

**A SPECIAL MEETING REVIEW EDITION**

**Highlights in Aggressive Non-Hodgkin Lymphoma  
From the 2017 American Society of Clinical  
Oncology Annual Meeting**

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**Special Reporting on:**

- Clinical and Biologic Covariates of Outcomes in ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucef (KTE-C19) in Patients With Refractory Aggressive Non-Hodgkin Lymphoma
- Radiotherapy to Bulky Disease Can Be Spared in Elderly DLBCL Patients With a Negative PET After Immunochemotherapy: Results of a Planned Interim Analysis of the OPTIMAL>60 Study of the DSHNHL
- Characterization of Anti-CD19 Chimeric Antigen Receptor T Cell-Mediated Tumor Microenvironment Immune Gene Profile in a Multicenter Trial (ZUMA-1) With Axicabtagene Ciloleucef
- CR Rates in Relapsed/Refractory Aggressive B-NHL Treated With the CD19-Directed CAR T-Cell Product JCAR017 (TRANSCEND NHL 001)
- Phase II Study of Single-Agent Copanlisib in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma
- Product Characteristics Associated With in Vivo Expansion of Anti-CD19 CAR T Cells in Patients Treated With Axicabtagene Ciloleucef
- Comparative Double-Blind Randomized Trial of 2 Rituximab Products in Patients With CD20+ Diffuse Large B-Cell Lymphoma

**PLUS Meeting Abstract Summaries**

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CAR T-cell therapies are investigational and not FDA approved

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## Clinical and Biologic Covariates of Outcomes in ZUMA-1: A Pivotal Trial of Axicabtagene Ciloleucel (KTE-C19) in Patients With Refractory Aggressive Non-Hodgkin Lymphoma

**D**iffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL).<sup>1</sup> Malignant cells of DLBCL are characterized by the expression of CD19, CD20, and CD79A, which are the classic B-cell

markers that are found on normal B cells. DLBCL is classified into 2 subtypes: germinal center B-cell-like (GCB) or non-GCB, which includes activated B-cell like (ABC) DLBCL. The standard first-line treatment for patients with DLBCL is rituximab

plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Patients who relapse are treated with salvage chemotherapy, followed by autologous stem cell transplant (SCT). Currently, there is no standard treatment for patients with refractory disease, which includes those who did not respond to first-line or salvage therapy and those who relapsed after SCT. Treatment with chemoimmunotherapy or SCT generally yields worse outcomes in patients with the non-GCB subtype vs those with GCB DLBCL.

Chimeric antigen receptor (CAR) T-cell therapy has been developed to enable genetically engineered T cells to recognize specific tumor antigens. Axicabtagene ciloleucel (KTE-C19) is an autologous CAR T-cell therapy with CD3 $\zeta$ /CD28-based signaling that targets cells expressing CD19. Production involves apheresis followed by enrichment for T cells, T-cell activation with anti-CD3 antibodies in the presence of interleukin-2, introduction of the CAR by retroviral transduction, expansion of the genetically modified T-cell population, and freezing and shipping to the clinical site. Dr Frederick Locke presented findings from the ZUMA-1 trial (A Phase 1-2 Multi-Center Study Evaluating KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma), which investigated CAR T-cell therapy in NHL patients.<sup>2,3</sup> This multicenter, registrational trial enrolled patients with refractory, aggressive NHL at 22 sites. The modified intent-to-treat cohort included 101 patients. The primary analysis provided data for 92 patients: 72 with DLBCL and 20 with primary mediastinal large B-cell lymphoma or transformed follicular lymphoma. Patients initially received

**Table 1.** Best Overall Response in the ZUMA-1 Trial<sup>a</sup>

	ZUMA-1 Phase 2 (mITT population)					
	DLBCL (n=77)		TFL/PMBCL (n=24)		Combined (n=101)	
	ORR	CR	ORR	CR	ORR	CR
Best Response (%)	82	49	83	71	82	54
Ongoing Response (%)	36	31	67	63	44	39

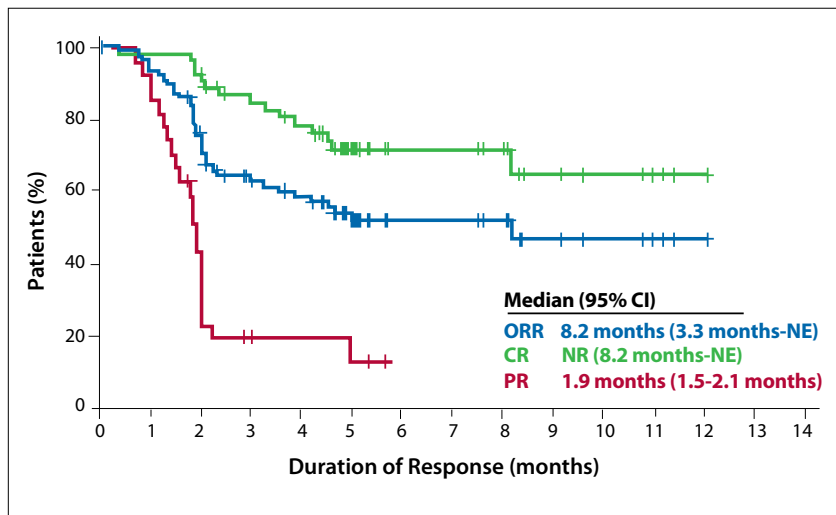
<sup>a</sup>According to investigator assessment.

CR, complete response; DLBCL, diffuse large B-cell lymphoma; mITT, modified intent-to-treat; ORR, objective response rate; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma; ZUMA-1, A Phase 1-2 Multi-Center Study Evaluating KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma.

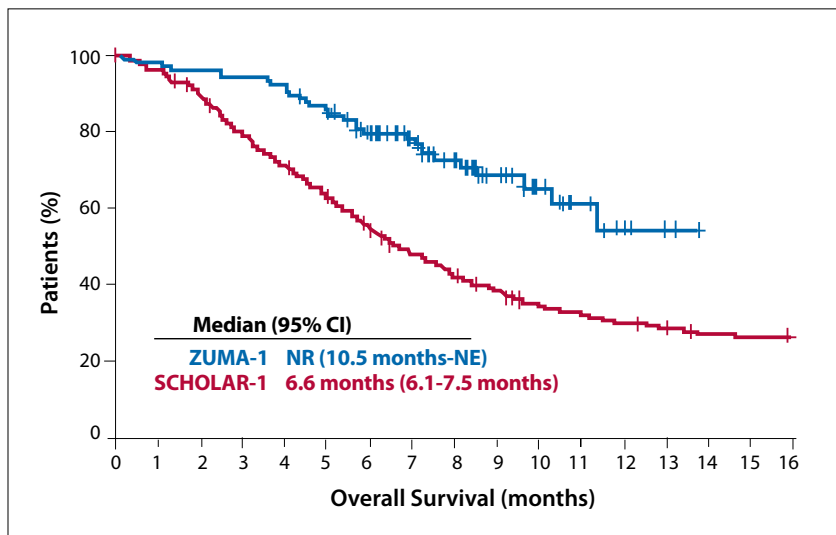
Data from Locke FL et al. ASCO abstract 7512. *J Clin Oncol.* 2017;35(15 suppl).<sup>3</sup>

### ABSTRACT SUMMARY L-MIND: MOR208 Combined With Lenalidomide in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma—A Single-Arm Phase II Study

An open-label, multicenter, single-arm, phase 2 study was conducted to evaluate MOR208 plus lenalidomide in patients with relapsed or refractory DLBCL who were not candidates for SCT (Abstract 7514). MOR208 is a humanized, Fc-engineered antibody that binds to CD19. Patients with relapsed or refractory DLBCL who had received 1 to 3 prior treatments received MOR208 (12 mg/kg) on days 1, 8, 15, and 22 of cycles 1 to 3 and then on days 1 and 15 of cycles 4 to 12. Patients also received daily lenalidomide (25 mg). Patients had a median age of 73 years (range, 47-82 years). Most patients had Ann Arbor stage III/IV disease (59%), and half had received 1 prior line of therapy. The ORR in 34 evaluable patients was 56%, including 32% CRs. With a median follow-up of 5.6 months, responses were ongoing in 16 of 19 patients (84%). The median time to response was 1.8 months. Treatment-related serious AEs occurred in 6 patients and included pneumonia, febrile neutropenia, agranulocytosis, bronchitis, tumor flare, and pyrexia. All 6 patients recovered. A reduction in the dose of lenalidomide was required in 12 patients (27%).



**Figure 1.** The duration of response among patients in the ZUMA-1 trial. CR, complete response; NE, not estimable; ORR, overall response rate; PR, partial response; ZUMA-1, A Phase 1-2 Multi-Center Study Evaluating KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Locke FL et al. ASCO abstract 7512. *J Clin Oncol.* 2017;35(15 suppl).<sup>3</sup>



**Figure 2.** Overall survival in the ZUMA-1 and SCHOLAR-1 studies. NE, not estimable; NR, not reached; SCHOLAR-1, Retrospective Non-Hodgkin Lymphoma Research; ZUMA-1, A Phase 1-2 Multi-Center Study Evaluating KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma. Adapted from Locke FL et al. ASCO abstract 7512. *J Clin Oncol.* 2017;35(15 suppl).<sup>3</sup>

conditioning therapy consisting of cyclophosphamide (500 mg/m<sup>2</sup>) and fludarabine (30 mg/m<sup>2</sup>) on each of 3 days. Patients then received an infusion of  $2 \times 10^6$  CAR T cells/kg.

