Poster
2121

Comparative Effectiveness of Axicabtagene Ciloleucel Versus Historical Standard of Care in Patients With Relapsed or Refractory Follicular Lymphoma: An Analysis of CIBMTR and SCHOLAR-5 Data

Swetha Kambhampati, MD*[1]; Hai-Lin Wang, MPH*[2]; Jiali Yan, MPH[2]; Alex F. Herrera, MD[1]; Matthew J. Frank, MD, PhD[3]; Leslie L. Popplewell, MD[1]; Nausheen Ahmed, MD[4]; Yi Lin, MD, PhD[5]; Frederick L. Locke, MD[6]; Paola Ghione, MD[7]; John G. Gribben, MD, DSc[8]; Timothy Best, PhD[2]; Christine Fu, PhD[2]; Sara Beygi, MD[2]; Markqayne D. Ray, PharmD[2]; John Bian, PhD[2]; Zhen-Huan Hu, MPH[2]; Fang Sun, MD, PhD[2]; Marcelo C. Pasquini, MD, MS[9]; and Caron A. Jacobson, MD[10]

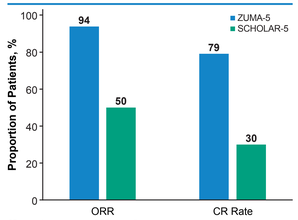
[1]*City of Hope National Medical Center, Duarte, CA, USA;* [2]*Kite, a Gilead Company, Santa Monica, CA, USA;* [3]*Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University, Stanford, CA, USA;* [4]*The University of Kansas Medical Center, Westwood, KS, USA;* [5]*Mayo Clinic Comprehensive Cancer Center, Rochester, MN, USA;* [6]*Moffitt Cancer Center, Tampa, FL, USA;* [7]*Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [8]*Center for Haemato-Oncology, Barts Cancer Institute, Queen University of London, London, UK;* [9]*Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI, USA; and* [10]*Dana-Farber Cancer Institute, Boston, MA, USA*

**Co-primary authors*

BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy that is approved for adults with relapsed or refractory (R/R) follicular lymphoma (FL)[1,2]
- Approval was based on the Phase 2, multicenter ZUMA-5 (NCT03105336) study of axi-cel in patients with R/R indolent non-Hodgkin lymphoma after ≥2 lines of therapy[3]
- A recent study compared patients with R/R FL treated with axi-cel in ZUMA-5 with a matched cohort of patients treated with standard of care (SOC) from the SCHOLAR-5 study[4]
  - A higher overall response rate (ORR) and complete response (CR) rate were observed for axi-cel versus SOC[4] (**Figure 1**)
- There is still a need to further understand the relative effectiveness of axi-cel versus SOC in real-world settings for the treatment of R/R FL, particularly in patient subgroups of interest, such as older patients

Figure 1. ORR and CR Rate for Patients in ZUMA-5 and SCHOLAR-5[3,4]



CR, complete response; ORR, overall response rate.

OBJECTIVE

- To examine comparative effectiveness outcomes of axi-cel versus historical SOC in patients with R/R FL treated with ≥2 lines of therapy in the real-world setting among patients of all ages and those aged ≥65 years

METHODS

Data Sources

- The real-world data were collected from the Center for International Blood and Marrow Transplant Research (CIBMTR®) registry: a prospective collection of patients with R/R FL who received commercial axi-cel
  - Patients from 74 centers in the United States were treated with axi-cel from March 2021 to May 2023 (data cutoff date: May 4, 2023)
- The SCHOLAR-5 study included data from patients with R/R FL who initiated a third or later line of therapy from 7 institutions in 5 countries extracted from 2014-2020 (subcohort A) and post-trial data for selected patients from the pivotal Phase 2 trial of idelalisib (DELTA trial; subcohort B)[5]
  - Progression-free survival (PFS) data were not collected in the DELTA trial, so subcohort B was excluded from the PFS analysis
  - The SCHOLAR-5 cohort in this analysis included patients with R/R FL enrolled from July 2014 to December 2020 (data cutoff date: March 23, 2021) who received historical SOC therapy
    - Chemotherapy ± anti-CD20 therapy (51% of patients)
      - Bendamustine + anti-CD20 (22% of patients)
    - Immunomodulatory drugs (18% of patients)
    - PI3K inhibitor–based therapies (6% of patients)

Patient Eligibility and Study Design

- Eligible patients were aged ≥18 years, had documented R/R FL, were histological Grade 1, 2, or 3a, and received ≥2 prior lines of therapy at index
- Patients were excluded if they had transformed diffused large B-cell lymphoma, central nervous system involvement, prior receipt of CAR T-cell therapy (or other non-transplant cellular therapies), or no post-index information on outcomes

