

Sixty-two patients received CAR T-cell therapy during the period evaluated. The analysis divided patients into 2 groups. The CAR T early group (n=25) received CAR T-cell therapy after 2 lines of chemotherapy or after ASCT that followed 2 lines of chemotherapy. Patients in the CAR T late group (n=37) received CAR T-cell therapy after at least 3 lines of chemotherapy or had received additional treatment after ASCT. Baseline characteristics were comparable between the subgroups. The rate of referral for the earliest possible CAR T indication was 40%.

The median follow-up for CAR T-cell therapy was 12.1 months. There was a trend toward better survival outcomes in the CAR T early group, although the endpoints did not achieve statistical significance. The 1-year EFS rate following CAR T-cell therapy was 48% in the early group and 30% in the late group (*P*=.055; Figure 4). One-year OS was 75% vs 56% (*P*=.053), respectively.

Among the 62 patients treated with CAR T-cell therapy, 14 received this therapy after ASCT (following 2 or 3 lines of chemotherapy) and 48 received it after other treatments (chemotherapy and/or immunotherapy). A bridging therapy was required by 43% vs 75%, respectively (*P*=.03). Survival outcomes tended to be better in patients who received CAR T-cell therapy after ASCT. The 1-year EFS rates were 57% vs 30% (*P*=.069), and 1-year OS was 77% vs 60% (*P*=.039).

The investigators also compared outcome among patients who received ASCT after 3 lines of chemotherapy (n=18) vs those who received CAR T-cell therapy after 2 lines of chemotherapy (n=15). Progressive disease following second-line therapy was reported in 44% vs 87% (*P*=.01). There were no significant differences in 1-year EFS (44% vs 40%) or OS (69% vs 65%) between the ASCT and CAR T-cell therapy groups.

The investigators concluded that there was a trend toward better survival outcomes when CAR T-cell therapy was used as indicated (ie, after 2 prior lines of therapy). Referral for earliest use of CAR T-cell therapy remains low. Large cohort studies with longer follow-up are required to elucidate the implications of treatment sequencing on survival outcomes.

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Primary Analysis of ZUMA-5: A Phase 2 Study of Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

Dr Caron Jacobson and colleagues presented the primary analysis of ZUMA-5, a multicenter, single-arm, phase 2 study of axicabtagene ciloleucel for the treatment of patients with relapsed/refractory indolent non-Hodgkin lymphoma.[1] The population included 124 patients with follicular lymphoma (grades 1 to 3a) and 22 patients with marginal zone lymphoma (nodal or extranodal). Patients had relapsed after 2 prior lines of therapy.

All patients received leukapheresis followed by conditioning chemotherapy.[1] Lymphodepleting chemotherapy consisted of fludarabine and cyclophosphamide. The dose of axicabtagene ciloleucel was 2 × 10^6 CAR T cells/kg. Axicabtagene ciloleucel was successfully manufactured for all enrolled patients. The primary efficacy analysis was performed on patients with at least 12 months of follow-up (84 patients with follicular lymphoma and 20 patients with marginal zone lymphoma). The safety analysis was performed on all treated patients (N=146).

Stage 3/4 disease was reported in 86% of patients overall, and 49% had high tumor bulk. The median number of prior therapies was 3 (range, 1-10). Most of the study population had advanced disease with high tumor bulk, and had progressed within 24 months of their first chemotherapy/immunotherapy regimen. Refractory disease was reported in 68%. Approximately one-fourth of patients had undergone ASCT.

The primary endpoint, ORR assessed by central radiology review in patients with follicular lymphoma, was 94%.[1] The ORR in all evaluable patients was 92%. Centrally reviewed ORR was consistent across key subgroups, including patients with a negative CD19 status. The median time to first response, evaluated in all patients, was 1 month (range, 0.8-3.1). A CR was reported in 80% of patients with follicular lymphoma and 76% of all evaluable patients. The marginal

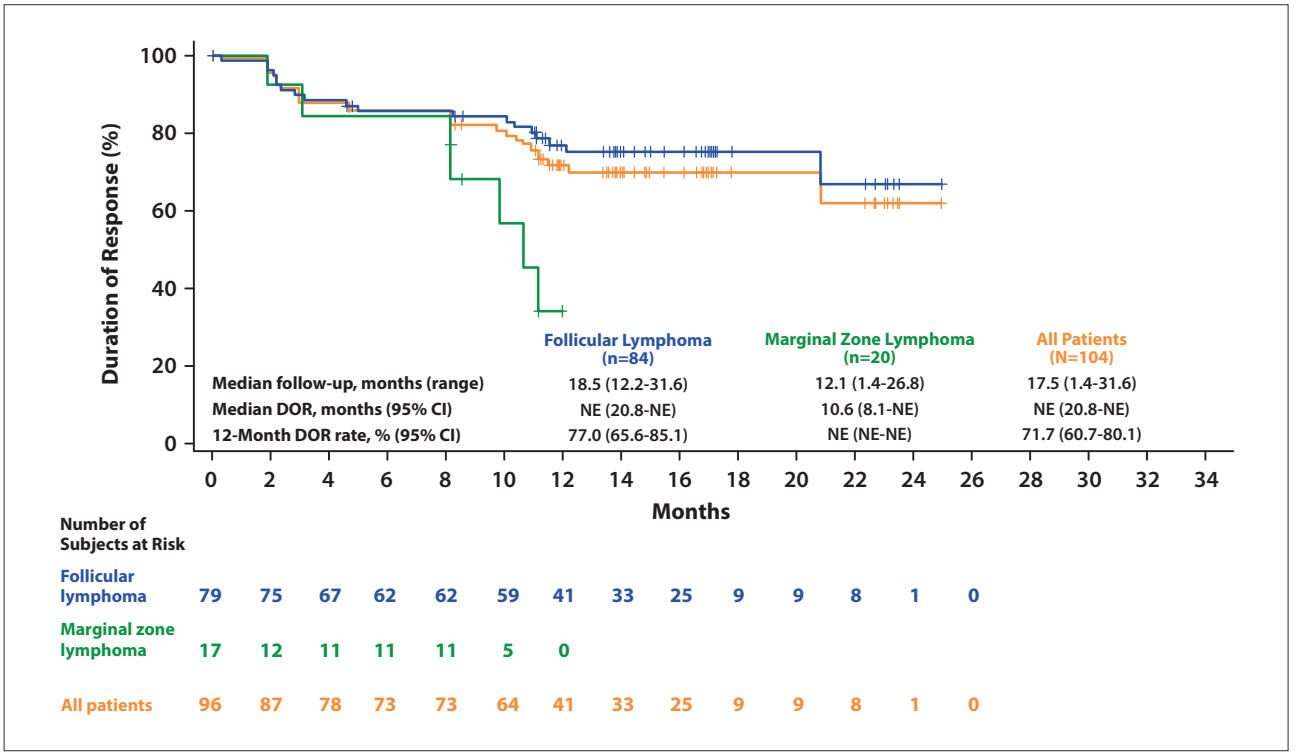

Figure 5. Duration of response among patients with follicular lymphoma or marginal zone lymphoma treated with axicabtagene ciloleucel in the phase 2 ZUMA-5 trial. DOR, duration of response; NE, not estimable. Adapted from Jacobson CA et al. ASH abstract 700. *Blood.* 2020;136(suppl 1).[1]