The patients' median age was 58

years (range, 23-76 years), and 24% were age 65 years or older. Two-thirds were male, 85% had stage III/IV disease, and 69% had received 3 or more prior therapies. The mean turnaround time from apheresis to delivery of

axicabtagene ciloleucel was 17 days.

After a median follow-up of 8.7 months, the objective response rate (ORR) was 82%, including a complete response (CR) rate of 54% (Table 1). The median duration of response was 8.2 months (95% CI, 3.3 to not estimable) for the entire study population and not reached in patients with a CR (Figure 1). The median progression-free survival (PFS) was 5.9 months (95% CI, 3.4-9.8 months). Results remained similar when analyzed according to age, disease stage, risk score, extranodal disease, bulky disease, tocilizumab use, corticosteroid use, and the line of treatment to which the patient was refractory. Median overall survival (OS) was not reached, and 6-month OS was 80%. The results compare favorably with the outcomes for patients with refractory aggressive disease in the SCHOLAR-1 (Retrospective Non-Hodgkin Lymphoma Research) meta-analysis, which demonstrated an ORR of 26%, including a CR rate of 8%, a median OS of 6.6 months, and a 6-month OS of 55% (Figure 2).<sup>4</sup> In ZUMA-1, 17 patients with ABC DLBCL had an ORR of 76%, including a CR rate of 59%, and 49 patients with GCB DLBCL had an ORR of 88%, with a 57% CR rate.

Adverse events (AEs) of grade 3 or higher were reported in 95% of patients. Cytokine-release syndrome of grade 3 or higher was observed in 13% of patients. In most patients, it resolved, with the exceptions of a patient with hemophagocytic lymphohistiocytosis and a patient with cardiac arrest. Neurologic events of grade 3 or higher were observed in 28% of patients. All episodes resolved, except in a patient who developed grade 1 memory impairment. The most common treatment-emergent AEs of grade 3 or higher were anemia (43%), neutropenia (39%), and decrease in neutrophil count (32%). Three patients died.

CAR T-cell exposure was associated with clinical response. Among patients with an ongoing response,

CAR T-cell exposure was 6.4-fold higher than in patients with no response ( $P=.0001$ ). Patients who responded and then relapsed had a 4.5-fold greater CAR T-cell exposure over patients with no response ( $P=.003$ ). The numerical value of the CAR T-cell area under the curve (AUC) was higher among patients with an ongoing response than in those who relapsed, but the difference was not statistically significant.

CD19 expression was detected among 74 patients (90%) at baseline.

The median CD19 H-score was 210 (range, 0-300). Response rates, CR rates, AEs, and levels of median peak CAR T cells did not differ according to the CD19 H-score. The use of tocilizumab or corticosteroids did not impact response rates, CAR T-cell levels, or toxicities.

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## Radiotherapy to Bulky Disease Can Be Spared in Elderly DLBCL Patients With a Negative PET After Immunochemotherapy: Results of a Planned Interim Analysis of the OPTIMAL>60 Study of the DSHNHL

In patients with lymphoma, radiation therapy is used primarily for consolidation.<sup>1</sup> Current tools allow localized delivery of radiation therapy to limit side effects. Several studies have examined whether radiation treatment can be reduced or eliminated in certain patient populations. Systemic chemoimmunotherapy has proven effective in patients with aggressive NHL. The phase 3 RICOVER-60 trial (Combination Chemotherapy With or Without Rituximab in Treating Older Patients With Non-Hodgkin's Lymphoma) investigated the role of additive radiotherapy for bulky and extralymphatic disease in patients with aggressive B-cell lymphoma.<sup>2,3</sup> RICOVER-60 enrolled patients ages 61 to 80 years. Enrollment criteria permitted any stage of disease and any international prognostic index (IPI) score.

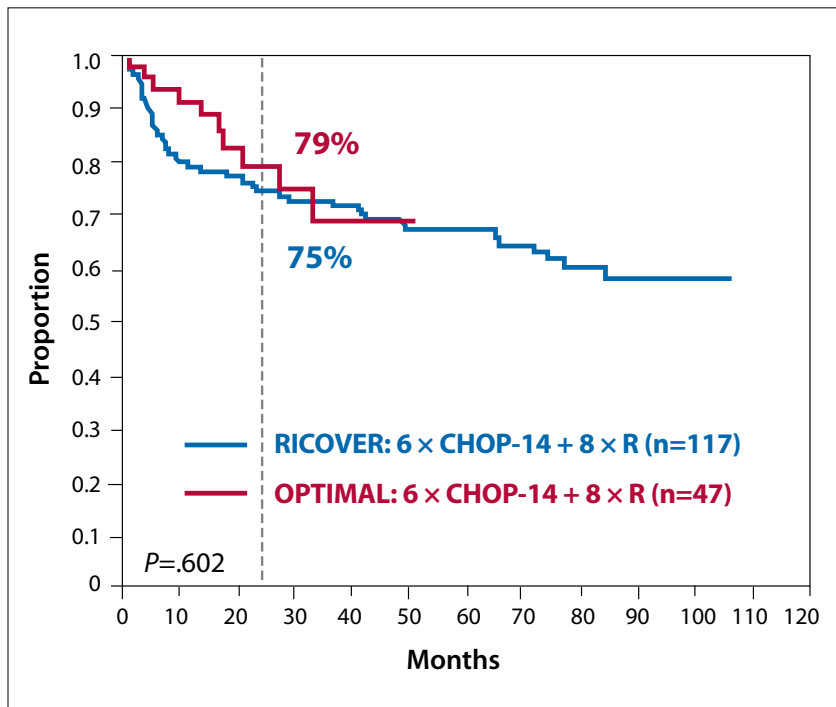
The trial initially investigated 4 treatment arms consisting of 6 or 8

cycles of CHOP alone or with rituximab (R-CHOP). Patients were also treated with involved-field radiotherapy at sites of initial bulky disease and extralymphatic involvement. However, the trial was stopped after a planned interim analysis showed improved PFS and OS for the patients treated with 6 cycles of R-CHOP administered every 14 days plus 2 additional courses of rituximab. The trial was prospectively amended to compare the same treatment without consolidation radiotherapy (RICOVER-noRTh).

After a median observation time of 39 months, a multivariate analysis of 78 patients from RICOVER-60 and 35 patients from RICOVER-noRTh showed a reduction in event-free survival for the patients with bulky disease who did not receive additive radiation therapy (HR, 2.1; 95% CI, 1.3-3.5;  $P=.005$ ). A trend toward inferiority without radiation was observed for PFS (HR, 1.8; 95%

CI, 1.0-3.3;  $P=.058$ ). The randomized phase 3 UNFOLDER trial (Unfavorable Low-Risk Patients Treated With Densification of R-Chemo Regimens) compared 6 cycles of R-CHOP administered every 14 or every 21 days, with or without radiation therapy, in patients with aggressive B-cell NHL.<sup>4</sup> Patients were ages 18 to 60 years and exhibited bulky disease or extranodal involvement at baseline. The trial demonstrated inferior event-free survival in patients who did not receive consolidative radiation (81% vs 65%;  $P=.004$ ). Both of the arms without radiotherapy were halted early based on increased rates of relapse.

Dr Michael Pfreundschuh presented the interim data from the open-label phase 3 OPTIMAL>60 trial (OPTIMAL>60 / DR. CHOP, Improvement of Therapy of Elderly Patients With CD20+ DLBCL Using Rituximab Optimized and Liposomal Vincristine). This study prospectively



**Figure 3.** Progression-free survival in the OPTIMAL>60 and RICOVER-60 studies. CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; OPTIMAL>60, OPTIMAL>60 / DR. CHOP, Improvement of Therapy of Elderly Patients With CD20+ DLBCL Using Rituximab Optimized and Liposomal Vincristine; R, rituximab; RICOVER-60, Combination Chemotherapy With or Without Rituximab in Treating Older Patients With Non-Hodgkin's Lymphoma. Adapted from Pfreundschuh M et al. ASCO abstract 7506. *J Clin Oncol.* 2017;35(15 suppl).<sup>5</sup>

#### ABSTRACT SUMMARY Total 1-Year Cost of Diffuse Large B-Cell Lymphoma Beyond First Line Therapy: A Retrospective Cohort Analysis

A retrospective cohort study estimated the costs associated with second-line treatment for DLBCL patients who relapsed after first-line treatment (Abstract e18333). The study included adults from a large research database who had received first-line R-CHOP for their DLBCL. The study defined nonrelapsed patients as those who did not receive second-line treatment for at least 2 years (n=1157), and second-line patients as those who received second-line therapy other than R-CHOP (n=217). Among the 61 patients who underwent a hematopoietic SCT within 1 year, 42.6% relapsed early, 24.6% relapsed late, and 32.8% had refractory disease (P=.05). Mean total cost of treatment was \$210,488 (standard deviation, \$172,851) in second-line patients and \$25,044 (standard deviation, \$32,441) in nonrelapsed patients. Among the second-line patients, the mean total 1-year cost was \$232,796 for those in early relapse, \$213,866 for those in late relapse, and \$191,079 in those who were refractory (P=.3314). For patients who underwent hematopoietic SCT, cumulative 1-year costs were \$301,426, and cumulative 2-year costs were \$421,739.

investigated whether consolidation with radiation therapy can be spared in elderly DLBCL patients with a negative positron emission tomography (PET) scan after R-CHOP therapy.<sup>5</sup> OPTIMAL>60 enrolled patients ages 61 to 80 years with CD20-positive DLBCL. Patients had an IPI score of 2 to 4, or an IPI of 1 with bulky disease. Patients were randomly assigned in a 2 x 2 factorial design to 6 cycles of standard CHOP or a modified version that replaced conventional vincristine with liposomal vincristine (2 mg/m<sup>2</sup>). Chemotherapy was administered in 14-day cycles. Half of the patients in each chemotherapy cohort received 8 cycles of rituximab (375 mg/m<sup>2</sup>) every 2 weeks, and half received 12 cycles of rituximab (375 mg/m<sup>2</sup>) on an optimized schedule starting 4 days prior to day 1 of chemotherapy and extending to day 238 (Opti-R). Patients with PET-positive bulky disease after 6 cycles of chemotherapy received radiation therapy (39.6 Gy).

