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Impact of Complete Response on Long-Term Survival Among Patients Receiving Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma

Armin Ghobadi, MD[1]; Theodora Anagnostou, MD[2]; Jacques Azzi, MD[2]; Mehdi Hamadani, MD[3]; Brent Logan, PhD[3]; Michael T. Hemmer, MS[4]; Sairah Ahmed, MD[5]; Sushma Bharadwaj, MD[6]; John H. Baird, MD[7]; Caron A. Jacobson, MD, MMSc[8]; Frederick L. Locke, MD[9]; Hai-Lin Wang, MPH[4]; Myrna Nahas, MD[4]; Timothy Best, PhD[4]; Sachin Vadgama, MPharm, MSc[4]; Zhen-Huan Hu, MPH[4]; and Marcelo C. Pasquini, MD, MS[3]

[1]Washington University, St. Louis, MO; [2]Mount Sinai Hospital System, New York, NY; [3]Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI; [4]Kite, a Gilead Company, Santa Monica, CA; [5]University of Texas MD Anderson Cancer Center, Houston, TX; [6]Stanford University, Palo Alto, CA; [7]City of Hope National Medical Center, Duarte, CA; [8]Dana-Farber Cancer Institute, Boston, MA; and [9]Moffitt Cancer Center, Tampa, FL.

CIBMTR® & Kite, a Gilead Company Collaboration Study

BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an anti-CD19 chimeric antigen receptor T-cell therapy approved for relapsed or refractory (R/R) large B-cell lymphoma (LBCL)[1,2]
- After 5 years of follow-up, 58% of patients with R/R LBCL in the ZUMA-1 study achieved a complete response (CR)[3]
  - Among those who achieved CR, the 5-year overall survival (OS) rate was 64% and median OS was not yet reached
- Published data have shown that beneficial short-term efficacy outcomes may correlate with superior long-term outcomes, including in the setting of diffuse LBCL (DLBCL)[4,5]
- The ability to evaluate long-term survival earlier in a patient's treatment journey could yield additional positive clinical outcomes

OBJECTIVES

- To evaluate CR as a time-to-event endpoint and identify prognostic factors associated with CR in patients with LBCL treated with axi-cel in real-world settings
- To evaluate OS in patients with ≥6 months of follow-up post-infusion of axi-cel by CR status at 6 months

METHODS

Figure 1. Study Design and Analysis

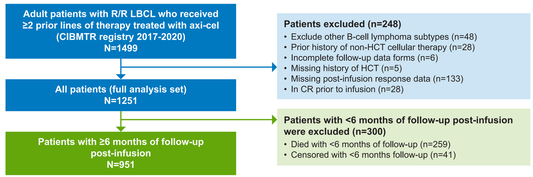
Prospective Cohort Study	• Data were prospectively collected as part of a PASS through the CIBMTR® registry of adult patients (≥18 years) with R/R LBCL treated with axi-cel between 2017 and 2020 • Data cutoff: **Sep 25, 2023**
Outcomes of Interest	• **Effectiveness:** CR, post-infusion REL/PD, PFS, and OS
Statistical Analysis	• CR and post-infusion REL/PD were estimated by cumulative incidence function[a] – Index date for CR defined as date of axi-cel infusion • PFS and OS were described via Kaplan-Meier estimate • Landmark analysis was conducted among patients with ≥6 months of follow-up post-infusion – Index date defined as 6 months post-infusion and subsequent outcomes were evaluated after index date – OS estimated for patients in CR (achieved and maintained CR) versus not in CR at 6 months post-infusion – PFS and REL/PD were estimated for patients in CR at 6 months – Cause-specific Cox regression models were fit to evaluate prognostic factors for CR, and for OS following landmark date of 6 months post-infusion[b]

[a] Competing risks for CR were post-infusion REL/PD, post-infusion anti-cancer treatment, or death. Competing risk for REL/PD was death without prior REL/PD. [b] Baseline factors considered in the multivariate models were age at infusion, sex, race/ethnicity, Eastern Cooperative Oncology Group performance status, number of prior lines of therapy, comorbidities prior to infusion (hepatic [moderate/severe], hepatic [mild], infection requiring antimicrobial treatment, renal [moderate/severe], pulmonary [severe], diabetes requiring non-diet treatment in the prior 4 weeks, severe underweight), disease factors at diagnosis (subtype, histologic transformation, Ann Arbor disease stage), disease factors prior to infusion (bulky disease, number of extranodal involvement sites, chemosensitivity), prior hematopoietic cell transplant, year of infusion, time from leukapheresis to infusion, and bridging therapy.