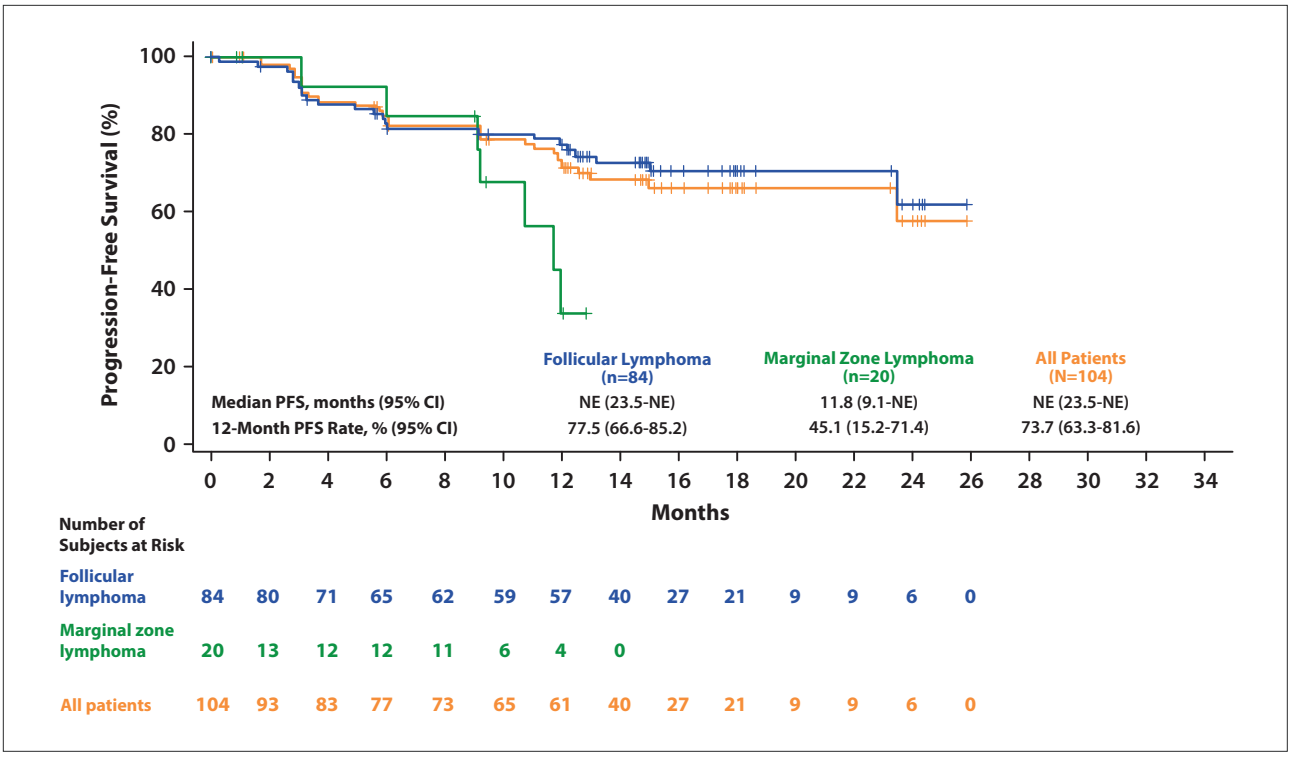

Figure 6. Progression-free survival among patients with follicular lymphoma or marginal zone lymphoma treated with axicabtagene ciloleucel in the phase 2 ZUMA-5 trial. NE, not estimable; PFS, progression-free survival. Adapted from Jacobson CA et al. ASH abstract 700. *Blood.* 2020;136(suppl 1).[1]

zone lymphoma arm was still accruing at the time of the report. Among this group, the ORR was 85% and the CR rate was 60%.

After a median follow-up of 17.5 months, the estimated duration of response had not been reached for all evaluable patients.[1] The 12-month duration of response rate was 71.7% for all patients and 77.0% for patients with follicular lymphoma (Figure 5). In patients with follicular lymphoma, responses to axicabtagene ciloleucel were maintained beyond 12 months in 78% of those with a CR and 17% of those with a partial response. The 12-month duration of response was 87% vs 14%, respectively. At the time of the primary analysis, data for the duration of response were immature for patients in the marginal zone lymphoma arm.

The median OS and progression-free survival (PFS) were not reached for all evaluable patients or for patients with follicular lymphoma (Figure 6).[1] Among all patients, the 12-month PFS rate was 73.7%, and the 12-month OS rate was 92.9%.

Grade 3 or higher AEs occurred in 86% of patients.[6] Most of these events were related to cytopenias (70%).[1] Grade 5 AEs occurred in 2 patients with follicular lymphoma and 1 patient with marginal zone lymphoma. One death was related to treatment (multisystem organ failure owing to cytokine release syndrome [CRS]).

CRS events of any grade were observed in 82% of all patients, whereas CRS of grade 3 or higher occurred in 7%. The median time to onset of CRS was 4 days, and the median duration of CRS was 6 days. The most common symptoms associated with CRS were pyrexia (96%) and hypotension (41%); treatments of these symptoms included tocilizumab (49%) and corticosteroids (17%).

Neurologic toxicities of any grade occurred in 60% of all patients. These events were grade 3 or higher in 19% of patients. The median time to onset of neurotoxicity was 7 days, and events persisted for a median of 14 days. The most frequent events were tremor (52%) and confused state (40%). Management of neurologic events consisted of corticosteroids in 36% of patients and tocilizumab in 6%.

CAR T-cell levels peaked 9 days after infusion. There was a trend toward higher CAR T-cell levels in patients with follicular lymphoma who had an ongoing response at 12 months. Patients who developed high-grade CRS and neurotoxicity had significantly higher peak CAR T-cell levels compared with those experiencing grade 0 to 2 events.

The median time to peak serum cytokines was less than 8 days, with most elevations resolving by 4 weeks.[1] Compared with patients with follicular lymphoma, those with marginal zone

lymphoma had a greater median-fold increase in several cytokines associated with both CRS and neurotoxicity. Among patients with follicular lymphoma, peak levels of key cytokines were associated with grade 3 or higher neurologic events. Similar trends were observed in patients with marginal zone lymphoma.

The investigators concluded that axicabtagene ciloleucel demonstrated high rates of response in indolent B-cell lymphoma and NHL. Longer follow-up will determine the durability of these responses. Based on the safety profile of axicabtagene ciloleucel, an evaluation of the feasibility for outpatient treatment is planned.

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CAR T Therapy for Lymphoma With Prophylactic Tocilizumab: Decreased Rates of Severe Cytokine Release Syndrome Without Excessive Neurologic Toxicity

Tocilizumab is a monoclonal antibody that targets the interleukin (IL) 6 receptor and is approved for the treatment of CRS. However, tocilizumab is not recommended for the treatment of mild CRS in the presence of neurotoxicity.[1-3] Caimi and colleagues conducted a retrospective analysis of patients with NHL treated with anti-CD19 CAR T-cell therapy at University Hospitals Seidman Cancer Center between 2018 and 2020.[4] In May 2019, administration of prophylactic tocilizumab at 8 mg/kg was initiated as a preventive measure against CRS. This treatment is administered 1 hour before the CAR T-cell infusion.

The study enrolled 28 adult patients.[4] Eight patients received no prophylaxis, and the remaining 20 received prophylaxis with tocilizumab. Two patients in the prophylaxis group received tisagenlecleucel, and all other patients were treated with a locally manufactured anti-CD19 CAR T-cell product with 4-1BB costimulatory signaling. Twenty-three of the patients treated with locally manufactured CAR T cells received fresh product infusion.

At baseline, total and CD3-positive lymphocyte counts were similar

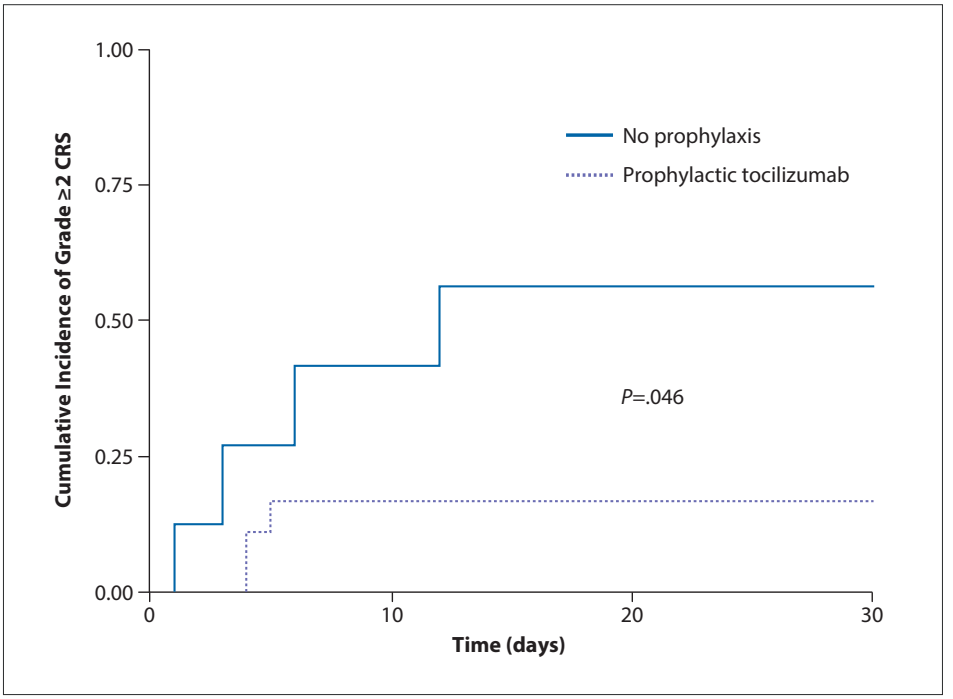

Figure 7. The cumulative incidence of grade 2 or higher cytokine release syndrome among patients who did or did not receive prophylaxis with tocilizumab before treatment with anti-CD19 CAR T-cell therapy. CAR, chimeric antigen receptor; CRS, cytokine release syndrome. Adapted from Caimi PF et al. ASH abstract 738. *Blood*. 2020;136(suppl 1).[4]

among all patients.[4] In the prophylaxis group, there was a trend toward lower levels of lactate dehydrogenase and lower total metabolic tumor volume before conditioning therapy; however, these differences did not reach statistical significance. Baseline ferritin was significantly lower in the group that received prophylaxis with tocilizumab (*P*=.043). Baseline C-reactive protein appeared to be lower in the prophylaxis group than in the group without prophylaxis, but this difference did not reach statistical significance (*P*=.07).