The planned interim analysis was conducted after 40% of expected results occurred. The results were compared with those from the group of patients in RICOVER-60 who received 6 cycles of R-CHOP every 14 days plus 2 extra doses of rituximab followed by radiation therapy to sites of bulky disease.

Data were available for 187 patients in the OPTIMAL>60 trial and 117 patients in the RICOVER-60 trial. Approximately half of patients in each cohort had bulky disease. There were some differences in the baseline demographics between the studies. Median patient age was 79 years in OPTIMAL>60 vs 68 years in RICOVER-60 (P=.021). Patients in the OPTIMAL>60 group had higher levels of lactate dehydrogenase (P=.022), fewer patients with an Eastern Cooperative Oncology Group (ECOG) performance status of greater than 1 (P=.001), more patients with extranodal involvement (P<.001), more patients with higher IPI scores

( $P=.041$ ), and fewer patients with B symptoms ( $P=.020$ ).

In the OPTIMAL>60 trial, PET was performed in 166 of 187 patients. Patients did not receive radiation therapy for several reasons, such as progressive disease (44%), medical reasons or toxicity (50%), and negative biopsy (6%). Among the 166 patients with bulky disease who underwent PET, 80 (48%) had PET-positive disease after 6 cycles of chemotherapy, and 62 of 187 patients received radiation therapy. In RICOVER-60, 67 of 117 patients (57%) were irradiated. Therefore, the relative reduction in radiation therapy for patients in OPTIMAL>60 was 42%.

Despite the higher prevalence of patients with unfavorable characteristics in OPTIMAL>60, the outcomes were noninferior compared with the

RICOVER-60 cohort. After a median observation time of 2 years, PFS was 79% in OPTIMAL>60 vs 75% in RICOVER-60 ( $P=.602$ ; Figure 3). Multivariate analyses showed no difference ( $P=.261$ ). OS was 88% vs 78%, respectively ( $P=.307$ ). The 2 treatments were again similar based on multivariate analysis ( $P=.121$ ). In OPTIMAL>60, the rates of PFS at approximately 45 months were an estimated 78% for patients who were PET-negative, 35% for patients with PET-positive disease who were not treated with radiation therapy, and 72% for PET-positive patients who received radiation therapy. Dr Pfreundschuh concluded that radiation therapy can be withheld without compromising outcomes in patients with PET-negative bulky disease after immunochemotherapy.

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## Characterization of Anti-CD19 Chimeric Antigen Receptor T Cell–Mediated Tumor Microenvironment Immune Gene Profile in a Multicenter Trial (ZUMA-1) With Axicabtagene Ciloleucel

The axicabtagene ciloleucel CAR molecule consists of 3 sections: (1) a single-chain variable domain that contains the binding portion of an anti-CD19 monoclonal antibody; (2) a hinge/transmembrane domain; and (3) an intracellular signaling domain.<sup>1</sup> The latter includes the signaling domains from CD28 and CD3 $\zeta$ . Antigen binding initiates intracellular signaling that results in T-cell activation and the release of key cytokines, chemokines, and effector molecules that lead to tumor cell death. In the phase 3 ZUMA-1 trial, treatment with axicabtagene ciloleucel significantly improved the ORR compared with the prespecified rate of 20% previously reported in patients with

refractory aggressive NHL ( $P<.0001$ ).<sup>2</sup> The CR rate was 7-fold higher than the historical control rate of 8%.<sup>3</sup>

To further characterize the effects of anti-CD19 CAR T-cell therapy, a post hoc analysis was conducted on data from ZUMA-1 to determine the immune gene signature of the tumor microenvironment after CAR T-cell infusion in patients with aggressive B-cell NHL.<sup>4</sup> Paired biopsies were collected before treatment with axicabtagene ciloleucel and within 3 weeks after treatment ended. Specimens were analyzed by digital gene expression using a prespecified bioinformatics algorithm to *IGES15* and *IGES21*, 2 genes believed to be involved in immune-mediated tumor regression.

The prespecified gene panel included genes associated with effector and Th1 cell functions; non-T-cell genes, such as those related to the interferon pathway; and genes that encode chemokines, immune checkpoints, and cytokines. Queried genes included those associated with T-cell cytotoxicity, differentiation, attraction, activation, and adhesion pathways; immune orientation; angiogenesis suppression; immune coinhibition; cancer stem cell pathways; and Th1 orientation. A posttreatment immune gene signature was derived through expression analysis and hierarchical clustering. Samples were compared using the Wilcoxon signed-rank test, with multiple test correction via the false discovery rate.

### ABSTRACT SUMMARY ZUMA-6: Phase 1-2 Multicenter Study Evaluating Safety and Efficacy of Axicabtagene CiloleuceL (KTE-C19) in Combination With Atezolizumab in Patients With Refractory Diffuse Large B-Cell Lymphoma

Atezolizumab is a humanized monoclonal antibody that binds to PD-L1. It has the potential to restore tumor-specific T-cell immunity. ZUMA-6 is an open-label, multicenter phase 1/2 study investigating axicabtagene ciloleuceL plus atezolizumab in patients with refractory DLBCL (Abstract TPS7572). The primary endpoint of phase 1 is to evaluate the incidence of dose-limiting toxicities after the first dose of atezolizumab, and the primary endpoint of phase 2 is to determine the CR rate. Secondary endpoints for phases 1 and 2 include the ORR, PFS, OS, duration of response, and changes to biomarkers pertaining to the efficacy and safety of CAR T-cell therapy. Eligible patients are adults with refractory DLBCL who develop disease progression or recurrence within 12 months of autologous SCT, and who had received adequate prior therapy. They must have an ECOG performance status of 0 or 1 and adequate organ function. Key exclusion criteria include a history of chronic lymphocytic leukemia with Richter transformation; clinically significant infections, autoimmune disorders, or malignant disorders; history or presence of central nervous system disease; and prior treatment with CD19-targeted therapy, immune checkpoint blockade or activator therapy, or allogeneic SCT. Recruitment is occurring in California, Florida, Massachusetts, and Texas.

Among the 14 paired samples included in the analysis, 12 were from DLBCL patients and 2 were from patients with primary mediastinal B-cell lymphoma or transformed follicular lymphoma. Six patients had ABC DLBCL, and 8 had GCB DLBCL. Patients had a median IPI score of 2 (range, 1-3) and had received a median of 3 prior lines of therapy (range, 2-3).

The median CAR peak levels were 28.3 cells/ $\mu$ L in the current analysis vs 41.9 cells/ $\mu$ L in ZUMA-1 overall (Table 2). Upregulated genes were associated with the T-cell signature, proliferation, activation, and effector molecules; chemoattractants; interferon I and II programs; immune checkpoints; and angiogenesis. Genes that were upregulated in at least 10 patients included *CD8A*, *IL-15*, *GZMA*, *GZMK*, *CCL5/RANTES*, *CX3CL1*, *STAT4*, *CTLA4*, and *PD-L1*. Expression of *CD8A*, *IL-15*, *GZMA*, *CCL5/RANTES*, *CX3CL1*, and *CTLA4* increased by greater than 2 log<sub>2</sub>. This analysis represents the first characterization of an immune gene signature in the tumor microenvironment soon after treatment with CAR T cells.

**Table 2.** Baseline Characteristics and Treatment Results in a Post Hoc Analysis of the ZUMA-1 Trial

	Current Gene Expression Study n=14 (%)	ZUMA-1 Overall N=101 (%)
<b>Baseline Characteristics</b>		
Tumor histology, n (%)		
DLBCL	12 (86)	77 (76)
PMBCL/TFL	2 (14)	24 (24)
Cell of origin, n (%)		
ABC	6 (43)	17 (17)
GCB	8 (57)	49 (49)
Unclassified	0	35 (35)
Median IPI score (range)	2 (1-3)	2 (1-3)
Median prior lines of therapy, n (range)	3 (2-3)	3 (2-4)
<b>Treatment Results</b>		
Median CAR peak levels, cells/ $\mu$ L (range)	28.3 (19.8-58.6)	41.9 (16.9-84.9)
ORR, n (%)	9 (64)	83 (82)

ABC, activated B cell; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; IPI, International Prognostic Index; ORR, objective response rate; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma; ZUMA-1, A Phase 1-2 Multi-Center Study Evaluating KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma.

