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Axicabtagene Ciloleucel (Axi-Cel) Versus Standard of Care (SOC) in Patients With Primary Refractory or Early Relapsed Large B-Cell Lymphoma (LBCL)

Jason R. Westin, MD, MS, FACP[1]; Olalekan O. Oluwole, MD, MBBS, MPH[2]; Marie José Kersten, MD, PhD[3]; David B. Miklos, MD, PhD[4]; Miguel-Angel Perales, MD[5]; Armin Ghobadi, MD[6]; Aaron P. Rapoport, MD[7]; Anna Sureda, MD, PhD[8]; Caron A. Jacobson, MD, MMSc[9]; Umar Farooq, MD[10]; Matthew L. Ulrickson, MD[11]; Tom van Meerten, MD, PhD[12]; Mahmoud Elsawy, MD, MSc[13]; Sridhar Chaganti, MD, PhD[14]; Michael Dickinson, MBBS, DMSc, FRACP, FRCPA[15]; Lori A. Leslie, MD[16]; Peter Vandenberghe, MD, PhD[17]; Yin Yang, MD, MS[18]; Christina To, MD[18,a]; Simone Filosto, PhD[18]; Justin Budka, PhD[18]; Saran Vardhanabhuti, PhD[18]; and Frederick L. Locke, MD[19]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Vanderbilt University Medical Center, Nashville, TN, USA; [3]Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands, on behalf of HOVON/LLPC; [4]Stanford University School of Medicine, Stanford, CA, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Washington University School of Medicine, St. Louis, MO, USA; [7]University of Maryland School of Medicine and Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA; [8]Institut Català d'Oncologia-Hospitalet, Barcelona, Spain; [9]Dana-Farber Cancer Institute, Boston, MA, USA; [10]University of Iowa, Iowa City, IA, USA; [11]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [12]University Medical Center Groningen, Groningen, Netherlands, on behalf of HOVON/LLPC; [13]Division of Hematology and Hematologic Oncology, Department of Medicine, Dalhousie University and QEII Health Sciences Center, Halifax, Nova Scotia, Canada; [14]University Hospital Birmingham NHS Trust, Birmingham, UK; [15]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; [16]John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ, USA; [17]University Hospitals Leuven, Leuven, Belgium; [18]Kite, a Gilead Company, Santa Monica, CA, USA; and [19]Moffitt Cancer Center, Tampa, FL, USA

BACKGROUND

- Historically, patients with primary refractory large B-cell lymphoma (LBCL) or those who relapse ≤12 months after first-line (1L) chemoimmunotherapy have had poor outcomes[1-3]
- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that is approved in many countries for relapsed or refractory (R/R) LBCL[4,5]
  - Axi-cel has demonstrated curative potential in the second-line ≤12 months after 1L therapy (2L; ZUMA-7; NCT03391466) and third-line or later line settings (ZUMA-1; NCT02348216)[6,7]
- In the Phase 3 ZUMA-7 study (NCT03391466), axi-cel demonstrated superior event-free survival (EFS), response rate, and overall survival (OS) versus standard of care (SOC) in patients with R/R LBCL intended for transplant[7,8]
  - At a median follow-up of 47.2 months, 54% and 47% of patients in the axi-cel and SOC treatment arms were alive, respectively[7]
- There remains a need to better understand the efficacy and safety outcomes in patients with early relapsed or primary refractory disease receiving axi-cel versus SOC
- It remains unclear what biological characteristics lead to primary refractoriness

OBJECTIVES

- To determine survival benefit of axi-cel versus SOC in the prespecified patient groups of primary refractory versus relapsed disease ≤12 months of 1L therapy in ZUMA-7
- To investigate tumor microenvironment differences between primary refractory and early relapsed disease