All-grade CRS occurred in 75% of patients who did not receive prophylaxis vs 50% of patients who did, but this difference was not significant (*P*=.401).[4] A statistically significant difference was seen in the rates of grade 2 or higher CRS, which were 62.5% vs 15.0%, respectively (*P*=.022). The median time to onset of CRS was 6 days (range, 1-12) without prophylaxis and 4 days (range 4-7) with prophylaxis, but this difference was not significant (*P*=.508). The cumulative incidence of CRS of grade 2 or higher was significantly lower in patients who received prophylaxis (*P*=.046; Figure 7). There was no difference in the incidence of neurologic events between the groups. All-grade neurologic events occurred in 38% of patients without prophylaxis and in 25% of patients with prophylaxis.

The ORR was 62.5% in the group without prophylaxis and 85.0% in the group that received prophylaxis (*P*=.3).[4] The CR rate was 50% vs 75%, respectively. The estimated 12-month OS was 74% for the entire cohort, 63% for patients who did not receive prophylaxis, and 78% for patients who received prophylaxis. There were no differences between the subgroups.

The use of prophylactic tocilizumab resulted in significantly lower levels of peak ferritin and C-reactive protein.[4] IL-6, which was comparable between the groups at baseline, increased substantially in the patients who received tocilizumab, and persisted for approximately 1 week before returning to baseline levels 2 weeks after CAR T-cell infusion. Additionally, patients treated with prophylactic tocilizumab had significantly lower plasma concentrations of IL-10 on day 2 (*P*=.033). No between-group differences were observed for other cytokines measured, including IL-8, interferon-γ, tumor necrosis factor–α, IL-1 β, macrophage inflammatory protein 1α and 1β, and monocyte chemoattractant protein 1. Furthermore, no differences were observed in plasma cytokine concentrations measured on day 6.

Study limitations include the small sample size and retrospective design.[4] The cohorts were sequential, and therefore the clinicians' experience might have influenced the outcomes of patients in the prophylaxis cohort. Infusion with a fresh and locally manufactured product may have affected the risk for CRS, as only 1 patient who received such a product developed a grade 3 or higher case of CRS.

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Retreatment With Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma in ZUMA-5

Retreatment with CAR T-cell therapy resulted in limited responses in patients with LBCL.[1] However, the clinical efficacy of CAR T-cell retreatment in patients with indolent NHL is unknown.[2] Chavez and colleagues reported on the outcomes of patients with relapsed/refractory indolent NHL who were re-treated with axicabtagene ciloleucel in the ZUMA-5 trial.[2] Key eligibility criteria for retreatment were disease progression following a CR or partial response at the 3-month assessment, and no evidence of CD19 loss in a biopsy taken after progression. In addition, the first infusion of axicabtagene ciloleucel had not led to grade 4 CRS or neurologic events, or life-threatening toxicities.

Among the 11 patients who were re-treated with axicabtagene ciloleucel, 9 had follicular lymphoma and 2 had marginal zone lymphoma.[2] Most patients had high-risk disease characteristics at baseline, and all relapsed patients who received retreatment had detectable CD19. After the first axicabtagene ciloleucel infusion, the ORR was 100%, including a CR rate of 91%. The median duration of response to the first infusion was 8.3 months.

Similarly, after retreatment, the ORR was 100% and the CR rate was 91%.[2] At a median follow-up of

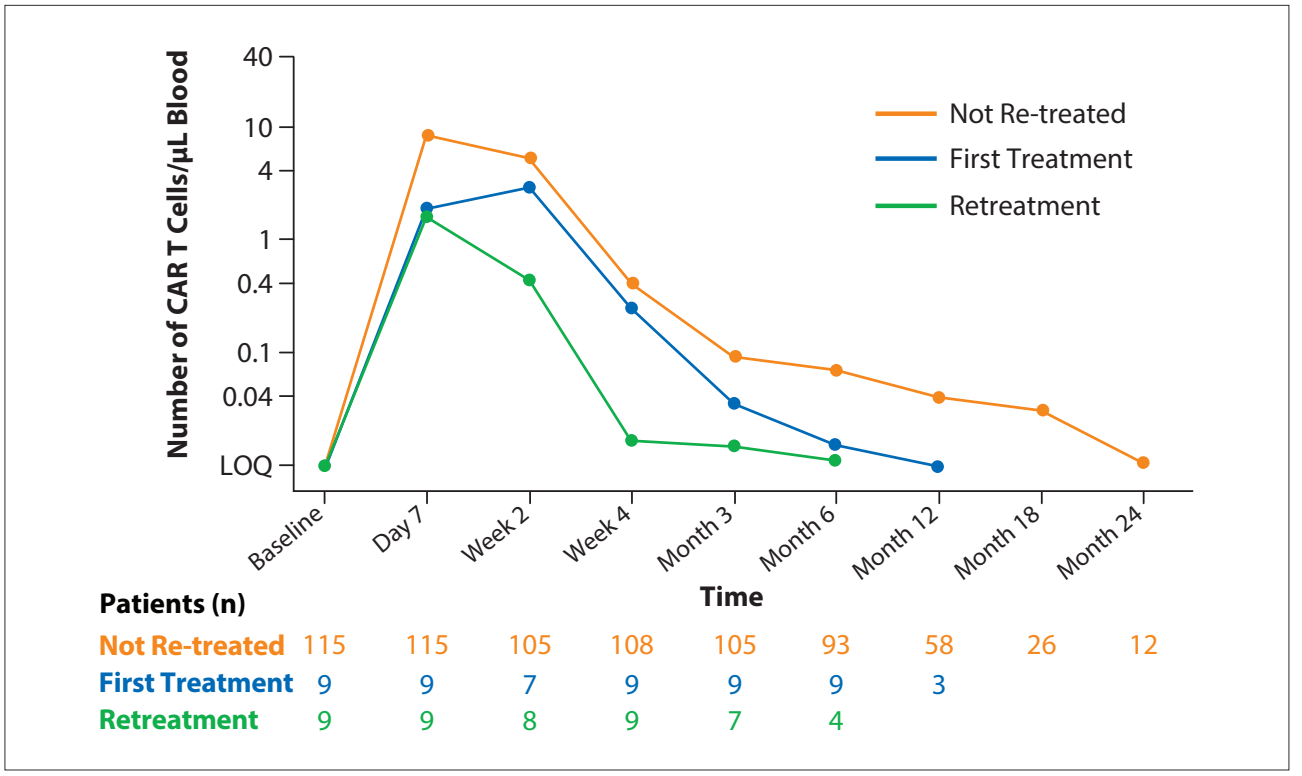

Figure 8. CAR T-cell levels over time among patients with follicular lymphoma who were or were not re-treated with axicabtagene ciloleucel in the ZUMA-5 trial. CAR, chimeric antigen receptor. LOQ, limit of quantification; Adapted from Chavez JC et al. ASH abstract 2036. *Blood.* 2020;136(suppl 1).[2]

2.3 months, the median duration of response to retreatment had not been reached. Responses were ongoing for 9 of the 11 patients (82%) at data cutoff. Response rates were similar regardless of whether the patient underwent a second round of apheresis, as well as whether the product was drawn from a second bag generated during the initial manufacturing process or from frozen peripheral blood mononuclear cells collected during initial apheresis.

CRS was reported in 64% of patients after the first treatment and 73% at retreatment.[2] Neurologic events occurred in 36% at both points. No cases of grade 3 or higher CRS or neurologic events were observed after retreatment. Furthermore, there were no differences in peak levels of the cytokines typically associated with severe CRS and neurologic events.

The characteristics of the products appeared to be similar at the first and second CAR T-cell infusions, with the exception of a higher frequency of naive and central memory T cells (C-C chemokine receptor type 7 [CCR7]) in patients who underwent a second apheresis before treatment.[2] Peak expansion of CAR T cells was similar at the first and second infusions in patients with follicular lymphoma (9.0 vs 13.2 cells/µL; Figure 8).[2] However, patients with follicular lymphoma who received retreatment had lower median peak CAR T cell levels at the first treatment than those who were not re-treated (13.2 vs 41.9 cells/µL). Peak CAR T-cell levels were normalized to tumor burden, as re-treated patients had a higher tumor burden before the first infusion than patients who were not re-treated (Figure 9). Peak expansion remained lower in re-treated patients when normalized to the tumor burden (0.003 vs 0.023 cells/µL × mm^2). Patients with follicular lymphoma had a lower tumor burden at retreatment than before the first infusion (847 vs 3981 mm^2).

The investigators concluded that these promising preliminary results revealed favorable responses to retreatment with axicabtagene ciloleucel in patients with follicular lymphoma and high-risk disease characteristics. Further analyses in a larger cohort with longer follow-up are merited.