Data from Galon J et al. ASCO abstract 3025. *J Clin Oncol*. 2017;35(15 suppl).<sup>4</sup>

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- Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory aggressive diffuse large B-cell lymphoma (DLBCL): results from the international SCHOLAR-1 study [ASCO abstract 7516]. *J Clin Oncol*. 2016;34(15 suppl).
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## CR Rates in Relapsed/Refractory Aggressive B-NHL Treated With the CD19-Directed CAR T-Cell Product JCAR017 (TRANSCEND NHL 001)

JCAR017 is a CAR T-cell product that targets CD19. It uses a defined composition of CD4 and CD8 T cells plus a 41BB costimulatory domain. Dr Jeremy Abramson presented findings from the phase 1 TRANSCEND NHL 001 trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma [NHL]), a multicenter, dose-finding study that evaluated lymphodepletion with fludarabine and cyclophosphamide followed by JCAR017 in patients with NHL.<sup>1</sup> The inclusion criteria were broader than in other studies, and permitted patients with an ECOG performance status of 0 through 2, involvement of the central nervous system, Richter transformation, and those who had relapsed after allogeneic bone marrow transplant. The study enrolled 71 patients with relapsed/refractory, aggressive B-cell NHL, including DLBCL, grade 3B follicular lymphoma, and mantle cell lymphoma. Three dose levels were included in the study protocol: dose level 1 was  $5 \times 10^7$  cells, dose level 2 was  $1 \times 10^8$  cells, and dose level 3 was  $1.5 \times 10^8$  cells.

The study provided 2 analyses of patients with DLBCL. The full data set included all DLBCL patients. The core analysis excluded patients with an ECOG score of 2 and/or in whom DLBCL had transformed from marginal zone lymphoma or chronic lymphocytic leukemia (Richter's transformation). Patients were followed for 24 months, after which the core patient group transitioned to a long-term protocol for follow-up extending up to 15 years after the last JCAR017 treatment. Among 88 patients who underwent apheresis, JCAR017 was producible for 86 (98%), and the

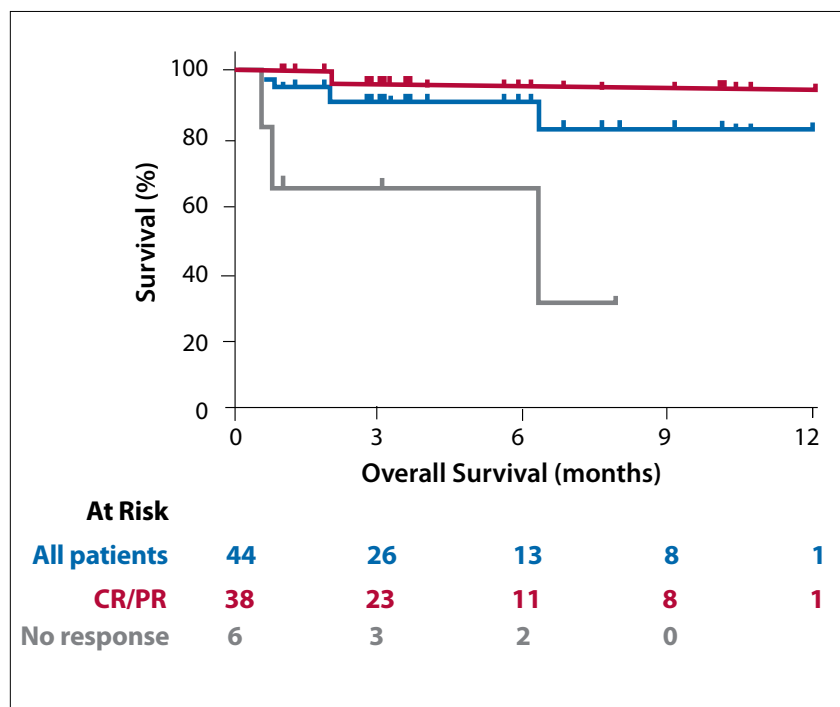
product met specifications for 78 patients (89%).

Data from the core group of 44 patients showed an ORR of 86% (38/44), with a CR rate of 59% (26/44). Three-month ORR was 66% (21/32), with a CR rate of 50% (16/32). Among 10 responders with at least 6 months of follow-up, 9 (90%) remained in response. Early data suggested a possible dose response at 3 months. In 19 patients treated at dose level 1, the ORR was 58% (11/19), with a CR rate of 42% (8/19). In 9 patients treated at dose level 2, the ORR was 78% (7/9), with a CR rate

of 56% (5/9). Among 38 patients who responded, 37 (97%) were alive and in follow-up as of the data cutoff date of May 4, 2017 (Figure 4).

For 54 patients treated across all dose levels, the ORR was 76% (41/54), with a CR rate of 52% (28/54). The 3-month ORR was 51% (21/41), and the 3-month CR rate was 39% (16/41).

Among 55 patients available for the safety analysis, 1 patient (2%) experienced severe cytokine-release syndrome, and 9 patients (16%) experienced severe neurotoxicity. No deaths were reported from cytokine-release



**Figure 4.** Response in the core group of patients with DLBCL from the TRANSCEND NHL 001 trial. CR, complete response; DLBCL, diffuse large B-cell lymphoma; PR, partial response; TRANSCEND NHL 001, Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma (NHL). Adapted from Abramson JS et al. ASCO abstract 7513. *J Clin Oncol.* 2017;35(15 suppl).<sup>1</sup>

syndrome or neurotoxicity. A dose/toxicity relationship was not apparent. The rate of severe cytokine-release syndrome was 3% (1/30) at dose level 1 and 0% (0/19) at dose level 2. The rate of severe neurotoxicity was 20% (6/30) at dose level 1 and 11% (2/19) at dose level 2. The most common treatment-emergent AEs were neutropenia (35%), cytokine-release syndrome (35%), and fatigue (31%). In the core group, 1 patient (2%) developed

severe cytokine-release syndrome, and 8 (18%) had severe neurotoxicity, both of which are concerns in patients treated with immunotherapy. Two-thirds of patients did not experience cytokine-release syndrome or neurotoxicity of any grade. An 82-year-old patient died on day 23 from diffuse alveolar damage that was considered related to treatment with fludarabine, cyclophosphamide, and JCAR017. This patient remained neutropenic

despite treatment with growth factors, broad-spectrum antibiotics, and antifungal therapies. The patient refused mechanical ventilation for progressive respiratory failure.

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## Phase II Study of Single-Agent Copanlisib in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

**D**LBCL accounts for approximately 30% of NHL cases, and approximately one-third of DLBCL patients have refractory disease or will relapse after standard treatment.<sup>1</sup> The ABC and GCB subtypes have different patterns of gene expression, as well as different prognoses. Constitutive upregulation of the phosphatidylinositol 3-kinase (PI3K)

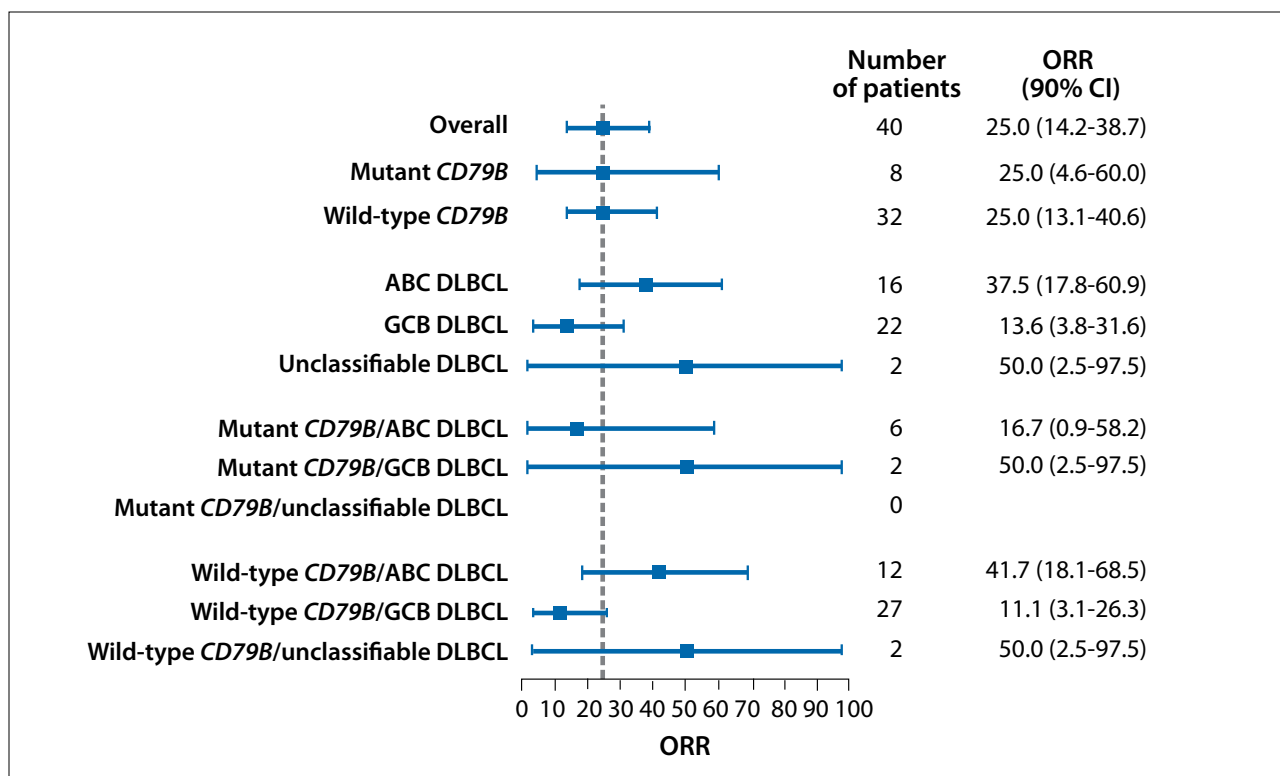
pathway has been observed in numerous tumor types, and simultaneous inhibition of PI3K $\alpha$  and PI3K $\delta$  has been shown to induce antitumor activity in preclinical ABC DLBCL models.<sup>2</sup> Copanlisib (BAY80-6946) is an intravenous, pan-class I PI3K inhibitor with preferential activity against p110 $\alpha$  and p110 $\delta$  isoforms, with IC<sub>50</sub> values of 0.5 nmol/L and 0.7 nmol/L,

respectively.<sup>3</sup> The first-in-human study demonstrated a maximum tolerated dose of 0.8 mg/kg, and pharmacokinetics were dose-proportional. The most common treatment-related AEs were nausea and transient hyperglycemia. Peak copanlisib exposure positively correlated with transient hyperglycemia. Among the 9 patients with NHL, responses were seen in all 6 patients with follicular lymphoma (1 CR and 5 partial responses [PRs] per investigator assessment). One patient with DLBCL achieved a PR as assessed by the investigator.