Axi-cel, axicabtagene ciloleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete response; HCT, hematopoietic cell transplantation; LBCL, large B-cell lymphoma; PASS, post-authorization safety study; PFS, progression-free survival; R/R LBCL, relapsed or refractory large B-cell lymphoma; REL/PD, relapse/progressive disease.

RESULTS

Figure 2. Study Cohort and Patient Disposition



Axi-cel, axicabtagene ciloleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete response; HCT, hematopoietic cell transplantation; R/R LBCL, relapsed or refractory large B-cell lymphoma.

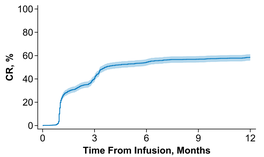
Table 1. Baseline Characteristics of Full Analysis Set

Characteristic	Full Analysis Set (N=1251)
Age, years, at infusion Median (range) <65, n (%) ≥65, n (%)	62 (19-86) 777 (62) 474 (38)
Male sex, n (%)	805 (64)
ECOG PS 0-1, n (%)[a]	1082/1136 (95)
No. of prior therapies, median (IQR)	3 (2-4)
Prior autologous HCT, n (%)[a]	357 (29)
Disease subtype at initial diagnosis, n (%) DLBCL PMBCL HGBCL	 1009 (81) 38 (3) 204 (16)
Double- or triple-hit lymphoma at initial diagnosis, n (%)[a]	186/729 (26)
Histologic transformation at initial diagnosis, n (%)	346 (28)
Bulky disease prior to infusion, n (%)[a,b]	55/922 (6)
Chemoresistant status prior to infusion, n (%)[a]	848/1108 (77)
Bridging therapy use, n (%)[a]	392/1218 (32)
Time from leukapheresis to infusion, days, median (IQR)	27 (25-32)

[a] Percentage calculated among patients with evaluable data. [b] Bulky disease defined as maximum nodal size >10 cm.
DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplantation; HGBCL, high-grade B-cell lymphoma; IQR, interquartile range; no., number; PMBCL, primary mediastinal B-cell lymphoma.

- Of the 1251 patients analyzed, median age was 62 years, median lines of prior therapy was 3, and median follow-up time was 36.9 months (range, 0.9-62.2; **Table 1**)

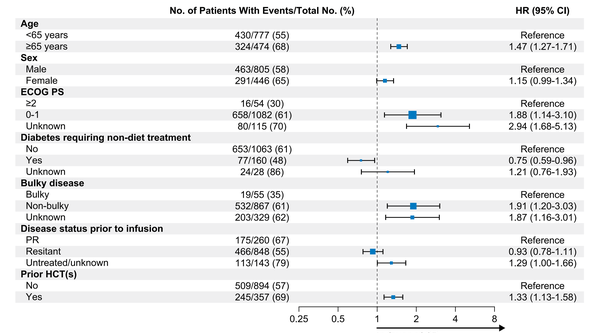
Figure 3. Cumulative Incidence of CR in Full Analysis Set[a]



- Among all 1251 patients analyzed
  - 59% of patients achieved CR post-infusion; 92% of which occurred within 6 months (**Figure 3**)
  - Cumulative incidence rates of CR were 41% (95% CI, 38-43) by 3 months, 54% (95% CI, 51-57) by 6 months, and 59% (95% CI, 56-61) by 12 months (**Figure 3**)

[a] Post-infusion REL/PD, anti-cancer therapy, or death were treated as competing risks to CR. Patients were censored at subsequent hematopoietic cell transplant and date of last contact (for those patients whose best response was partial response or stable disease and had not experienced a competing risk).
CR, complete response; no., number; REL/PD, relapse/progressive disease.

Figure 4. Multivariate Analysis of Baseline Factors Associated With Cumulative Incidence of CR in Full Analysis Set



CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplantation; HR, hazard ratio; no., number; PR, partial response.

- Multiple baseline factors were associated with earlier CR, including older age, female sex, lower Eastern Cooperative Oncology Group performance score, non-bulky disease, and history of prior hematopoietic cell transplantation (HCT; **Figure 4**)

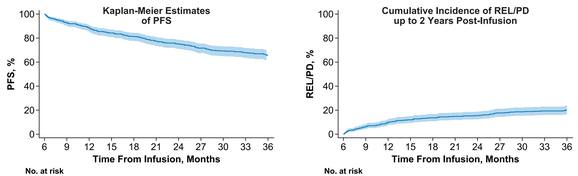
Table 2. Baseline Characteristics of Patients With ≥6 Months of Follow-Up Post-Infusion (N=951)