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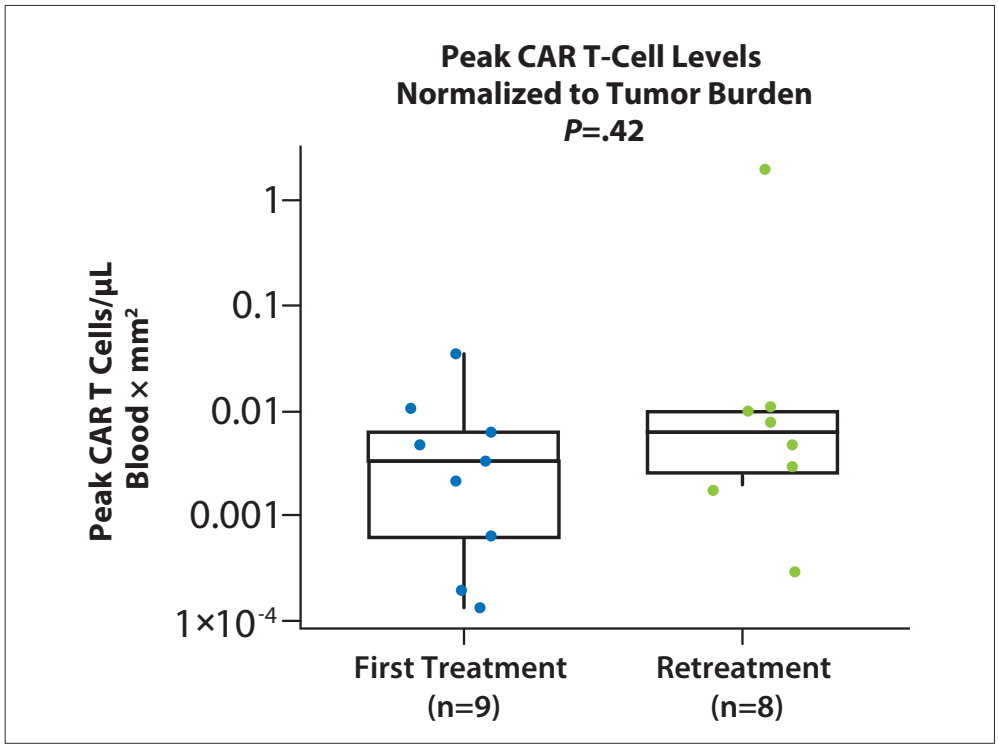

Figure 9. Peak CAR T-cell levels at first treatment and at retreatment among patients in the ZUMA-5 trial. CAR, chimeric antigen receptor. Adapted from Chavez JC et al. ASH abstract 2036. *Blood.* 2020;136(suppl 1).[2]

ZUMA-19: A Phase 1/2 Multicenter Study of Lenzilumab Use With Axicabtagene Ciloleucel in Patients With Relapsed or Refractory Large B-Cell Lymphoma

Proactive strategies that reduce the occurrence of neurologic events are needed to improve the safety of CAR T-cell therapy.[1] During the tumor challenge, CAR T cells produce granulocyte-macrophage colony–stimulating factor (GM-CSF), which leads to myeloid activation and expansion, as well as cytokine production.[2,3] In the ZUMA-1 study, levels of GM-CSF were significantly associated with grade 3 or higher neurologic toxicity. However, no direct association was observed between levels of GM-CSF and ORR.[4] GM-CSF may provoke inflammatory events that lead to neurologic reactions, and inhibition of GM-CSF has the potential to improve the safety of CAR T-cell therapy without impacting efficacy.[1] In preclinical models of toxicity associated with CAR T-cell therapy, neutralization of GM-CSF prevented AEs and enhanced CAR T-cell activity.[5]

Lenzilumab, a humanized monoclonal antibody, neutralizes GM-CSF.[1] The phase 1/2 ZUMA-19 trial will evaluate the potential of lenzilumab to reduce the risk for axicabtagene ciloleucel–related CRS and neurotoxicity in patients with relapsed/refractory LBCL. The trial is currently enrolling participants across sites in the United States. The primary objective of phase 1 will be to evaluate the safety of sequenced therapy with lenzilumab and axicabtagene ciloleucel. The primary objective of the phase 2 portion will be to evaluate the incidence of grade 2 or higher neurologic toxicity with sequenced therapy at the recommended dose of lenzilumab.

Dr Saad Kenderian and colleagues described the study schema for ZUMA-19.[1] The trial will enroll adult patients with LBCL that was refractory to chemotherapy or had relapsed after at least 2 lines of systemic therapy. Other enrollment criteria include a good performance status (ECOG score of 0 or 1), at least 1 measurable lesion, and prior treatment with at least a CD20 monoclonal antibody and an anthracycline-containing chemotherapy. The trial will exclude patients who have a history of Richter transformation chronic lymphocytic leukemia, ASCT within 6 weeks of the axicabtagene ciloleucel infusion, allogeneic stem cell transplant, and prior CD19-targeted therapy or prior CAR T-cell therapy.

After leukapheresis, patients will receive treatment with bridging therapy with corticosteroids (if needed) and conditioning chemotherapy with

fludarabine and cyclophosphamide. The first cohort of patients will then receive lenzilumab at dose level 1, 6 hours before the infusion of axicabtagene ciloleucel. Additional patients will be enrolled in a second cohort to receive lenzilumab at dose level 2 followed by treatment with axicabtagene ciloleucel. Based on the incidence of dose-limiting toxicities identified in phase 1, GM-CSF axis suppression will also be evaluated to inform the recommended phase 2 dose. Each step in the phase 1 dose-escalation trial will be gated based on the incidence of dose-limiting toxicities.

A safety review team will evaluate data from phase 1 after 3 and 6 patients have been assessed for 28 days following CAR T-cell infusion.[1] The team will provide a recommendation regarding further study conduct in phase 1 and progression to phase 2. During the phase 2 trial, the safety review team will meet after 14 patients have been treated and followed for at least 28 days. The primary analysis will be performed after 30 patients treated with the recommended phase 2 dose of lenzilumab followed by axicabtagene ciloleucel have been evaluated for response at 6 months.

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The First Retrospective Commercial Claims–Based Analysis of CAR T–Treated Patients With Relapsed or Refractory Large B-Cell Lymphoma

Dr Lincy Lal and colleagues retrospectively analyzed the Optum Research Database, one of the largest providers of commercial and Medicare Advantage health plans in the United States, to compare health care resource utilization and costs before and after CAR T-cell therapy.[1] The study enrolled adult patients with relapsed/refractory LBCL after 2 lines of therapy. Patients were continuously enrolled in a health care plan for at least 3 months before and 6 months after the CAR T-cell infusion, which occurred within a 2-year period beginning January 2017. This date is after the commercial launch of tisagenlecleucel and axicabtagene ciloleucel.[2,3]

The study included 109 patients, with a mean age of 59 years.[1] Most patients were men (59%), and had received CAR T-cell therapy through a commercial health insurance claim (70%). Their mean Charlson Comorbidity Index was 3.6 before the CAR T-cell infusion. Thirty (28%) patients received CAR T-cell therapy through a clinical trial.

CAR T-cell therapy was administered in an inpatient setting in 82% of cases, whereas 42% of patients required transfer to an intensive care unit.[1] The median hospital length of stay was 18 days for clinical trial patients vs 21 days for non–clinical trial patients. The length of stay in an intensive care unit was 7 days vs 11 days, respectively.

The total standardized costs associated with CAR T-cell therapy were similar regardless of whether patients were treated in the hospital as an inpatient ($529,546; n=63), in the hospital as an outpatient ($521,677; n=16), or through a clinical trial ($360,499; n=30).[1]

Utilization of health care resources was significantly lower after the infusion of CAR T-cell therapy.[1] This decrease was driven by fewer ambulatory visits (–46%), emergency room visits (–49%), and outpatient pharmacy prescriptions (–24%). The mean total health care costs were almost 50% lower after CAR T-cell therapy; mean costs were $128,174 per patient per month before CAR T-cell therapy and $65,786 per patient per month after therapy (P=.008; Figure 10). This difference was predominantly driven by significant reductions in ambulatory costs.

This analysis of claims data was limited by the fact that the accuracy of claims coding can be variable.[1] In this study, medication-specific codes indicating the use of axicabtagene ciloleucel or tisagenlecleucel were rarely seen. Furthermore, health care utilization and costs were based on observations relative to the CAR T-cell infusion and were not adjusted to account for the baseline characteristics of the patients.