Copanlisib was evaluated in a phase 2 study of patients with relapsed or refractory DLBCL.<sup>4</sup> The study's primary objective was to determine the ORR of single-agent copanlisib and to identify predictive biomarkers. Secondary objectives included safety, tolerability, efficacy, and identification of potential predictive biomarkers for further evaluation. The open-label, multicenter, single-arm study included patients with relapsed or refractory DLBCL who had received at least 1 prior line of immunochemotherapy and who were ineligible or unwilling to receive myeloablative chemotherapy and SCT. Fresh or archival tumor

### ABSTRACT SUMMARY Results of GROC-Rev Salvage Regimen: Gemcitabine, Rituximab, and Oxaliplatin Chemotherapy With Revlimid for Relapsed/Refractory Aggressive Non-Hodgkin Lymphoma

Prognosis is poor among NHL patients who do not have at least a PR after salvage therapy. To improve the CR rate associated with salvage chemotherapy, lenalidomide was added to the combination regimen known as GROC, which consists of rituximab (375 mg/m<sup>2</sup>, day 1), gemcitabine (1250 mg/m<sup>2</sup>, day 2), and oxaliplatin (100 mg/m<sup>2</sup>, day 2), plus pegfilgrastim (6 mg day 3), administered every 14 days (Abstract 7556). Patients without a PR or CR after 2 cycles of GROC and patients who did not have a CR after 6 cycles of GROC crossed over to lenalidomide (25 mg daily) for cycles of 3 weeks on, 1 week off. Patients who had a CR with lenalidomide continued treatment for 2 years. Eligible patients underwent autologous SCT as consolidation. At 2 years, OS was 45% and PFS was 35% for the 33 patients in the overall study population. The ORR before crossover was 39%. Among 22 patients who crossed over to lenalidomide, 5 (23%) achieved a CR or PR after crossover, making them eligible for autologous SCT. Patients who responded to lenalidomide had a 100% survival rate vs 10% for nonresponders ( $P < .001$ ).



**Figure 5.** Differences in ORR among biomarker subgroups in a phase 2 study of copanlisib. ABC, activated B-cell; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; ORR, overall response rate. Adapted from Lenz G et al. ASCO abstract 7536. *J Clin Oncol.* 2017;35(15 suppl).<sup>4</sup>

biopsy samples after the most recent line of therapy were required from all patients. Copanlisib (60 mg) was administered intravenously throughout an hour on days 1, 8, and 15 of a 28-day cycle until the patient developed progressive disease or unacceptable toxicity. Dose reductions to 45 mg were permitted. Pretreatment tumor samples were analyzed for *CD79B* and DLBCL cell-of-origin genes.

The study included 67 patients, who had a median age of 69 years (range, 25-93 years). Most patients had stage III/IV disease (82%) and 4 to 6 target lesions (54%). The median number of prior lines of therapy was 3 (range, 1-13). Among the 67 patients who received at least 1 dose of study therapy, 9 had mutant *CD79B* and 45 had wild-type *CD79B*. (The status was missing in the remainder.) Thirty patients had GCB DLBCL and 19 had ABC DLBCL. (The subtype was missing or unclassifiable in 18 patients.)

The per protocol cohort included 40 patients who had received at least 1 complete cycle of study therapy and who had data for at least 1 post-treatment tumor assessment, known *CD79B* mutation status, and cell-of-origin assessment. Among these patients, 16 had ABC DLBCL, 22 had GCB DLBCL, and 2 had an unclassifiable subtype. These patients had an ORR of 25%, with half CRs and half PRs. ORR was higher among patients with ABC DLBCL vs those with GCB DLBCL (Figure 5). A further 30% of patients achieved stable disease. Presence of the *CD79B* mutation did not impact the ORR. The ORR was 37.5% in patients with ABC DLBCL vs 13.6% in those with GCB DLBCL. In the per protocol cohort, the median duration of response was 113 days for 10 evaluable patients. Among 40 evaluable patients, the median PFS was 84 days. In the entire study population of 67 patients, the median OS was 224

days (95% CI, 104-327 days).

The most common gene mutations or rearrangements detected by next-generation sequencing were in *BCL2* (54%), *TP53* (41%), *BCL6* (30%), *MYC* (22%), and *CD79B* (19%). Copanlisib showed similar antitumor activity irrespective of the *MYD88* mutation status. ORR was longer in patients with the *TNFAIP3* mutation, and PFS was shorter in patients with the *NFKB1A* mutation.

In the entire study population, 97% of patients experienced at least 1 treatment-emergent AE, most commonly hypertension (40%), diarrhea (37%), and hyperglycemia (33%). Serious AEs occurred in 66% of the patients. Treatment-emergent AEs led to 14 deaths (21%), but none of them were related to copanlisib. Treatment-emergent AEs required dose reduction in 13% of patients, dose interruption or delay in 51% of patients, and discontinuation in 25% of patients.

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# Product Characteristics Associated With in Vivo Expansion of Anti-CD19 CAR T Cells in Patients Treated With Axicabtagene Ciloleucel

A prespecified interim analysis of the phase 3 ZUMA-1 trial demonstrated that axicabtagene ciloleucel was associated with a CR rate of 54% in patients with refractory aggressive NHL.<sup>1</sup> Expansion of CAR T cells after infusion was associated with an increased likelihood of objective response. Patients with an objective response had a 5.4-fold increase in CAR T-cell expansion compared with patients who did not ( $P=.0002$ ).

Dr Frederick Locke presented results of a post hoc analysis evaluating associations between CAR T-cell expansion in patients and CAR T-cell product characteristics, including T-cell phenotypes, cell expansion rates during manufacturing, and the number of infused T cells according to phenotype.<sup>2</sup> Characteristics of axicabtagene ciloleucel prior to infusion were modeled against levels of anti-CD19 CAR T cells in the blood after infusion. After conditioning with fludarabine and cyclophosphamide, patients received a single intravenous infusion of axicabtagene ciloleucel administered at a target dose of  $2 \times 10^6$  anti-CD19 CAR T cells/kg. Anti-CD19 CAR T cells were analyzed by flow cytometry to identify the surface markers CD3, CD4, CD8, CCR7, and CD45RA. CCR7 and CD45RA were used to distinguish between naive T cells ( $T_N$ : CCR7<sup>+</sup>, CD45RA<sup>+</sup>),

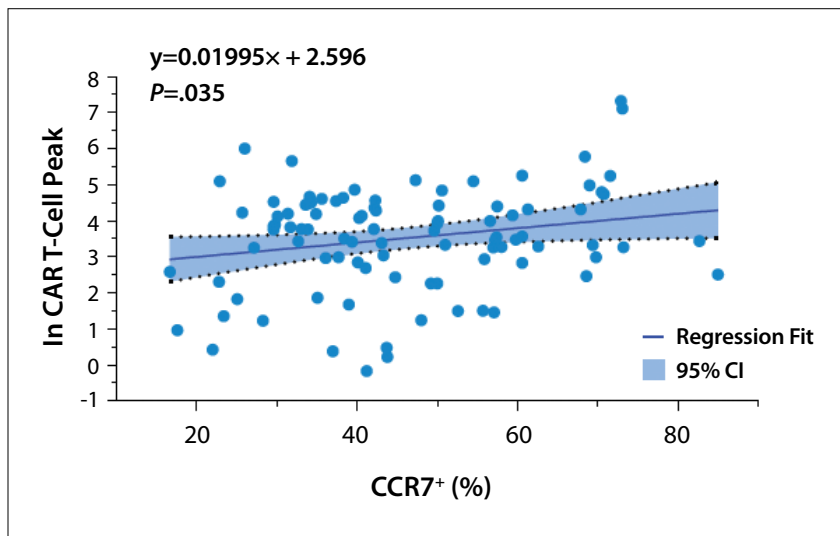
central memory T cells ( $T_{CM}$ : CCR7<sup>+</sup>, CD45RA<sup>-</sup>), effector memory T cells ( $T_{EM}$ : CCR7<sup>-</sup>, CD45RA<sup>-</sup>), and effector T cells ( $T_{EFF}$ : CCR7<sup>-</sup>, CD45RA<sup>+</sup>). DLBCL cell of origin was assessed centrally by gene expression profiling. The Wilcoxon 2-sample test and linear regression were used to determine the relationship between product characteristics and expansion.