Statistical Analyses

- Imbalance in observed prognostic risk factors between the 2 treatment groups was adjusted via a propensity score analysis using standardized mortality ratio weighting (SMRW; **Figure 2**)
- The primary analyses included weighted univariable analysis and multivariable logistic (ORR and CR rate) or Cox PFS and overall survival (OS) regressions that were adjusted for the covariates after SMRW
  - A subanalysis of patients aged ≥65 years was conducted using the same methods as the primary analysis

Figure 2. Study Design and Analysis

Treatment
- Axi-cel versus SOC

Index Date
- Axi-cel: date of infusion
- SOC: initiation date of the last eligible systemic therapy

Effectiveness Outcomes
- ORR, CR rate, PFS, and OS
- Safety outcomes were not studied because of differences in the safety profiles between axi-cel and SOC

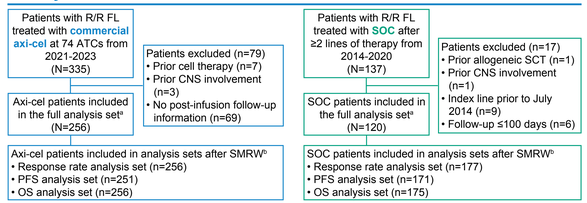
Covariates
- Demographic, baseline characteristics, and prognostic risk variables were considered for SMRW to mitigate imbalance between axi-cel and SOC

Statistical Analysis
- Univariable: descriptive statistics with and without SMRW[a]
- Multivariable: logistic and Cox regressions in the SMR-weighted population[b]

[a] SMRW was calculated separately for each of the 3 effectiveness outcomes (response rates, PFS, and OS) and then separately for the subgroup of patients aged ≥65 years.
[b] A stepwise selection at *P*< 05 was used to select covariates for the multivariate models; candidate variables were age (<65 vs ≥65 years), sex, Eastern Cooperative Oncology Group performance status (0-1 vs ≥2), FL subtype (1 vs 2 vs 3a vs unknown), disease stage at diagnosis (I to II vs III to IV vs unknown), elevated LDH at index (yes vs no vs unknown), hemoglobin at index (<12 vs ≥12 g/dL vs unknown), bulky disease at index (yes vs no vs unknown), number of prior lines of therapy (2 vs 3 vs 4 vs ≥5 vs unknown), prior autologous stem cell transplantation status (yes vs no), prior anti-CD20 mAb + alkylating agent (yes vs no vs unknown), time from start of last prior line to index (<12 vs ≥12 months), and response to last prior line of treatment (relapsed vs refractory vs unknown).
Axi-cel, axicabtagene ciloleucel; CR, complete response; FL, follicular lymphoma; LDH, lactate dehydrogenase; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care; SMRW, standardized mortality ratio weighting.

RESULTS

Figure 3. Study Cohort of the Full Analysis Set Before SMRW and the 3 Analysis Sets After SMRW



[a] The median follow-up time was 7 months in the axi-cel and 37 months in the SOC datasets.
[b] The number of patients in the SOC cohort were weighted for equivalence to real-world data, and the weighted number of patients included in the analysis sets for response rate, PFS, and OS were based on patient data availability.
Axi-cel, axicabtagene ciloleucel; ATC, authorized treatment center; CNS, central nervous system; FL, follicular lymphoma; OS, overall survival; PFS, progression-free survival; R/R, relapsed or refractory; SCT, stem cell transplantation; SMRW, standardized mortality ratio weighting; SOC, standard of care.

Table 1. Baseline Characteristics of Patients of All Ages

Characteristic, %[a]	Full Analysis Set (Before SMRW)		Response Rate Analysis Set (After SMRW)		PFS Analysis Set (After SMRW)		OS Analysis Set (After SMRW)	
	Axi-Cel (n=256)	SOC (n=120)	Axi-Cel (n=256)	SOC (n=177)	Axi-Cel (n=251)	SOC (n=171)	Axi-Cel (n=256)	SOC (n=175)
Age ≥65 years	38	57	38	50	37	49	38	50
Male	58	54	58	53	58	54	58	54
ECOG PS ≥2[b]	2	5	2	7	2	5	2	6
Grade 3a (vs 1 or 2)	37	12	37	28	36	28	37	27
Elevated LDH	34	58	34	36	34	35	34	36
≥3 Prior lines of therapy[c]	83	58	83	52	87	49	83	51
Prior SCT	14	17	14	15	14	14	14	14
Time from start of last prior line to index ≥12 months	36	60	36	37	36	39	36	39
Refractory to last prior line[d]	79	73	79	81	79	79	79	81

[a] Descriptive statistics were calculated among patients with available information, and no imputation was performed for missing values. [b] Variable not considered in SMRW due to lack of variability. [c] Variable not considered in SMRW due to missing data. [d] Refractory was defined as partial remission, stable disease, or progressive disease.
Axi-cel, axicabtagene ciloleucel; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplantation; SMRW, standardized mortality ratio weighting; SOC, standard of care.