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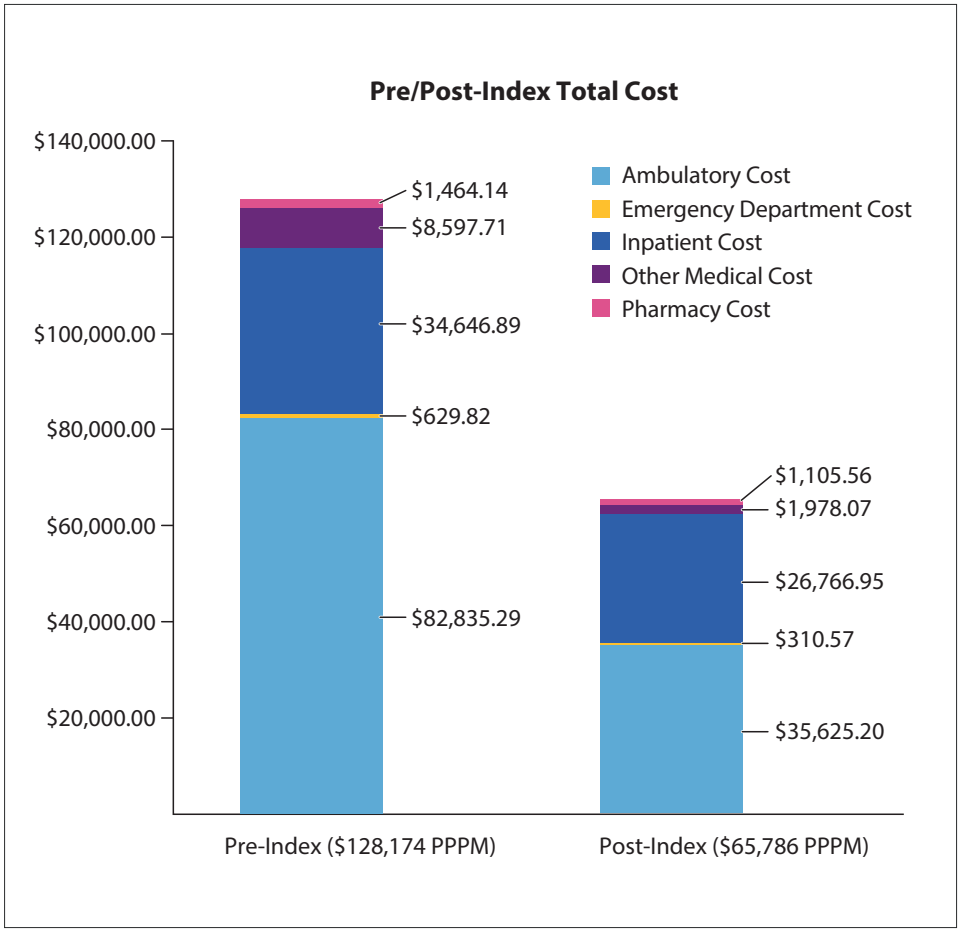

Figure 10. Total health care costs before vs after treatment with CAR T-cell therapy in a retrospective commercial claims–based analysis. CAR, chimeric antigen receptor; PPPM, per patient per month. Adapted from Purdum A et al. ASH abstract 1224. *Blood.* 2020;136(suppl 1).[1]

Steroid Use, Advanced Stage Disease, and ≥3 Lines of Prior Chemotherapy Are Associated With a Higher Risk of Infection Following CD19 CAR T-Cell Therapy for B-NHL: Real World Data From a Large UK Center

A retrospective review evaluated data for 60 adult patients with B-cell NHL treated with tisagenlecleucel (n=19) or axicabtagene ciloleucel (n=41) to identify the incidence and outcome of infection.[1] The patients were not treated with prophylactic antibiotics. Intravenous immunoglobulin was administered for hypogammaglobulinemia in patients with recurrent infections (n=4).

Within 28 days of the CAR T-cell infusion, 44 infections were reported in 28 patients (47%). After day 28, 19 events were reported in 9 patients (15%). Infections were severe in 9 patients (15%) and life-threatening in 7 patients (12%). Two infections resulted or contributed to a patient's death (3.3%). The infections were categorized as bacterial in 56%, respiratory viral in 24%, viral (other) in 14%, and fungal in 6%. Six patients (10%) developed viral reactivations, consisting of cytomegalovirus (n=1), BK virus in the blood or urine (n=2), human herpesvirus 6 (n=1), or adenovirus (n=2). One late COVID-19 infection was reported. There was no association between early infection and severity of CRS (P=.43) or with the use (P=.94) or dose of tocilizumab (P=.54).

Advanced disease (stage 3 or higher) at the time of the CAR T-cell infusion was associated with a higher risk of any infection (odds ratio, 4.2; 95% CI, 1.3-13.4; P=.016). Previous treatment with 3 or more lines of therapy was associated with a higher risk of early infection (odds ratio, 3.0; 95% CI, 1.0-8.9; P=.048). Treatment with corticosteroids corresponded with

a higher risk of early (and overall) infection (odds ratio, 3.0; 95% CI, 1.0-8.6; *P*=.048). Immune effector cell-associated neurotoxicity syndrome was associated with infection after day 30 (*P*=.021). In multivariate analyses, use of corticosteroids (*P*=.03) and treatment with 3 or more lines of prior therapy (*P*=.021) were associated with infections that occurred by 28 days of infusion. A higher risk of any infection corresponded with corticosteroid use (*P*=.049) and disease stage before infusion (*P*=.023).

Reference

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Interim Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients With High-Risk Large B-Cell Lymphoma

ZUMA-12 is a phase 2 multicenter, open-label, single-arm study evaluating the efficacy, safety, and pharmacokinetics of axicabtagene ciloleucel when used as a component of first-line therapy in patients with high-risk LBCL.[1] The trial enrolled adult patients with disease defined either through histology or the International Prognostic Index (IPI; score of ≥3). Patients had good performance status (0 or 1) and had received 2 cycles of chemoimmunotherapy consisting of an anti-CD20 monoclonal antibody and an anthracycline. Additionally, patients had a positive interim positron emission tomography assessment (Deauville score of 4 or 5).

After patients were enrolled in the study and underwent leukapheresis, they were permitted to receive nonchemotherapy bridging therapy if necessary.[1] Patients subsequently received conditioning chemotherapy with fludarabine and cyclophosphamide 3 to 5 days before the infusion of axicabtagene ciloleucel (2 × 10^6 CAR T cells/kg). As of August 25, 2020, 37 patients were enrolled in the trial. Thirty-two patients received conditioning chemotherapy followed by axicabtagene ciloleucel infusion. An additional 3 patients were waiting for CAR T-cell infusion at the time of data cutoff. The median age of the 32 patients who received the CAR T-cell

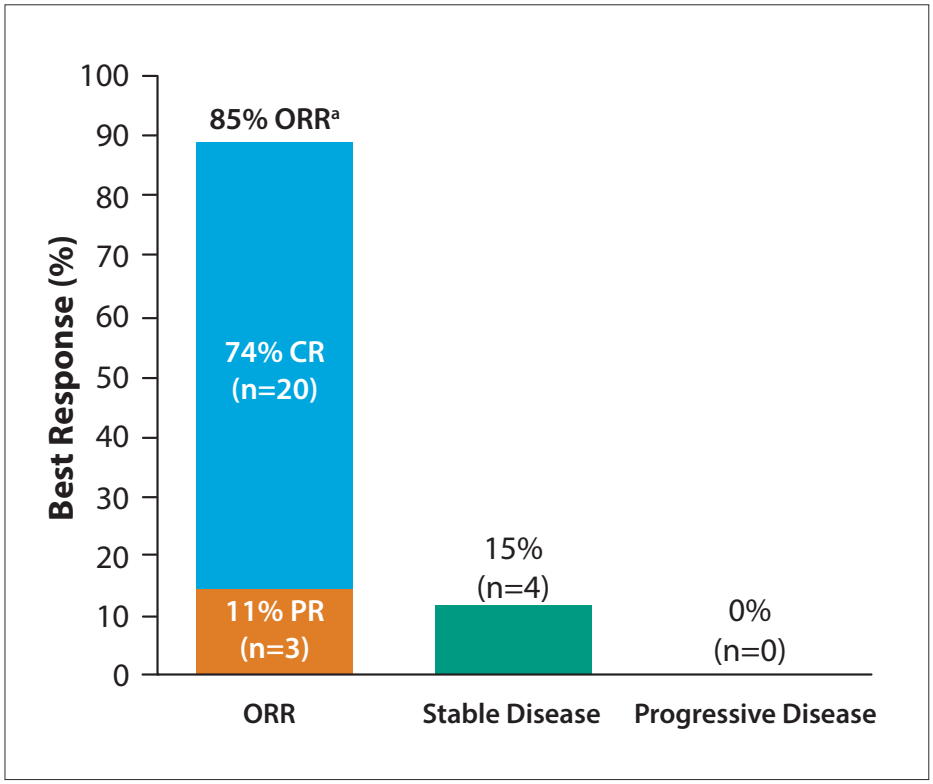

Figure 11. Best response among patients with at least 1 month of follow-up treated with axicabtagene ciloleucel in the phase 2 ZUMA-12 trial. CR, complete response; ORR, overall response rate; PR, partial response. [a]In the cohort evaluable for safety (n=32), the ORR was 88% and the CR rate was 78%. Adapted from Neelapu SS et al. ASH abstract 405. *Blood.* 2020;136(suppl 1).[1]