METHODS

- In ZUMA-7, eligible patients were randomized 1:1 to axi-cel or SOC (chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation in responding patients) and stratified by 1L therapy response and second-line age-adjusted International Prognostic Index (sAAIPI)
- A prespecified subgroup analysis was conducted in patients with primary refractory disease (no complete response to 1L treatment) and early relapsed disease (relapse ≤12 months of 1L therapy)
  - Data cutoff was January 25, 2023
- Descriptive statistics summarized baseline patient and disease characteristics, efficacy outcomes, and safety outcomes
  - Kaplan–Meier method was used to assess time-to-event outcomes, including OS, EFS per investigator, and progression-free survival (PFS) per investigator
  - Estimated hazard ratios (HRs) and 2-sided 95% CIs for axi-cel versus SOC were calculated from stratified Cox regression models
- Preinfusion tumor biopsies were collected and used to assess levels of gene expression signatures and immune cell infiltration by Nanostring IO-360™, RNAseq, and multiplex immunohistochemistry

RESULTS

Table 1. Baseline Patient and Disease Characteristics

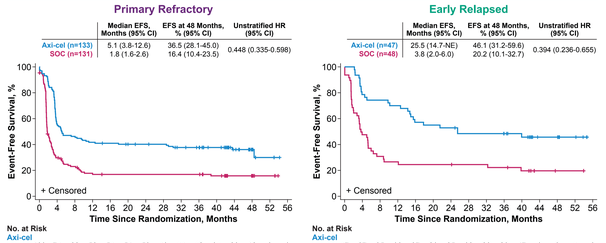
Characteristic	Primary Refractory			Early Relapsed		
	Axi-Cel n=133	SOC n=131	Overall n=264	Axi-Cel n=47	SOC n=48	Overall n=95
Median age, years (IQR)	58 (51-65)	58 (49-67)	58 (50-66)	58 (52-67)	62 (49.5-67.5)	61 (52-67)
≥65	37 (28)	39 (30)	76 (29)	14 (30)	19 (40)	33 (35)
Male sex, n (%)	80 (60)	97 (74)	177 (67)	30 (64)	30 (63)	60 (63)
Disease stage III-IV, n (%)	102 (77)	105 (80)	207 (78)	37 (79)	41 (85)	78 (82)
Derived sAAIPI total score of 2, n (%)	68 (51)	61 (47)	129 (49)	18 (38)	18 (38)	36 (38)
Disease type per investigator, n (%)						
DLBCL not otherwise specified	77 (58)	84 (64)	161 (61)	33 (70)	32 (67)	65 (68)
HGBL with or without *MYC* and *BCL2* and/or *BCL6* rearrangement	34 (26)	22 (17)	56 (21)	9 (19)	5 (10)	14 (15)
TFL	14 (11)	17 (13)	31 (12)	5 (11)	10 (21)	15 (16)
T-cell/histiocyte-rich LBCL	5 (4)	5 (4)	10 (4)	0	1 (2)	1 (1)
Other	3 (2)	3 (2)	6 (2)	0	0	0
Elevated LDH levels preinfusion, n (%)[a]	80 (60)	74 (56)	154 (58)	21 (45)	20 (42)	41 (43)

[a] Defined as LDH greater than upper limit of normal per local laboratory reference range.
Axi-cel, axicabtagene ciloleucel; BCL, B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; HGBL, high-grade B-cell lymphoma; IQR, interquartile range; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; sAAIPI, second-line age-adjusted International Prognostic Index; SOC, standard of care; TFL, transformed follicular lymphoma.

- Baseline characteristics for subgroups of patients with primary refractory or early relapsed LBCL were generally balanced between arms and similar among patients within each arm (**Table 1**)
  - Patients with primary refractory LBCL had elevated sAAIPI, higher frequency of high-grade B-cell lymphoma, and higher lactate dehydrogenase levels compared with patients with early relapsed LBCL

RESULTS *(Continued)*

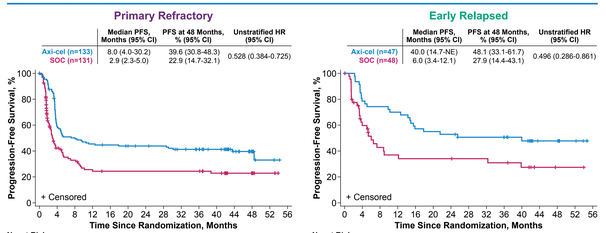
Figure 1. EFS in Patients With Primary Refractory and Early Relapsed LBCL Who Received Axi-Cel vs SOC



Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; HR, hazard ratio; LBCL, large B-cell lymphoma; NE, not estimable; SOC, standard of care.