Characteristic	In CR at 6 mo (n=518)[a]	Not in CR at 6 mo (n=433)[a]
Age, years, at infusion median (IQR) Median (range) <65, n (%) ≥65, n (%)	 **63 (19–85)** **289 (56)** **229 (44)**	 **60 (20–86)** **290 (67)** **143 (33)**
Male sex, n (%)	311 (60)	282 (65)
ECOG PS 0-1, n (%)[b]	**461/466 (99)**	**386/404 (96)**
No. of prior therapies, median (IQR)	3 (2–4)	3 (2–4)
Prior autologous HCT, n (%)[b]	**179/518 (35)**	**99/433 (23)**
Disease subtype at initial diagnosis, n (%) DLBCL PMBCL HGBCL	 438 (85) 14 (3) 66 (13)	 343 (79) 20 (5) 70 (16)
Double- or triple-hit lymphoma at initial diagnosis, n (%)[b]	62/280 (22)	64/259 (25)
Histologic transformation at initial diagnosis, n (%)	135 (26)	119 (27)
Bulky disease prior to infusion, n (%)[b,c]	**9/376 (2)**	**27/327 (8)**
Chemoresistant status prior to infusion, n (%)[b]	304/431 (71)	298/397 (75)
Bridging therapy use, n (%)[b]	**127/503 (25)**	**141/422 (33)**
Time from leukapheresis to infusion, days, median (IQR)	27 (26–31)	27 (25–32)

[a] Bold text indicates statistically significant difference for characteristic between patients in CR, and not in CR, at 6 mo post-infusion. [b] Percentage calculated among patients with evaluable data. [c] Bulky disease defined as maximum nodal size >10 cm. Fisher's exact test was used to analyze categorical variables and Wilcoxon rank sum test was used to test continuous variables.
CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplantation; HGBCL, high grade B-cell lymphoma; IQR, interquartile range; mo, month; no., number; PMBCL, primary mediastinal B-cell lymphoma.

- Of the 951 patients with ≥6 months of follow-up post-infusion, 518 were in CR at 6 months and 433 were not in CR at 6 months
- Patients who were in CR at 6 months had a higher median age, lower ECOG PS, were more likely to have a prior autologous HCT, and less likely to have bulky disease or received prior bridging therapy than patients not in CR at 6 months (**Table 2**)

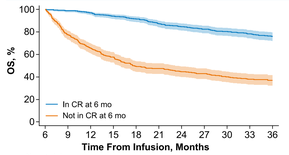
Figure 5. PFS and Cumulative Incidence of REL/PD Among Patients With CR at 6 Months



CR, complete response; no., number; PFS, progression-free survival; REL/PD, relapse/progressive disease.

- Among patients with CR at 6 months (n=518), 2-year estimated PFS rate was 75% (95% CI, 71-79) and 2-year estimated cumulative incidence of REL/PD was 16% (95% CI, 13-19; **Figure 5**)

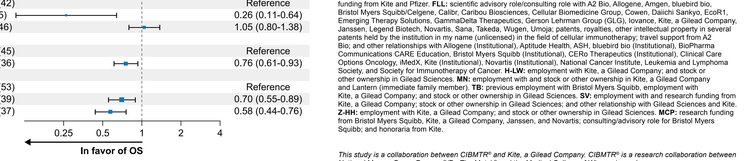
Figure 6. Adjusted OS in Patients With ≥6 Months Follow-Up by CR Status at 6 Months Post-Infusion[a]



- Among patients with ≥6 months of follow-up post-infusion, patients who achieved CR had significantly improved OS versus patients who did not achieve CR (hazard ratio, 4.11 [95% CI, 3.32-5.09]; **Figure 6**)

[a] Direct adjusted survival[a] based on a stratified Cox regression model adjusted for the following: age at infusion, disease subtype at initial diagnosis, year of infusion.
CR, complete response; mo, month; no., number; OS, overall survival.

Figure 7. Multivariate Analysis of Baseline Factors Associated With OS Among Patients With ≥6 Months of Follow-Up



CR, complete response; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; HR, hazard ratio; mo, month; no., number; OS, overall survival; PMBCL, primary mediastinal B-cell lymphoma.

- Patient age, number of lines of prior therapy, year of infusion, and disease subtype were found to be associated with OS after 6 months post-infusion (**Figure 7**)

CONCLUSIONS

- In real-world settings, most complete responders achieved CR by 6 months following axi-cel infusion for the treatment of R/R LBCL
- Patients who were in CR 6 months post-infusion experienced significantly improved OS compared with patients who were not in CR at 6 months
  - Risk of mortality was approximately 4.5 times greater for 6-month survivors not in CR, even while accounting for other clinically meaningful baseline factors
  - Among those patients in CR at 6 months, the 2-year post-infusion PFS and REL/PD rates were 75% and 16%, respectively
- CR should be assessed for potential surrogacy as a measure for survival in future clinical trial design

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DISCLOSURES

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