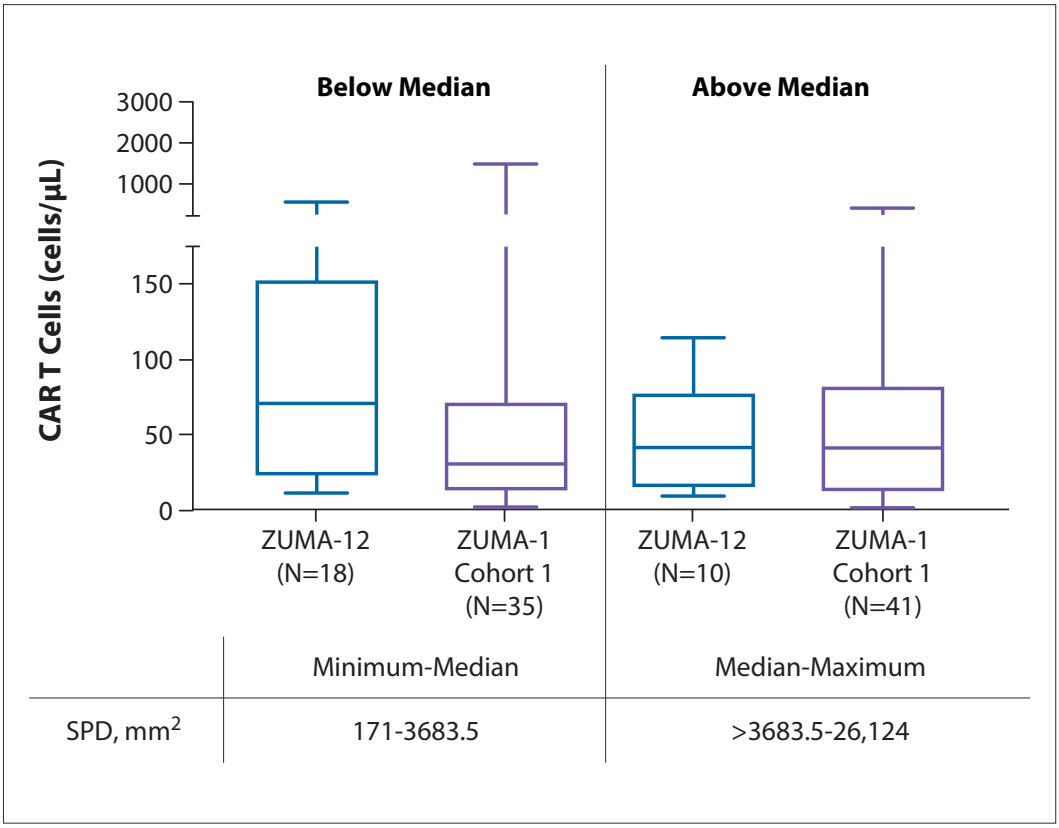

Figure 12. CAR T-cell expansion in the ZUMA-12 trial of axicabtagene ciloleucel. CAR, chimeric antigen receptor; SPD, sum of product diameters. Adapted from Neelapu SS et al. ASH abstract 405. *Blood.* 2020;136(suppl 1).[1]

infusion was 61 years. Two-fifths of patients were ages 65 years or older. Most patients had advanced-stage disease (88%), double-hit or triple-hit lymphoma (53%), and an IPI score of at least 3 (72%). Half of the patients had a Deauville score of 4.

Dr Sattva Neelapu presented an interim efficacy analysis of treated patients who had at least 1 month of follow-up (n=27).[1] After a median follow-up of 9.3 months, the primary endpoint of ORR was 85% (Figure 11). A CR was reported in 74% of patients. An ongoing response at the time of data cutoff was reported in 70% of patients. The median time to an initial objective response and to a CR was 1 month for both endpoints. Among the patients with a partial response or stable disease at the 1-month assessment, 19% subsequently converted to a CR. The median duration of response, PFS, and OS were not reached.

The safety analysis was based on the full set of 32 treated patients.[1] The most common grade 3 or higher AEs attributed to axicabtagene ciloleucel were encephalopathy (16%), elevated alanine aminotransferase (9%), and decreased neutrophil count (9%). There was a single grade 5 event, which was attributed to severe respiratory syndrome coronavirus 2 infection.

All 32 patients developed any-grade CRS, but only 3 patients (9%) experienced a grade 3 or higher case.[1] The median time to onset of CRS was 4 days (range, 1-10). The median duration of CRS was 6 days (range, 1-13). The most common manifestations of CRS were pyrexia (100%), chills (25%), and hypotension (25%). CRS tended to occur approximately 4 days after the CAR T-cell infusion and lasted a median of 6 days. Treatments for CRS included tocilizumab (53%) and corticosteroids (25%). There were no grade 4 or 5 CRS events.

Neurologic events of any grade were observed in 69% of patients; 25% of patients experienced grade 3 or higher events.[1] Neurologic events tended to occur 9 days after CAR T-cell infusion and lasted a median of 6 days. These events were managed with corticosteroids in 24% of patients. Two events were unresolved at the time of data cutoff (both grade 1 events). The 2 neurologic events of grade 4 resolved.

The total number of T cells and CAR T cells infused was comparable in the ZUMA-12 trial and the pivotal ZUMA-1 trial.[1,2] However, there was a higher frequency of CCR7-positive, CD45RA-positive T cells in ZUMA-12 (34%) compared with ZUMA-1 (14%). A higher frequency of CCR7-positive, CD45RA-positive T cells in the preinfusion product was associated with greater expansion of CAR T cells

as compared with ZUMA-1, which suggests improved T-cell fitness in first-line treatment.

The median tumor burden was lower in ZUMA-12 than in ZUMA-1 (2091 vs 3684 mm^2).[1,2] However, there was greater CAR T-cell expansion among patients in ZUMA-12 who had a tumor burden below the median (Figure 12). The median time to peak CAR T cells in the blood was 8 days for ZUMA-12.

Pharmacokinetic profiles were similar for double-hit and triple-hit LBCL with IPI scores of at least 3. Furthermore, several cytokines, including IL-6 and IL-8, were associated with grade 3 or higher cases of CRS and neurologic events in ZUMA-12, consistent with prior findings in ZUMA-1.[1,2]

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Results From LUMMICAR-2: A Phase 1b/2 Study of Fully Human B-Cell Maturation Antigen-Specific CAR T Cells (CT053) in Patients With Relapsed and/or Refractory Multiple Myeloma

CT053 is a fully human B-cell maturation antigen (BCMA)-specific CAR T-cell product that is manufactured in 8 to 10 days and cryopreserved for administration.[1] CT053 has received orphan drug designation by US and European regulatory agencies. LUMMICAR is a phase 1b/2 study evaluating the efficacy, safety, and tolerability of CT053 in patients with relapsed/refractory multiple myeloma.[1] Eligible patients had good performance status and had received at least 3 prior lines of therapy, including a CD38 monoclonal antibody, and were considered refractory to the last line of therapy. There was no selection based on BCMA expression. Patients underwent apheresis and then outpatient lymphodepletion with fludarabine (25 mg/m^2 for 3 days) and cyclophosphamide (500 mg/m^2 for 2 days) before inpatient CAR T-cell infusion. Patients were monitored for 6 months and followed long-term.

The objective of the phase 1 study was to evaluate safety and tolerability, as well as to identify the maximum tolerated dose of CT053 that can be moved forward to a phase 2 trial.[1] The secondary objectives included assessment of efficacy, as well as pharmacokinetics of CT053. The phase 2 study will evaluate the efficacy of CT053 in patients with relapsed multiple myeloma.

Twenty patients were enrolled in the dose-escalation phase of the study; 14 received dose level 0 ($1.5\text{-}1.8 \times 10^8$ cells) and 6 received dose level 1 ($2.5\text{-}3.0 \times 10^8$ cells).[1] Their median age was 62 years, 65% were women, and 55% had high-risk cytogenetics. Most patients (85%) were considered to be triple-refractory, and half were considered penta-refractory. The majority of patients (85%) required bridging therapy for multiple myeloma after apheresis.

The ORR was 94% (17 of 18 patients) after a median follow-up of 6 months. This rate included 5 patients with a CR and 5 patients with a very good partial response. The depth of response appeared to continue to improve with longer follow-up.