- EFS was improved with axi-cel vs SOC in primary refractory (HR, 0.448; 95% CI, 0.335-0.598) and in early relapsed LBCL (HR, 0.394; 95% CI, 0.236-0.655; **Figure 1**)

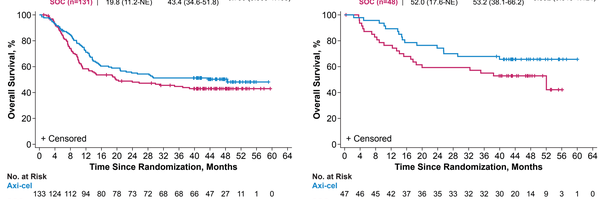
Figure 2. PFS in Patients With Primary Refractory and Early Relapsed LBCL Who Received Axi-Cel vs SOC



Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; NE, not estimable; PFS, progression-free survival; SOC, standard of care.

- PFS was improved with axi-cel versus SOC in primary refractory (HR, 0.528; 95% CI, 0.384-0.725) and in early relapsed LBCL (HR, 0.496; 95% CI, 0.286-0.861; **Figure 2**)

Figure 3. OS in Patients With Primary Refractory and Early Relapsed LBCL Who Received Axi-Cel vs SOC



Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; NE, not estimable; NR, not reached; OS, overall survival; SOC, standard of care.

- OS was numerically prolonged with axi-cel versus SOC in primary refractory (HR, 0.790; 95% CI, 0.565-1.103) and in early relapsed LBCL (HR, 0.592; 95% CI, 0.313-1.121; **Figure 3**)
- Patients with early relapsed LBCL appeared to have longer EFS, PFS, and OS versus patients with primary refractory LBCL in either arm of the study
- Globally, patients who received axi-cel had longer EFS, PFS, and OS compared with those who received SOC, regardless of early relapsed or primary refractory disease

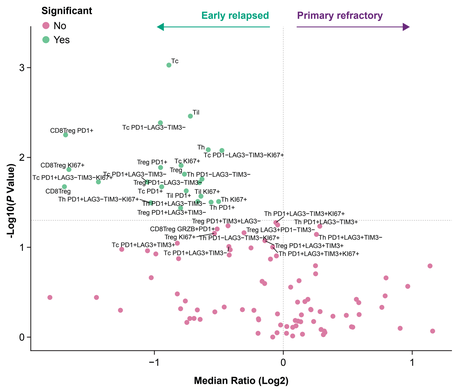
Table 2. Key Safety Data

Characteristic, n (%)	Primary Refractory		Early Relapsed	
	Axi-Cel n=123	SOC n=123	Axi-Cel n=47	SOC n=45
Any TEAE	123 (100)	123 (100)	47 (100)	45 (100)
Grade ≥3 TEAE	112 (91)	99 (80)	43 (91)	41 (91)
Any CRS	112 (91)	-	45 (96)	-
Grade ≥3 CRS	8 (7)	-	3 (6)	-
Any neurologic events[a]	98 (80)	72 (59)	40 (85)	32 (71)
Grade ≥3 neurologic events	31 (25)	12 (10)	13 (28)	5 (11)
Additional AEs of interest				
Neutropenia	59 (48)	19 (15)	16 (34)	10 (22)
Thrombocytopenia	13 (11)	28 (23)	9 (19)	13 (29)

[a] Searched by system organ class.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; SOC, standard of care; TEAE, treatment-emergent adverse event.