Product characteristics obtained from 98 to 101 samples showed a median transduction rate of 52.6%

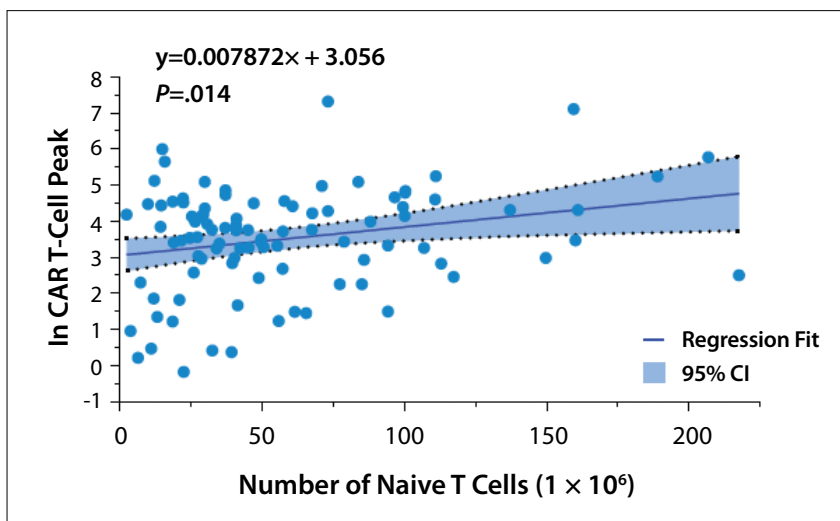
(quartile 1 [Q1], 21.6%; quartile 3 [Q3], 85.1%). The median ratio of CD4:CD8 cells was 0.87 (Q1, 0.54; Q3, 1.87). The median percentages of T-cell types were 13.9%  $T_N$ , 26.1%  $T_{CM}$ , 37.9%  $T_{EM}$ , and 15.4%  $T_{EFF}$ . The median ratio of  $T_N + T_{CM} / T_{EM} + T_{EFF}$  was 0.7 (Q1, 0.5; Q3, 1.3). The median doubling time during manufacturing was 1.5 days (Q1, 1.3; Q3, 1.7). Anti-CD19 CAR T cells were successfully manufactured from starting material obtained by apheresis that had diverse

### ABSTRACT SUMMARY Phase I Dose Escalation of Ibrutinib and Buparlisib in Relapsed/Refractory Diffuse Large B-Cell Lymphoma, Mantle Cell Lymphoma, and Follicular Lymphoma

A phase 1 dose escalation trial investigated the combination of ibrutinib, an oral inhibitor of Bruton tyrosine kinase, and buparlisib, an oral pan-PI3K inhibitor, in patients with relapsed or refractory DLBCL, mantle cell lymphoma, or follicular lymphoma (Abstract 7544). The ibrutinib/buparlisib dose levels were 420 mg and 80 mg, respectively, for dose level 1; 560 mg and 80 mg for dose level 2; and 560 mg and 100 mg for dose level 3. Among 16 patients, dose-limiting toxicities consisted of grade 3 anorexia (1 case at dose level 1) and grade 2 cerebrovascular infarct of preexisting pituitary adenoma (1 case at dose level 3). Three-fourths of patients required dose reductions of either ibrutinib or buparlisib. A treatment-related AE of at least grade 3 occurred in 50% of patients. The most common treatment-related AEs were hyperglycemia, diarrhea, elevated total bilirubin, and thrombocytopenia. One patient died of ventricular tachycardia. The median time on therapy was 3.67 months (range, 0.8-11.4 months). Three patients with mantle cell lymphoma achieved a CR on combination therapy and continued to receive ibrutinib monotherapy while in remission. The maximum tolerated dose was established as ibrutinib (560 mg) plus buparlisib (100 mg) once daily.



**Figure 6.** The percentage of naive T cells and effector memory T cells in axicabtagene ciloleucel was associated with CAR T-cell peak levels. CAR, chimeric antigen receptor. Adapted from Locke FL et al. ASCO abstract 3023. *J Clin Oncol.* 2017;35(15 suppl).<sup>2</sup>



**Figure 7.** The number of naive T cells corresponded with peak levels of anti-CD19 CAR T cells. CAR, chimeric antigen receptor. Adapted from Locke FL et al. ASCO abstract 3023. *J Clin Oncol.* 2017;35(15 suppl).<sup>2</sup>

characteristics in terms of the proportion of CD3-positive cells and the proportion of T<sub>N</sub> and T<sub>CM</sub> cells.

In 96 evaluable patients, the median peak concentration was 41.9 cells/ $\mu$ L (Q1, 15.8; Q3, 83.9). The median AUC was 462.3 cells/ $\mu$ L  $\times$  days (Q1, 147.6; Q3, 930.4). Upon infusion, CAR T cells expanded rapidly, reaching peak levels within 2 weeks. An association was observed between the percentage of T<sub>N</sub> and T<sub>CM</sub> (CCR7<sup>+</sup>) cells in axicabtagene ciloleucel and CAR T-cell peak levels ( $P=.035$ ; Figure 6). The number of T<sub>N</sub> cells corresponded to peak levels of anti-CD19 CAR T cells ( $P=.014$ ; Figure 7). The cell doubling time during manufacturing was associated with peak anti-CD19 CAR T-cell levels in the blood after infusion ( $P=.037$ ).

This post hoc analysis was potentially confounded by heterogeneity in the baseline tumor burden, which was not assessed, and baseline CD19 expression, which could influence CAR T-cell expansion after infusion. The authors suggested that the findings from this analysis could potentially be used to optimize the manufacture of CAR T-cell products.

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## Comparative Double-Blind Randomized Trial of 2 Rituximab Products in Patients With CD20+ Diffuse Large B-Cell Lymphoma

Rituximab is approved in combination with CHOP or another anthracycline-based regimen for the first-line treatment of patients with CD20-positive DLBCL.<sup>1</sup> DRL-rituximab is in development as a potential biosimilar of a commercially available formulation of rituximab. Previous analyses of rituximab and DRL-rituximab have shown similar properties and behavior.<sup>2</sup>

The 2 rituximab products were compared in a study that evaluated their pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity in patients with DLBCL.<sup>3</sup> This double-blind, parallel-group, comparative clinical trial was conducted at 44 centers across India. Patients with previously untreated DLBCL were randomly assigned to receive treatment with rituximab or DRL-rituximab in combination with CHOP for 6 treatment cycles. Eligible patients had

histologically confirmed, CD20-positive DLBCL of stage II to IV (per Ann Arbor or Cotswold criteria). Patients were ages 18 to 60 years and had an ECOG performance status of 0 to 2, with adequate liver and renal function. Key exclusion criteria included primary central nervous system, effusional, or intravascular DLBCL; or bulky disease exceeding a dimension of 10 cm or involving more than one-third of the chest diameter. Rituximab or DRL-rituximab, both administered at 375 mg/m<sup>2</sup>, were administered intravenously throughout 4 hours in combination with CHOP on day 1 of each 21-day cycle. A delay of up to 14 days between cycles was permitted. The primary endpoint was to compare the AUC from day 0 to 21 (AUC<sub>day0-21</sub>) and the maximum plasma concentration (C<sub>max</sub>) during cycle 1.

The study randomly assigned 76 patients to receive DRL-rituximab

and 75 to rituximab. Baseline demographics and patient characteristics were generally well-balanced between the 2 arms. Patients had a median age of 47.2 ± 11.75 years in the DRL-rituximab arm and 44.4 ± 11.46 years in the rituximab arm. The median time since diagnosis was 26 to 27 months (range, 6-242 months), 77% to 82% of patients had extranodal involvement, and 29% to 33% had B symptoms. Pharmacokinetic parameters in cycle 1 were similar. The generalized least squares mean ratio for DRL-rituximab/rituximab was 100.0 (90% CI, 97.72-114.01) for AUC<sub>(day 0-21)</sub> and 96.19 (90% CI, 88.54-104.38) for C<sub>max</sub>. In the modified intent-to-treat population, the ORR was 83.6% for DRL-rituximab (n=61) vs 84.8% for rituximab (n=66), reflecting a difference of -1.24 (95% CI, -18.66 to 15.98; Table 3). In the per protocol population, the ORR was 82.1% for patients treated with DRL-rituximab (n=58) vs 87.1% for patients treated with rituximab (n=62), reflecting a difference of -4.95 (90% CI, -22.76 to 13.19). The pharmacokinetic criterion for similarity was met in cycle 6, with geometric mean ratios of DRL-rituximab/rituximab of 88.94 (90% CI, 80.28-98.53) for AUC<sub>(0-21 days)</sub> and 94.62 (90% CI, 88.07-101.66) for C<sub>max</sub>. Steady state was achieved from cycle 4 onward for both antibodies.

The frequencies of treatment-emergent AEs were similar for both arms. Treatment-emergent AEs of grade 3/4 were observed in 72.6% of patients in the DRL-rituximab arm vs 85.3% in the rituximab arm. Treatment-related deaths were reported in 2.6% of patients in the DRL-rituximab arm vs 1.3% in the rituximab arm. B-cell depletion was

**Table 3.** ORR at Cycle 6 in a Trial Comparing 2 Rituximab Products

ORR at End of Treatment	DRL-Rituximab	Rituximab	Difference (95% CI) <sup>a</sup>
Full analysis set			
n	61	66	-1.24 (-18.66 to 15.98)
ORR, n (%)	51 (83.6)	56 (84.8)	
95% CI <sup>b</sup>	71.9-91.8	73.9-92.5	
Per protocol population			
n	56	62	-4.95 (-22.76 to 13.19)
ORR, n (%)	46 (82.1)	54 (87.1)	
95% CI <sup>b</sup>	69.6-91.1	76.1-94.3	

<sup>a</sup>95% CI for risk difference was calculated using the Newcombe-Wilson score method.