- There were clear imbalances between the covariates in the full analysis set without SMRW (**Table 1**)
  - The proportion of patients with elevated lactate dehydrogenase (LDH) was 34% in the axi-cel dataset and 58% in the SOC dataset
  - The proportion of patients with time from start of last prior line to index ≥12 months in the axi-cel and SOC datasets was 36% and 60%, respectively
- After SMRW, the imbalance in the covariates between axi-cel and SOC treatment in the 3 analysis sets was significantly mitigated; however, a residual imbalance remained (standardized mean difference [SMD] >0.2) in the proportions of patients aged ≥65 years and those with ≥3 lines of prior therapy
- The slight differences in the weighted sample size between the 3 different analysis sets reflects the use of SMRW

Table 2. Baseline Characteristics of Patients Aged ≥65 Years

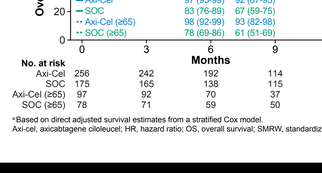
Characteristic, %[a]	Full Analysis Set (Before SMRW)		Response Rate Analysis Set (After SMRW)		PFS Analysis Set (After SMRW)		OS Analysis Set (After SMRW)	
	Axi-Cel (n=97)	SOC (n=68)	Axi-Cel (n=97)	SOC (n=78)	Axi-Cel (n=94)	SOC (n=70)	Axi-Cel (n=97)	SOC (n=78)
Male	52	51	52	49	51	52	52	50
ECOG PS ≥2[b]	1	6	1	12	1	9	1	10
Grade 3a (vs 1 or 2)	37	13	37	33	39	31	37	34
Elevated LDH	39	58	39	43	39	43	39	34
≥3 Prior lines of therapy[c]	81	53	81	50	81	47	81	50
Prior SCT	11	13	11	10	11	9	11	10
Time from start of last prior line to index ≥12 months	48	65	48	47	49	51	48	47
Refractory to last prior line[d]	80	69	80	80	79	77	80	80

[a] Descriptive statistics were calculated among patients with available information, and no imputation was performed for missing values. [b] Variable not considered in SMRW due to lack of variability. [c] Variable not considered in SMRW due to missing data. [d] Refractory was defined as partial remission, stable disease, or progressive disease.
Axi-cel, axicabtagene ciloleucel; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; SCT, stem cell transplantation; SMRW, standardized mortality ratio weighting; SOC, standard of care.

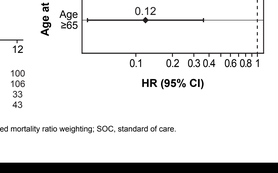
- SMRW for the analysis subgroups of patients aged ≥65 years were performed separately
- Compared with the distributions of the covariates in patients of all ages receiving axi-cel, the proportion of patients with elevated LDH was slightly higher in patients aged ≥65 years before SMRW (34% vs 39%, respectively), and the proportion of patients with time from start of last prior line to index ≥12 months was higher among patients aged ≥65 years before SMRW (36% vs 48%, respectively; **Table 2**)
- After SMRW, the imbalance in all the covariates in patients aged ≥65 years was significantly improved between axi-cel and SOC, except in patients with Eastern Cooperative Oncology Group performance status ≥2, patients with ≥3 lines of prior therapy, and patients who were refractory to the last prior line of therapy (SMD >0.2)

Figure 4. Univariable/Multivariable Logistic Regression Analysis of ORR and CR Rate After SMRW

Effectiveness Outcomes With Axi-Cel Versus SOC (SMRW)



Adjusted ORs With Axi-Cel Versus SOC (SMRW)

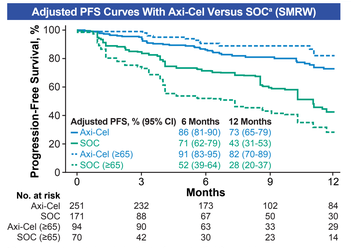


Axi-cel, axicabtagene ciloleucel; CR, complete response; OR, odds ratio; ORR, overall response rate; SMRW, standardized mortality ratio weighting; SOC, standard of care.