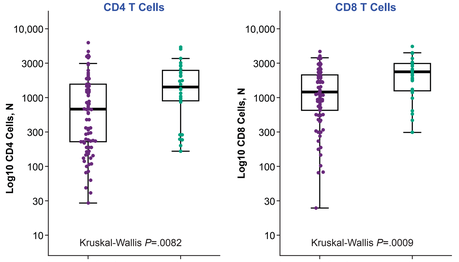
- Safety profiles for patients with primary refractory or early relapsed LBCL were comparable within both arms of the study (**Table 2**)

Figure 4. Immune Cell Population Densities in Patients With Primary Refractory vs Early Relapsed LBCL[a]



[a] Assessed by multiplex immunohistochemistry.
LBCL, large B-cell lymphoma.

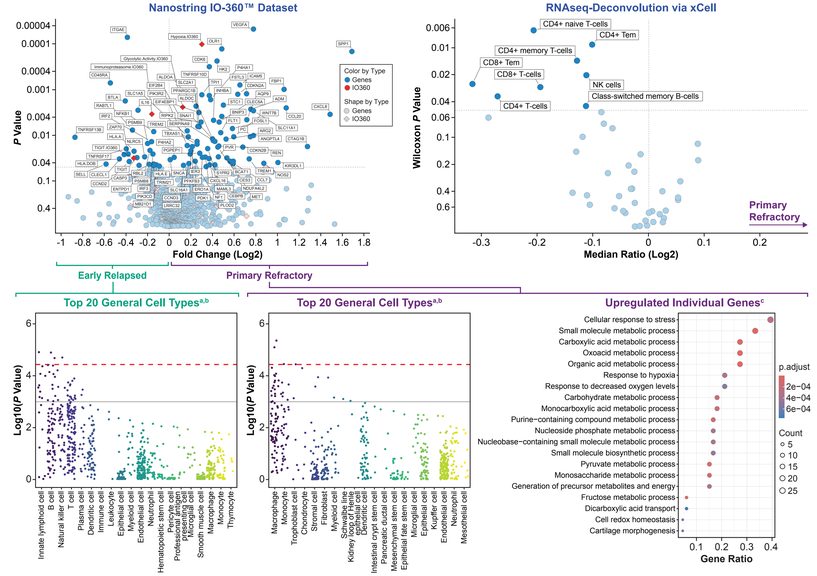
Figure 5. CD4 and CD8 T-Cell Frequencies in Baseline Tumor in Patients With Primary Refractory vs Early Relapsed LBCL[a]



[a] Assessed by multiplex immunohistochemistry.
LBCL, large B-cell lymphoma.

- Significantly higher infiltration of CD4 and CD8 T cells (*P*<.05; **Figures 4 and 5**) was observed in patients with early relapsed versus primary refractory LBCL

Figure 6. Gene Expression Signatures in Patients With Primary Refractory vs Early Relapsed LBCL



[a] Assessed by WebC SEA. [b] Dashed red line indicates the Bonferroni-corrected significance threshold; gray line indicates the nominal significance threshold. [c] Assessed by GO analysis.
GO, gene ontology; LBCL, large B-cell lymphoma; WebC SEA, Web-based Cell-type-Specific Enrichment Analysis.

- Upregulation of hypoxia and glycolytic activity and lower T-cell infiltration was observed in patients with primary refractory LBCL compared with early relapsed LBCL (**Figure 6**)
  - Enrichment of macrophages/monocytes, fibroblasts, myeloid cells, and stromal cells was observed in patients with primary refractory LBCL
  - More lymphoid cell infiltration was observed in patients with early relapsed LBCL

CONCLUSIONS

- Overall, EFS, PFS, and OS were markedly improved in patients who received axi-cel versus SOC in ZUMA-7, regardless of early relapse or primary refractory disease
- The magnitude of improvement was numerically greater in the early relapsed group compared with the primary refractory group
- Based on results herein, patients with lower levels of T-cell infiltration may be more likely to fail 1L chemoimmunotherapy and should be monitored closely for referral to CAR T-cell therapy
- These findings support prompt referral of patients with either relapsed or refractory LBCL for axi-cel as a preferred 2L SOC
- The analysis of tumor microenvironment was a post hoc analysis and carries the limitations inherent to such analysis types

DISCLOSURES

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