Poster
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Real-World Safety Outcomes of Axicabtagene Ciloleucel in Patients With Diffuse Large B-Cell Lymphoma and Follicular Lymphoma in Europe and United States: A Systematic Review and Meta-Analysis

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BACKGROUND

- The volume of real-world evidence (RWE) of axicabtagene ciloleucel (axi-cel) safety has increased following its approvals in relapsed/refractory (R/R) large B-cell lymphoma (LBCL) and follicular lymphoma (FL)[1-4]
  - Notably, there has been a marked increase in large national registries in European settings reporting real-world safety data[5-7]
  - Several recent RWE studies around the world have documented evolving adverse event management strategies[3-8]
- This growth in literature provided an opportunity to expand on a previous systematic literature review (SLR) of axi-cel, focusing on safety in its approved indications[9]

OBJECTIVE

- To report an updated SLR synthesizing RWE on axi-cel safety in R/R diffuse LBCL (DLBCL) and FL, quantifying evidence through meta-analyses between the United States (US) and Europe, and over time

METHODS

Systematic Literature Review

- Embase and MEDLINE were searched for eligible studies published in or after 2017, along with 10 conferences that were hand-searched for relevant abstracts
  - Eligible studies included observational analyses of axi-cel in R/R DLBCL and/or R/R FL that reported safety outcomes
  - Studies of clinical trial participants and case reports were excluded
- All publications were critically appraised by 2 independent reviewers and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[10]
- Cohort mapping involved combining publications from the same source (eg, a single center or registry) into the same patient cohort
- Data extraction was done in dual and independently
- Study quality was assessed using the Newcastle-Ottawa Scale (NOS)[11]

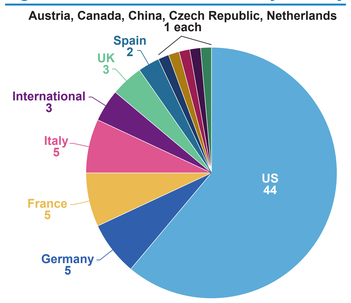
Meta-Analyses

- Evidence was synthesized by region (US, Europe, and Other) and time (cohorts ending before vs starting in or after December 2019)
  - Random effects were implemented using DerSimonian-Laird methods[12]
- Meta-analyses were conducted only on non-overlapping cohorts to avoid double counting of patients
  - If the same centers contributed to multiple cohorts, only the cohort with the larger sample size was included

RESULTS

- A total of 6972 records were identified (41 through hand searches); 206 publications on 73 cohorts were included in the final evidence base
  - One cohort reporting a prognostic subgroup was removed from the analysis, with 72 cohorts remaining for the final analysis
  - Most cohorts were retrospective cohort studies
  - Almost all publications reported DLBCL cohorts, along with some more recent publications that included both DLBCL and FL; only 1 cohort had exclusively patients with FL
- Several recent full-text publications were from European registries
  - US cohorts generally started earlier than those in Europe
- Overall, cohorts had high quality scores in selection and outcomes domains (score of 3 each on the NOS)
  - Full-text publications or conference presentations were available for 54 cohorts, and only 18 cohorts had reports limited to abstracts
- The 72 patient cohorts included in the final analysis were primarily US based; the remaining cohorts were mostly in Europe, with a single cohort each in China and Canada (**Figure 1**)
  - One study included patients from Israel and the US
- Several single-center cohorts overlapped with multicenter registry cohorts, with the highest level of overlap observed with the US-based CIBMTR registry

Figure 1. Distribution of Cohorts by Country



UK, United Kingdom; US, United States.