ABSTRACT SUMMARY One-Year Follow-Up of ZUMA-2, the Multicenter, Registrational Study of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma

KTE-X19 is an autologous anti-CD19 CAR T-cell therapy currently being evaluated in the ZUMA-2 trial in patients with relapsed/refractory mantle cell lymphoma (Abstract 1120). At a median follow-up of 17.5 months, the ORR was 92% (67% CR rate), with ongoing durable responses in 48% of all patients evaluable for efficacy at time of data cutoff. Among the patients who achieved a CR, 70% remained in response. The ongoing response rates were largely consistent among prognostic subgroups with high-risk disease characteristics. However, the median values for duration of response, PFS, and OS were not reached at the time of the analysis. KTE-X19 therapy had a manageable safety profile with extended follow-up. No new safety signals were observed since the primary analysis. Among 57 patients evaluable for efficacy with data available at baseline, 48 (84%) had detectable B cells at baseline. Compared with patients without a response to treatment, peak CAR T-cell expansion was higher in patients with an ongoing response at 12 months and those who relapsed at 12 months. Additional mechanistic studies are ongoing to further understand the observed pharmacokinetic relationship between response and durability.

The median transgene positivity of the infused product was 28% (range, 13%-57%).[1] The most common toxicity was cytopenia owing to lymphodepletion. Grade 3 or higher hematologic toxicities were observed in all patients, whereas grade 3 or higher infections and infestations were seen in 2 patients (10%). One patient died from unrelated cardiac arrest 127 days after the CT053 infusion.

All-grade CRS was reported in 80% of patients, and all-grade neurotoxicities were observed in 16%.[1] No grade 3 or higher cases of CRS occurred. One patient in the dose level 0 group experienced a grade 3 or higher neurologic event. The median onset to CRS or neurotoxicity was 1 to 2 days, and the median duration was approximately 4 days. One-third of patients required treatment with an infusion of tocilizumab, and approximately 20% of patients received corticosteroids.

CT053 effectively depleted bone marrow plasma cells within 4 weeks, regardless of the dose.[1] Most patients experienced a 25% to 50% reduction in monoclonal proteins throughout the first month. CT053 also normalized serum free light chain levels and reduced soluble BCMA levels by at least 90% within 1 month.

CT053 cells were detected at 3 to 7 days after infusion, and peak expansion occurred within 14 days of infusion.[1] There was no significant difference in median peak vector copies between the 2 dose levels, and CAR T cells persisted for at least 6 months.

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Highlights in CAR T-Cell Therapy From the 62nd American Society of Hematology Annual Meeting and Exposition: Commentary

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Presentations in chimeric antigen receptor (CAR) T-cell therapy at the 62nd American Society of Hematology (ASH) meeting provided updates and new data from studies in aggressive large-cell lymphoma. Data were also presented for earlier treatment strategies and other new settings.

CAR T-Cell Therapy in Aggressive B-Cell Non-Hodgkin Lymphoma

Axicabtagene ciloleucel was the second CAR T-cell therapy approved by the US Food and Drug Administration (FDA), and the first approved for adult patients with lymphoma.[1] The FDA approved axicabtagene ciloleucel based on results of the ZUMA-1 trial, which enrolled patients with refractory aggressive B-cell non-Hodgkin lymphoma.[2] At the ASH meeting, I presented data from a 4-year follow-up analysis of ZUMA-1.[3] The analysis showed that the proportion of patients who were still alive after a single infusion of axicabtagene ciloleucel remained constant, at approximately 44%. This analysis provided data for both the modified intention-to-treat cohort as well as the intention-to-treat cohort. The modified intention-to-treat population included patients who not only had their T cells collected, but also received the CAR T-cell infusion. The intention-to-treat population included all patients who had their T cells collected, regardless of whether they received the infusion. The intention-to-treat population included 10 additional patients who did not receive the CAR T-cell infusion for a variety of reasons. The analysis found that the addition of these patients to the data set had minimal impact on the rates of overall response and complete response. There was also very little difference in the median overall survival and the rate of 4-year overall survival. The take-home message from this analysis is that because axicabtagene ciloleucel is manufactured in a

ABSTRACT SUMMARY Outcomes of Patients in ZUMA-9, a Multicenter, Open-Label Study of Axicabtagene Ciloleucel in Relapsed/Refractory Large B-Cell Lymphoma for Expanded Access and Commercial Out-of-Specification Product

The ZUMA-9 trial compared outcomes in patients treated with axicabtagene ciloleucel administered before commercial availability (cohort 1) vs patients treated with an out-of-specification commercial product (cohort 2; Abstract 2100). In cohort 1, the ORR was 76%, the CR was 64%, and the median OS was 23.8 months, compared with 82%, 54%, and 25.8 months, respectively, in the ZUMA-1 trial. In cohort 2, the ORR was 53%, the CR rate was 36%, and the median OS had not been reached. The frequency and type of treatment-emergent AEs were consistent across ZUMA-9 and ZUMA-1. In the ZUMA-9 trial, only 1 of 6 grade 5 events was related to axicabtagene ciloleucel (systemic mycosis in cohort 2). Grade 3 or higher CRS was less prevalent in ZUMA-9, and there were no grade 5 CRS events. There was a higher incidence of neurologic events in ZUMA-9 (cohorts 1 and 2 low viability subset); however, they tended to occur later than in ZUMA-1. The median peak levels of CAR T cells, CAR T-cell expansion, and peak serum interferon-γ were lower in ZUMA-9 cohort 2 vs ZUMA-1.

relatively quick time frame—17 days from door to door—and because 99% of the time it is possible to produce the CAR T-cell product, there is high fidelity between the proportion of patients who undergo apheresis to manufacture the T-cell product and those who receive the T cells as therapy. This observation is reflected in the fact that the outcomes were similar between patients in the intention-to-treat and modified intention-to-treat cohorts.

The analysis also examined the kinetics of CAR T cells over time in patients who maintained their response for more than 2 years, as well as what happens to the B cells throughout that period. Previous reports indicated that although gene-marked CAR T cells persist in the blood for many years after a CAR T-cell infusion, there is recovery of B cells in these patients, even in those with an ongoing response.[4] These gene-marked CAR T cells are not necessarily still exerting an anti–B-cell immune response. In this update, the investigators further characterized these B cells in terms of clonality and diversity. We showed that nearly the entire B-cell repertoire was reconstituted in these patients. Therefore, persistence of CAR T cells was not necessarily linked to ongoing recovery in the ZUMA-1 trial.[2]

Data from the ZUMA-1 trial and other early studies of CAR T-cell therapy have provided information about biomarkers that can predict for toxicities.[2,5] Those patients who have elevated levels of granulocyte-macrophage colony–stimulating factor (GM-CSF) are at increased risk for developing high-grade neurologic toxicity.[5] Other data suggest that the neurologic toxicity might be attributable to cytokine production by the monocytes and macrophages that are stimulated by the GM-CSF.[6] The ZUMA-19 study is an ongoing trial that is evaluating the addition of lenzilumab, an anti–GM-CSF antibody used prophylactically with axicabtagene ciloleucel, in patients with relapsed and refractory large B-cell lymphoma.[7] The aim of the study is to decrease rates of high-grade neurologic toxicity, and thus make administration of these products safer. The trial is currently enrolling patients.

In the ZUMA-1 study, a cohort of the patients received prophylactic tocilizumab in an attempt to improve the toxicity profile.[2] Tocilizumab is an interleukin 6 (IL-6) receptor antibody. Although the patients in this cohort appeared to have a lower rate of high-grade cytokine release syndrome, there was a suggestion that they had a slightly increased incidence of high-grade neurologic toxicity. This toxicity was thought to be associated with higher levels of IL-6 in both the blood and the central nervous system. Dr Paolo Caimi presented a retrospective analysis of patients who received CAR T-cell therapy, with or without prophylactic tocilizumab, at a single institution.[8] The patients in this study had received a 4-1BB CAR T-cell therapy as opposed to a CD28 CAR T-cell therapy (such as axicabtagene ciloleucel). The study compared outcomes among patients who did or did not receive prophylactic tocilizumab. Patients who received tocilizumab had lower rates of severe cytokine release syndrome and no excess neurologic toxicity. It should be noted that neurologic toxicity is less common with 4-1BB CARs vs CD28 CARs.[2,9,10] In addition, the group of patients who did not receive prophylactic tocilizumab had characteristics that may have increased their risk of developing neurologic toxicity, including high tumor burden, high pretreatment levels of lactate dehydrogenase, and inflammatory markers. With these differences in the control arm and the comparator arm, it is difficult to draw conclusions from this study. It is not known whether prophylactic tocilizumab is helpful or harmful in this setting.

Since the FDA approval of CAR T-cell therapy, several real-world analyses have examined efficacy and safety among a broader group of patients who might not meet the eligibility criteria for a clinical trial. Data suggest that the response rates and durability are similar to those in clinical trials, and toxicity is not increased.[11] At the ASH meeting, Dr Lincy Lal presented results from the first retrospective commercial claims–based analysis of CAR T-cell therapy in patients with relapsed and refractory large B-cell lymphoma.[12] This study included an

analysis of cost-effectiveness. There is concern about the cost of CAR T cells, both the product itself and the expense of associated care. An interesting aspect of this study is that it evaluated the cost of care and utilization of health care resources for patients before and after treatment with CAR T-cell therapy. The cost of care was lower after treatment with CAR T-cell therapy than in the months preceding it, suggesting that CAR T-cell therapy may be a cost-effective way of treating relapsed large-cell lymphoma given the definitive and finite nature of this therapy.