<sup>b</sup>95% CI (unadjusted or adjusted) for the individual treatment proportion was calculated using the exact Clopper-Pearson method.

ORR, overall response rate.

Data from Shah S et al. ASCO abstract 7550. *J Clin Oncol*. 2017;35(15 suppl).<sup>3</sup>

### **ABSTRACT SUMMARY Anti-Infective Prophylaxis With Aciclovir and Cotrimoxazole to Reduce the Rate of Infections and Therapy-Associated Deaths in Elderly Patients With DLBCL Undergoing R-CHOP Immunochemotherapy**

In the DENSE-R-CHOP-14 trial, anti-infective treatment with cotrimoxazole and aciclovir in addition to ciprofloxazine during days of severe leukocytopenia reduced the rate of grade 3/4 infections in elderly patients with DLBCL (Murawski N et al. *Ann Oncol.* 2014;25[9]:1800-1806). The same prophylactic anti-infective strategy was further evaluated in elderly DLBCL patients undergoing R-CHOP immunochemotherapy in 2 studies: RICOVER-60 and OPTIMAL>60 (Abstract 7539). Patients in OPTIMAL>60 received anti-infective prophylaxis consisting of ciprofloxazine (500 mg daily) plus cotrimoxazole (2 double-strength doses twice per week) and aciclovir (4 × 400 mg daily). Patients in RICOVER-60 were elderly and received anti-infective prophylaxis consisting of ciprofloxazine (500 mg daily) during days of severe leukocytopenia. The median age was 69 years in RICOVER-60 and 71 years in OPTIMAL>60. With intensified anti-infective prophylaxis, rates of infection were similar in the 4 treatment arms of OPTIMAL>60. Rates of grade 3/4 infections per cycle were 6% in RICOVER-60 and 4% in OPTIMAL>60 ( $P=.007$ ). Rates of grade 3/4 infections per patients were 28% in RICOVER-60 and 18% in OPTIMAL>60 ( $P=.004$ ). Treatment-related deaths occurred in 7% of patients in RICOVER-60 vs 2% of those in OPTIMAL>60 ( $P=.003$ ).

confirmed in 98.2% of patients in the DRL-rituximab arm vs 98.4% of patients in the rituximab arm (difference, -0.14; 95% CI, -18.03 to 17.86). B-cell repletion was observed in 74.4% of patients in the DRL-rituximab arm vs 61.9% of patients in the rituximab arm (difference, 12.5; 95% CI, -9.61 to 33.47). The median times to B-cell depletion and repletion in both arms were comparable.

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## Highlights in Aggressive Non-Hodgkin Lymphoma From the 2017 American Society of Clinical Oncology Annual Meeting: Commentary

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It is an exciting time to be a medical oncologist. Chimeric antigen receptor (CAR) T cells are gene-engineered immune effector cells that represent a new paradigm in the management of cancer. In 2017, the US Food and Drug Administration (FDA) is expected to approve multiple anti-CD19 CAR T-cell products for B-cell malignancies, including pediatric acute lymphoblastic leukemia and adult diffuse large B-cell lymphoma (DLBCL). Practicing oncologists must be aware of the efficacy of CAR T-cell therapy and its serious, but reversible, toxicities. Several abstracts at the 2017 American Society of Clinical Oncology (ASCO) meeting presented data from pivotal clinical trials evaluating the safety, efficacy, and biomarkers of these therapies for aggressive B-cell non-Hodgkin lymphoma.

Dr Jeremy Abramson from Massachusetts General Hospital presented interim results from the TRANSCEND trial (Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-Cell Non-Hodgkin Lymphoma [NHL]), which evaluated JCAR017 in patients with non-Hodgkin lymphoma.<sup>1</sup> This industry-sponsored, multicenter phase 1 trial is testing different cell doses of an anti-CD19 CAR T-cell therapy with a 4-1BB costimulatory domain in patients with aggressive B-cell lymphomas. Both CD4 and CD8 CAR T cells are important for the eradication of tumors following

adoptive transfer,<sup>2</sup> so the trial prespecified the CD4:CD8 T-cell composition in the CAR T-cell product. The trial enrolled patients with several histologies, including mantle cell lymphoma, primary mediastinal B-cell lymphoma, grade 3B follicular lymphoma, and DLBCL. Patients with relapsed/refractory disease were permitted. Among 91 patients that had cells collected by apheresis, CAR T cells were successfully manufactured in 89. However, in 7 of these patients, the product was labeled as nonconforming, which likely meant that those CAR T-cell products did not meet the prespecified CD4:CD8 T-cell ratios yet were otherwise suitable for infusion. All patients received lymphodepleting chemotherapy with fludarabine 30 mg/m<sup>2</sup> and cyclophosphamide 300 mg/m<sup>2</sup> daily for 3 days prior to the JCAR017 infusion. Dr Abramson reported on safety data for all B-cell lymphoma patients who received a conforming CAR T-cell product at any dose level (n=55).<sup>1</sup> For efficacy data, he also presented a “CORE” DLBCL group (n=44) that excluded patients with an Eastern Cooperative Oncology Group score of 2 or higher, those with mantle cell lymphoma, and those with CLL or Richter’s transformation.

CAR T cells are known to cause 2 main classes of toxicities: cytokine-release syndrome and neurologic toxicity, both of which are generally reversible. Cytokine-release syndrome can

occur when CAR T cells become activated after encountering their target, CD19, on the surface of B cells. The CAR T cells release cytokines, chemokines, and effector molecules, which lead to fevers. Severe cytokine-release syndrome can manifest as hypotension, hypoxia, or coagulopathy. While delirium can accompany high fevers from cytokine-release syndrome, the CAR T-cell related encephalopathy may be subsequent to cytokine-release syndrome. The exact pathophysiology of neurologic toxicities remains unclear.

No significant differences in toxicities were reported at different dose levels. The median onset of cytokine-release syndrome symptoms was 5 days, and only 1 patient with DLBCL developed severe grade 3/4 cytokine-release syndrome (2%). The median time of onset of neurologic toxicity was 11 days after infusion of the CAR T cells and was severe (grade 3/4) in 18% of patients. Only 11% of patients had onset of cytokine-release syndrome within 72 hours after administration of JCAR017. The toxicities were generally reversible, with a median time to resolution of cytokine-release syndrome and neurologic toxicities of 5 and 11 days, respectively. These findings suggest that it might be feasible to administer JCAR017 on an outpatient basis at centers with outpatient hematopoietic stem cell transplant programs. Patients could be followed



daily to identify toxicities and undergo hospitalization if needed.

Dr Abramson also reported on encouraging response rates for the DLBCL cohort.<sup>1</sup> In the CORE group of DLBCL patients (n=44)—those who received the predefined CD4:CD8 CAR T cell product—the objective response rate was 86% and the complete response rate was 59%. These interim analysis data were less intriguing for patients who had refractory disease, defined as stable disease or progressive disease in response to their last line of chemotherapy, with 33% having an objective response at 3 months.

Results from correlative analyses were overall consistent with those from earlier reports from CAR T-cell trials, with a notable exception pertaining to the predefined CD4:CD8 composition. First, a partial response is less likely to lead to a durable response as compared with a complete response. Second, the expansion of CAR T cells correlated with response durability and neurotoxicity, which has been described in other CAR T-cell trials. Unfortunately, this suggests that simply increasing the expansion of CAR T cells to promote increased responses is also likely to increase toxicity: targeted and rational approaches to abrogate cytokine-release syndrome and neurologic toxicities must be tested. Finally, the importance of the predefined CD4:CD8 ratio remains unclear, especially considering that 10% of the DLBCL patients treated in the study received a nonconforming CAR, and some of these patients still achieved a response.

Although the overall response rate and complete response rates seen with JCAR017 in DLBCL are promising, longer follow-up and a greater number of patients treated at a stable dose level are required to fully understand the efficacy and safety of the therapy, as well as the manufacturing success rate. It remains unclear if a predefined CD4:CD8 T-cell ratio is necessary or

whether JCAR017 can put truly chemorefractory DLBCL patients into durable remissions.

Several analyses were presented on the ZUMA-1 trial (A Phase 1-2 Multi-Center Study Evaluating KTE-C19 in Subjects With Refractory Aggressive Non-Hodgkin Lymphoma), the first multicenter study evaluating the safety and efficacy of anti-CD19 CAR T cells in patients with refractory NHL. ZUMA-1 is a phase 1/2 trial evaluating the CAR T-cell therapy axicabtagene ciloleucel (formerly known as KTE-C19), and the phase 1 results were previously published in *Molecular Therapy*.<sup>3</sup> At ASCO, I presented results of the primary analysis of the pivotal phase 2 portion of the trial.<sup>4</sup> Axicabtagene ciloleucel targets CD19 and has a CD28 costimulatory domain. The phase 2 trial tested patients with truly chemotherapy-refractory DLBCL, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma. Chemotherapy refractory was defined as patients who had stable disease or progressive disease as a best response to their last chemotherapy, or patients who relapsed within 12 months of a prior autologous hematopoietic stem cell transplant. This strictly defined homogeneous patient population must be acknowledged as having an extremely poor prognosis, even when compared with the “relapsed/refractory” heterogeneous patients eligible for most lymphoma trials. Many patients also had high-risk features. An International Prognostic Index of 3 or 4 was reported in 48%, 85% had stage III/IV disease at enrollment, and 54% were refractory to 2 consecutive lines of therapy. ZUMA-1 patients can be compared with those in the SCHOLAR-1 study (Retrospective Non-Hodgkin Lymphoma Research), a historical control that evaluated patients with similar characteristics and demonstrated a low 8% chance of obtaining a complete response to standard therapies.<sup>5</sup> Clearly, new therapies are needed for

this patient population.