RESULTS *(Continued)*

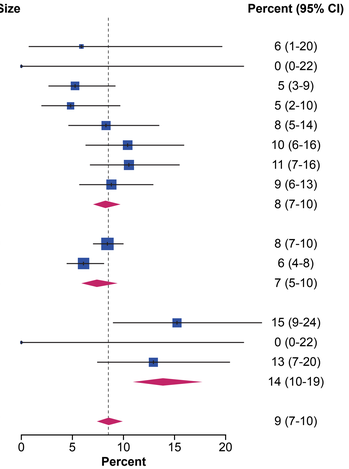
Table 1. Meta-Analysis of Patient Characteristics

Characteristic (95% CI)	Europe		United States		Other	
	N Cohorts	Estimate	N Cohorts	Estimate	N Cohorts	Estimate
Males, %	7	62.9 (59.4-66.3)	2	63.2 (59.4-66.9)	2	59.0 (49.5-67.2)
Median age, years	9	58.3 (55.8-60.7)	2	62.1 (61.4-62.7)	2	57.0 (54.2-59.9)
Median follow-up, months	5	11.4 (9.4-13.3)	1	25.1 (24.8-25.4)	–	–
Median prior lines, n	8	2.6 (2.2-3.0)	2	3.5 (2.5-4.5)	1	2.0 (1.7-2.3)
Prior ASCT, %	8	23.5 (18.0-29.9)	2	19.6 (9.4-36.3)	2	23.0 (3.8-69.5)
High LDH, %	6	38.5 (18.8-62.9)	2	22.7 (13.8-35.0)	–	–
DLBCL, %	8	70.8 (60.8-79.1)	2	80.4 (77.8-82.8)	2	77.0 (66.5-84.8)
PMBCL, %	6	9.3 (4.6-17.8)	1	3.0 (2.2-4.1)	2	4.0 (1.8-10.1)
TFL, %	6	16.8 (8.7-30.2)	2	5.6 (0.4-48.0)	2	11.0 (1.4-50.4)
HGBL, %	1	13.8 (9.1-20.4)	1	16.2 (14.3-18.3)	1	7.0 (3.3-13.8)
Double/triple-hit disease, %	5	14.4 (7.6-25.7)	1	14.7 (13.0-16.7)	1	27.0 (10.4-53.3)
IPI ≥3, %	6	43.8 (37.3-50.5)	11	45.3 (35.2-55.9)	1	50.0 (40.9-60.1)
ECOG ≥2, %	6	9.6 (8.0-11.5)	1	4.4 (3.4-5.6)	1	31.0 (22.5-40.3)
Bridging therapy, %[a]	8	81.8 (76.3-86.3)	2	13.6 (5.0-32.1)	1	69.0 (59.7-77.5)
Median time from apheresis to infusion, days	5	37.8 (35.1-40.6)	2	27.6 (26.6-28.5)	1	21.0 (19.9-22.1)

Values accounted for likely patient overlap among cohorts.
[a] Rates reflect how bridging therapy was captured in each cohort.
ASCT, autologous stem cell transplantation; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma.

- Patient characteristics were largely consistent between US and European cohorts, with the following exceptions (**Table 1**)
  - Median follow-up was numerically shorter in European cohorts vs those in the US (11.4 vs 25.1 months)
  - Median time from apheresis to infusion was numerically longer in Europe than in the US (37.8 vs 27.6 days), though within the range of the previous report[9]
- There was a shift toward a more clinically advanced population in the RWE studies than clinical trials of axi-cel, with inclusion of bridging therapy, allogeneic stem cell transplantation, and Eastern Cooperative Oncology Group score ≥2 being the most common factors that would have led to clinical trial ineligibility[13,14]

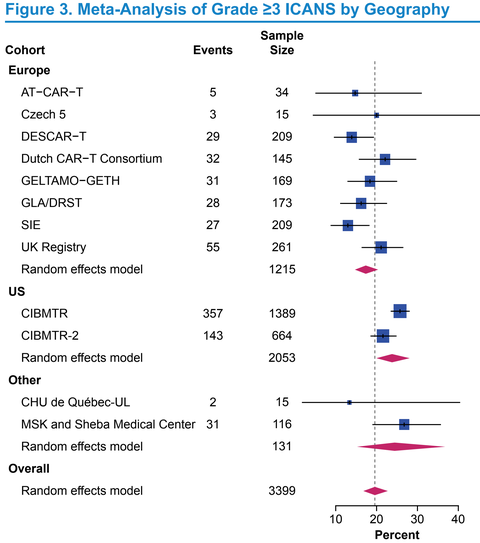
Figure 2. Meta-Analysis of Grade ≥3 CRS by Geography