Moving CAR T cells up a line of therapy in high-risk large B-cell lymphoma is of particular interest, in order to spare patients ineffective therapies and because CAR T cells derived from a patient may work better if he or she has received less immunosuppressive therapy. We are awaiting the results of phase 3 clinical trials of second-line therapy comparing axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel vs the standard of care, which is salvage chemotherapy and autologous transplant.[13-15] At the ASH meeting, Dr Sattva Neelapu presented the results of an interim analysis of ZUMA-12, an open-label, phase 2 trial that evaluated axicabtagene ciloleucel in the "first-line" setting.[16] The trial enrolled patients with large B-cell lymphoma at high risk, which was defined as a high International Prognostic Index score or double-hit cytogenetics. All patients received 2 cycles of up-front chemoimmunotherapy, and then underwent restaging based on the results of a positron emission tomography (PET) scan. Patients without a complete response after 2 cycles of therapy received axicabtagene ciloleucel at that point, which was considered to be the first-line setting. The rates of overall response and complete response were very high, at 85% and 74%, respectively. The study lacked a control arm, so the comparison is against a historical control. However, these rates are higher than those reported in patients who continue treatment with chemotherapy after 2 cycles of up-front chemotherapy do not achieve a complete response according to PET.[17,18] The responses appeared durable. After a median follow-up of 9.3 months, 70% of patients had an ongoing response at data cutoff. The toxicity profile was similar to that seen with the use of axicabtagene ciloleucel in later lines of therapy.[2] An interesting finding was that the profile of the T cells used to manufacture the product in the ZUMA-12 trial was more favorable than that found in ZUMA-1.[2] The patients who were less heavily pretreated had a higher proportion of CCR7-positive, CD45RA-positive T cells compared with the more heavily pretreated patients in the ZUMA-1 study. This difference was associated with higher peak CAR T-cell expansion, which might account for the greater degree of efficacy.

The open-label ZUMA-9 study was created after completion of the ZUMA-1 study—while axicabtagene ciloleucel was under FDA review—to provide patients with continued access to treatment. These patients were enrolled into cohort 1 of ZUMA-9. Once axicabtagene ciloleucel was approved by the FDA, a second cohort was opened, which enrolled patients who had received axicabtagene ciloleucel products that did not meet FDA release specifications. I presented results of the ZUMA-9 trial at the ASH meeting.[19] The population in cohort 1 was essentially the same group of patients who had received treatment in ZUMA-1. Efficacy and toxicity endpoints were similar among patients in cohort 1 and ZUMA-1. For cohort 2, there were some interesting findings. Treatment with products that would not have met FDA release specifications led to lower rates of overall response and complete response compared with ZUMA-1. CAR T-cell expansion was more muted than in ZUMA-1. The proportion of healthy T cells in the T-cell product was less favorable. However, the patients in this cohort still had a better outcome compared with historical controls. Therefore, the efficacy achieved with CAR T-cell products that do not meet FDA specifications might be lower compared with standard CAR T-cell products, but it still exceeds that reported with other available treatments.

Newer Settings for CAR T-Cell Therapy

Several presentations at the ASH meeting provided data for axicabtagene ciloleucel in newer settings outside of aggressive B-cell non-Hodgkin lymphoma. The phase 2 ZUMA-5 study evaluated axicabtagene ciloleucel in relapsed and refractory indolent B-cell non-Hodgkin lymphoma.[20] These patients had already received third-line therapy and beyond. Available treatments would likely achieve few complete responses and response durations ranging from 10 to 13 months.

In ZUMA-5, axicabtagene ciloleucel led to high rates of complete response, at approximately 76% for all patients and 80% for those with follicular lymphoma.[20] Many of the responses were durable. At 17.5 months, 64% of patients with follicular lymphoma had an ongoing response. The safety profile was more favorable in patients with follicular lymphoma than in patients with aggressive B-cell non-Hodgkin lymphoma. There were lower rates of any-grade cytokine release syndrome, high-grade cytokine release syndrome, and high-grade neurologic toxicity. In addition, these toxicities, when they occurred, arose later in the treatment course; this is important because it has implications for the possibility of outpatient dosing. The results of this study were exciting to see in patients with an historically incurable disease. Longer follow-up will indicate whether axicabtagene ciloleucel, or any of the CAR T-cell therapies, have the potential to cure patients with these diseases.

Dr Julio Chavez presented data for patients in the ZUMA-5 study who were re-treated with axicabtagene ciloleucel after relapse.[21] In ZUMA-5, retreatment with axicabtagene ciloleucel was an option for patients who maintained their response for at least 3 months and then relapsed. Eleven patients were re-treated; most had follicular lymphoma. Almost all of these patients had a complete response to their first line of therapy with axicabtagene ciloleucel. Their duration of response to their first infusion ranged from approximately 5 months to a year. The response rate to the second infusion of axicabtagene ciloleucel was 100%. Follow-up was short, so it is not known if these responses were durable. The patients' levels of CAR T-cell expansion were similar at the initial treatment and upon retreatment. Many patients who were re-treated had a lower tumor burden. There is a theory that a high ratio of CAR T-cell expansion to tumor burden may predict for durable remissions. Long-term follow-up will reveal whether retreatment in a patient with a lower tumor burden, combined with the same level of CAR T-cell expansion, leads to more durable responses than were seen with initial treatment.

Dr Michael Wang presented a follow-up analysis of the ZUMA-2 study, which evaluated brexucabtagene autoleucel in patients with relapsed or refractory mantle cell lymphoma previously treated with chemoimmunotherapy and a BTK inhibitor.[22,23] Brexucabtagene autoleucel has the same CAR T-cell construct as axicabtagene ciloleucel. The only difference is that brexucabtagene autoleucel has an extra step in the manufacturing process that purges the product of any CD19-positive circulating tumor cells. The update showed excellent durability of response. The median duration of response, progression-free survival, and overall survival had not been reached at a median follow-up of 17.5 months.[22] Like follicular lymphoma, mantle cell lymphoma is historically incurable. Longer-term follow-up from ZUMA-2 will show whether treatment is changing the natural history of the disease and turning an incurable lymphoma into a curable one.

Evolving Strategies

Dr Rongli Zhang presented results from a Chinese study of anti-CD19 CAR T-cell therapy in patients with B-cell ALL.[24] CD19 CAR T cells are approved for pediatric and young adult patients with B-cell ALL. For these patients, the best course of treatment after CD19 CAR T-cell therapy is unknown. Approximately 50% of these patients will be cured. It is unclear whether patients with a good response should undergo allogeneic stem cell transplant or observation. The study by Dr Zhang approached this question from a different perspective. Many patients with B-cell ALL will have received an allogeneic stem cell transplant before they are eligible for CAR T-cell therapy. Treatment with CAR T cells is given after relapse. Historically, CAR T cells have been manufactured by collecting the T cells from the patients themselves, which should be donor-derived T cells, because the patient's immune system will be reconstituted by the donor. Then, the T cells are administered back to the patient. An alternative is to manufacture the CAR T-cell product with T cells from donors, who are not cancer patients and who have not been exposed to cancer therapies. These T cells should therefore be stronger.

The study by Dr Zhang suggested that this strategy is a feasible option for the treatment of patients after allogeneic stem cell transplant. The study was performed in a small group of patients and lacked a control arm. It did not provide data for key endpoints, such as graft-vs-host disease.

The FDA is expected to approve CAR T-cell therapies that are directed against the B-cell maturation antigen (BCMA), which is expressed on plasma cells. This target is highly attractive in multiple myeloma. The CAR itself is derived from a murine antibody fragment, which might be rejected in some patients. The phase 1b/2 LUMMICAR-2 study evaluated a fully humanized BCMA CAR T cell.[25] The hope is that a fully humanized product will lead to less host rejection of the CAR itself, resulting in longer persistence and/or greater expansion and, ultimately, greater efficacy and durability of response. The early results from this study appear promising. This dose-finding study evaluated 2 doses, and lacked a comparator arm. The response rate was 94%, with 5 complete responses, 5 very good partial responses, and 7 partial responses. The treatment cleared plasma cells from the bone marrow. There was rapid reduction in free light chains.

It is not known whether this treatment will be associated with longer persistence or greater expansion. In patients with multiple myeloma, BCMA CARs are associated with high response rates, but short durations of response ranging from 9 to 12 months.[26] The hope is that expanding CAR T-cell persistence or improving CAR T-cell expansion may lead to deeper and more durable responses

Disclosure

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