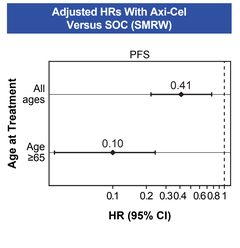
- The ORR was 92% (CR rate, 84%) in all patients treated with axi-cel and was 67% (CR rate, 37%) in all patients treated with SOC (**Figure 4**)
  - ORR and CR rate were consistent in both treatments among the subgroup of patients aged ≥65 years
- The unadjusted results were consistent with the odds ratios estimated from the logistic regressions, which showed statistically significantly higher response rates with axi-cel versus SOC

Figure 5. Multivariable Cox Regression Analysis of PFS After SMRW

Adjusted PFS Curves With Axi-Cel Versus SOC[a] (SMRW)



Adjusted HRs With Axi-Cel Versus SOC (SMRW)

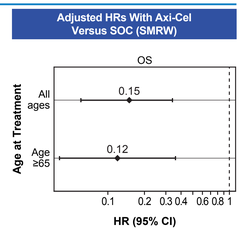


[a] Based on direct adjusted survival estimates from a stratified Cox model.
Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; PFS, progression-free survival; SMRW, standardized mortality ratio weighting; SOC, standard of care.

Figure 6. Multivariable Cox Regression Analysis of OS After SMRW

Adjusted OS Curves With Axi-Cel Versus SOC[a] (SMRW)

Adjusted HRs With Axi-Cel Versus SOC (SMRW)



[a] Based on direct adjusted survival estimates from a stratified Cox model.
Axi-cel, axicabtagene ciloleucel; HR, hazard ratio; OS, overall survival; SMRW, standardized mortality ratio weighting; SOC, standard of care.

- Adjusted PFS was higher with axi-cel versus SOC after multivariable Cox regression with SMRW (**Figure 5**)
  - Six-month PFS rates were 86% with axi-cel and 71% for SOC among patients of all ages and 91% and 52%, respectively, for patients aged ≥65 years
  - In patients of all ages, a benefit with axi-cel versus SOC was observed (hazard ratio [HR], 0.41); in patients age ≥65 years, the HR was 0.10, suggesting a more pronounced benefit with axi-cel versus SOC in the older subgroup
- Adjusted OS was higher with axi-cel versus SOC after multivariable Cox regression with SMRW (**Figure 6**)
  - Six-month OS rates were 97% with axi-cel and 83% for SOC among patients of all ages and 98% and 78%, respectively, in patients aged ≥65 years
  - The HR with axi-cel versus SOC in patients aged ≥65 years (HR, 0.12) was similar to that in patients of all ages (HR, 0.15), suggesting a consistent benefit of axi-cel over SOC regardless of age

CONCLUSIONS

- The results of this study demonstrated that axi-cel was more effective in the real world than historical SOC in patients with R/R FL, which is broadly consistent with results reported in a previous study that examined axi-cel use in a clinical trial[4]
- A subgroup analysis of patients aged ≥65 years showed that these patients also benefited significantly from axi-cel versus historical SOC
- These findings suggest that axi-cel addresses an unmet medical need in patients with R/R FL after ≥2 lines of therapy
- Limitations in the analysis include differences in the treatment timeframe between cohorts and potential gaps in data reporting in real-world cohorts
- Future research is needed to explore real-world outcomes with axi-cel treatment in patients with R/R FL, including
  - Use of data with more comprehensive patient-level prognostic risk factors (eg, progression of disease within 24 months after initial diagnosis)
  - Longer follow-up, given the 7-month median follow-up time for patients treated with axi-cel in the CIBMTR dataset
  - An analysis of the comparative effectiveness of axi-cel versus contemporary SOC (eg, bispecific antibodies)

REFERENCES

1. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2022.
2. YESCARTA® (axicabtagene ciloleucel) [summary of product characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2022.
3. Jacobson CA, et al. *Lancet Oncol*. 2022;23:91-103.
4. Ghione P, et al. *Blood*. 2022;140:851-860.
5. Gopal AJ, et al. *N Engl J Med*. 2014;370:1008-1018.

ACKNOWLEDGMENTS

- The patients, families, friends, and caregivers
- Medical writing support was provided by Edward Sheetz, PhD, and Christine N. Morrison, PhD, of Nexus Global Group Science, funded by Kite, a Gilead Company
- This study was funded by the National Cancer Institute (CIDR [U24 CA233032]) and Kite, a Gilead Company
- This study is a collaboration between CIBMTR and Kite, a Gilead Company. CIBMTR® is a research collaboration between National Marrow Donor Program®/ Be The Match® and the Medical College of Wisconsin, and operates the Cellular Immunotherapy Data Resource (CIDR)

DISCLOSURES

Full author disclosures are available through the virtual meeting platform

Presented at the 2023 American Society of Hematology Annual Meeting