The ZUMA-1 study enrolled 111 patients.<sup>4</sup> CAR T cells were successfully manufactured in 99% of patients. The study showed a rapid turnaround time for manufacture of the CAR T cells. It took an average of 17 days from collection of the CAR T cells to delivery back to the treating center. Ten patients did not receive the therapy, primarily owing to serious adverse events related to disease progression while waiting for axicabtagene ciloleucel manufacture. Patients could not be treated with bridging chemotherapy after cells were collected for manufacture. Before receiving CAR T-cell infusion, patients received a nonmyeloablative, low-dose conditioning chemotherapy regimen of fludarabine at 30 mg/m<sup>2</sup>/day and cyclophosphamide at 500 mg/m<sup>2</sup>/day on day -5, day -4, and day -3. On day 0, hospitalized patients received a single intravenous infusion of axicabtagene ciloleucel at a target dose of 2 × 10<sup>6</sup> CAR-positive T cells/kg.

Among the 101 patients who went on to receive axicabtagene ciloleucel, the median follow-up was 8.7 months at the time of the primary analysis. The objective response rate was 82%, and the complete response rate was 54%. These data compare very favorably to SCHOLAR-1, which showed a 26% objective response rate and 8% complete response rate.<sup>5</sup> The median overall survival was not yet reached. At 6 months, the median overall survival was 80%, compared with a 55% 6-month survival in SCHOLAR-1, suggesting that this therapy is positively impacting survival.

At the time of the data cutoff, 44% of patients had an ongoing response. Among patients who achieved a complete response, the median duration of that response was not reached, with a lower bound of the 95% CI of at least 8.2 months, so it seems highly likely that these patients will remain in remission for many months. High-risk features were not predictive of different response rates,

suggesting that axicabtagene ciloleucel may be equally effective even in high-risk patients.

Molecular subgroup analysis was available and able to classify 66 patients into activated B cell (ABC) or germinal center B cell–like (GCB) subtypes. The overall response rate was 76% among the 17 patients with ABC and 88% among the 49 patients with GCB. The CR rates were similar, at 59% and 57%, respectively. Axicabtagene ciloleucel can be effective and lead to clinical responses in both ABC and GCB subgroups.

Levels of CD19 in the tumor were quantified by a validated immunohistochemical analysis called the H-score. Patients with very low expression of CD19 still had an objective response rate of 84% and a complete response rate of 58%. Therefore, selection of patients for this type of therapy by CD19 immunohistochemical expression is not likely to increase benefit.

The toxicities were as predicted by prior single-center CAR T-cell trials. Grade 3 or higher cytokine-release syndrome was seen in 13% of patients, and grade 3 or higher neurologic events were seen in 28%. Episodes of cytokine-release syndrome and neurologic toxicity were generally reversible. Three patients (3%) experienced grade 5 adverse events not attributable to lymphoma progression. The rates of severe toxicity decreased from the time of the interim analysis to the time of the primary analysis, suggesting that physicians became more comfortable with managing the toxicities and, per the protocol guidelines, they intervened at an earlier stage, possibly preventing progression to greater severity. Importantly, use of the interleukin (IL) 6 receptor antibody tocilizumab and corticosteroids to manage toxicities did not impact treatment outcomes.

Given such high response rates, the risk-to-benefit ratio appears favorable for these patients, who have no other treatment options. It was encouraging to see these results in a large multicenter study. We were able

to demonstrate the feasibility of the therapy, including the management of toxicity across different centers, many of which had no prior experience with CAR T-cell therapy. The pivotal primary analysis results of the ZUMA-1 trial are likely to lead to FDA approval of this therapy for aggressive B-cell lymphoma. It will be necessary to evaluate these patients with longer follow-up to better understand how therapy impacts long-term outcome.

Another analysis of the ZUMA-1 trial focused on the product characteristics associated with *in vivo* expansion of anti-CD19 CAR T cells in patients treated with axicabtagene ciloleucel.<sup>6</sup> The expansion of CAR T cells was associated with an objective response (partial response or a complete response), as well as neurologic events. Among patients with an objective response, the area under the curve of CAR T cells—as measured over the first 28 days after infusion by quantitative polymerase chain reaction in the peripheral blood—was 5.4-fold higher than in patients who did not have an objective response. Patients with severe neurologic toxicity of grade 3 or higher had a 2.6-fold higher area under the curve of CAR T cells in the peripheral blood as compared with patients who had no or mild neurologic toxicity. In contrast, severe cytokine-release syndrome did not correlate with levels of CAR T cells.

Evaluation of the CAR T-cell product characteristics focused on the CD4:CD8 ratio and on the naive T cell, central memory T cell, and effector memory T cell subsets in the final product. The final axicabtagene ciloleucel product had higher percentages of naive T cells and central memory T cells as compared with the apheresis material that was collected. The percent of these naive T cells and central memory T cells in the product correlated with the peak CAR T-cell levels in the blood. This confirms that the more naive the CAR T cells are—the less differentiated—the more robustly they will expand after

infusion. This is important because CAR T-cell expansion correlates with outcomes. There was no correlation between the CD4:CD8 ratio and CAR T-cell expansion.

Dr Jérôme Galon, Dr John Rossi, and colleagues aimed to characterize the CD19 CAR T-cell mediated tumor microenvironment gene profile in the ZUMA-1 trial.<sup>7</sup> This interesting post hoc analysis compared paired biopsies. Per the study protocol, patients underwent a tumor biopsy before they had cells collected for CAR T-cell manufacture, and then again 1 to 3 weeks after infusion of axicabtagene ciloleucel. These 2 biopsies were evaluated with a limited set gene expression profile using the NanoString platform. The analysis found upregulation of immune genes within the tumor tissue early after axicabtagene ciloleucel therapy, including elevation of chemoattractive homing signals for T cells, T-cell proliferative signals, and cytotoxic signals, as well as T-cell activation and effector function genes. Interestingly, upregulation was seen not only in signaling molecules like STAT-4, cytokines like IL-15, and activation signals like granzymes, but also in immune checkpoints within the tumor microenvironment, such as CTLA-4 and programmed death (PD) ligand 1. This finding suggests that early after therapy, there is a response that aims to shut down this artificially overactive immune response against the lymphoma. These data suggest a role for combination regimens, such as checkpoint blockade with CAR T-cell therapy. The ZUMA-6 study is a trial in progress that was highlighted at ASCO.<sup>8</sup> This ongoing combination trial is evaluating axicabtagene ciloleucel followed by the PD ligand 1–blocking antibody atezolizumab in patients with refractory DLBCL. Axicabtagene ciloleucel is given at the same cell dose level and after the same conditioning chemotherapy as used in ZUMA-1. Atezolizumab (1200 mg) is administered every 21 days for 4 doses after infusion of axicabtagene ciloleu-

cel, starting on day 21 in cohort 1, day 14 in cohort 2, and day 1 in cohort 3. A dose expansion phase will occur at the selected dose schedule. This trial is enrolling patients, and data are not yet available.

## Conclusion

Abstracts highlighted at the 2017 ASCO annual meeting herald a new treatment paradigm for cancer therapy: CAR T-cell therapy. Encouraging results suggest that CAR T-cell therapy is highly likely to receive FDA approval and will be the best therapeutic option for fit DLBCL patients with truly chemorefractory disease. When patients relapse, referral to centers with CAR T-cell therapy programs is paramount. Randomized phase 3 trials of CAR T-cell therapy compared with

autologous transplant are needed to determine if it should be the standard of care at first relapse.

## Disclosure

*Dr Locke has served as a scientific advisor to Kite Pharma, and a consultant to Cellular Biomedicine Group Inc.*

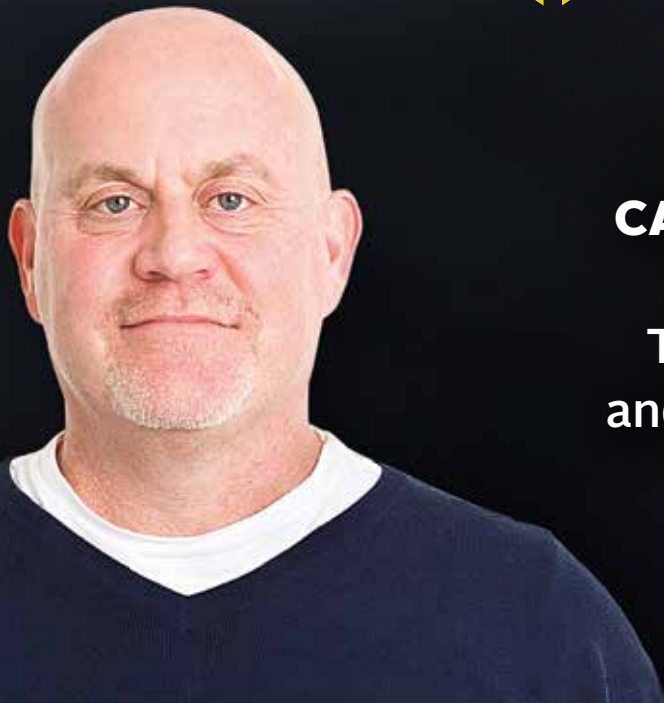
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CAR T-cell therapies are investigational and not FDA approved

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