CIBMTR-2 was a more recent cohort, with infusion dates not overlapping with CIBMTR.
AT-CAR-T, Austrian CAR-T Network; CAR-T, chimeric antigen receptor T-cell therapy; CHU de Québec-UL, Centre Hospitalier Universitaire de Québec-Université Laval; CIBMTR, Center for International Blood and Marrow Transplant Research; CRS, cytokine release syndrome; Czech 5, five treatment centers in Czechia; DESCAR-T, Dispositif d'Enregistrement et Suivi des patients traités par CAR-T; GELTAMO-GETH, Grupo Español de Trasplante Hematopoyético y Terapia Celular; GLA/DRST, German Lymphoma Alliance/Deutsches Register für Stammzelltransplantation; MSK, Memorial Sloan Kettering; SIE, Societa Italiana di Ematologia; UK, United Kingdom; US, United States.

- Estimated incidence of any grade cytokine release syndrome (CRS) was 88% (95% CI, 85-91) for Europe and 82% (95% CI, 81-84) for the US
- Grade ≥3 CRS was estimated at 8% (95% CI, 7-10) for Europe and 7% (95% CI, 5-10) for the US (**Figure 2**)
- The rate of Grade ≥3 CRS numerically reduced from 11% (95% CI, 7-16) before December 2019 to 8% (95% CI, 5-12) afterward

Figure 3. Meta-Analysis of Grade ≥3 ICANS by Geography



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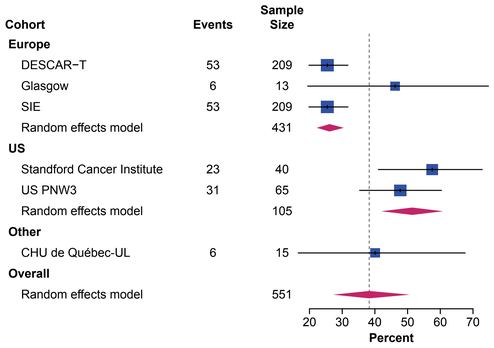
- Estimated incidence of any grade immune effector cell-associated neurotoxicity syndrome (ICANS) was 47% (95% CI, 41-53) for Europe and 50% (95% CI, 40-60) for the US
- The incidence of Grade ≥3 ICANS was numerically lower in Europe (17% [95% CI, 15-20]) than the US (24% [95% CI, 20-28]) (**Figure 3**)
  - The estimates for Grade ≥3 ICANS for both the US and Europe were within the range of the ZUMA-1 rates[13,15]
- Grade ≥3 ICANS numerically reduced after December 2019 from 24% (95% CI, 17-33) to 20% (95% CI, 16-25)

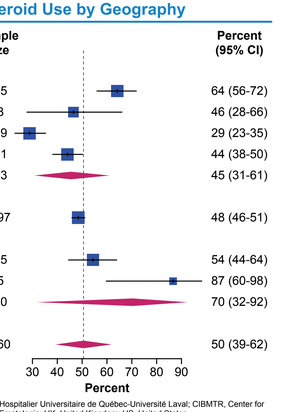
Figure 4. Meta-Analysis of Prolonged Grade ≥3 Neutropenia by Geography



Prolonged neutropenias were those present at or after 1 month post-infusion (Day 28 or 30).
CHU de Québec-UL, Centre Hospitalier Universitaire de Québec-Université Laval; DESCAR-T, Dispositif d'Enregistrement et Suivi des patients traités par CAR-T; PNW3, Seattle Cancer Care Alliance, and Fred Hutchinson Cancer Research Center; SIE, Societa Italiana di Ematologia; US, United States.

- Estimated incidence of any grade prolonged neutropenia in Europe was 47% (95% CI, 31-63; US-based data were not available)
- Estimated incidence of Grade ≥3 prolonged neutropenia (present at or after 1 month post-infusion) was higher in the US (51% [95% CI, 42-61]) than in Europe (26% [95% CI, 22-30]; **Figure 4**)
- A similar trend between regions was observed with thrombocytopenia and anemia

Figure 5. Meta-Analysis of Corticosteroid Use by Geography



CAR-T, chimeric antigen receptor T-cell therapy; CHU de Québec-UL, Centre Hospitalier Universitaire de Québec-Université Laval; CIBMTR, Center for International Blood and Marrow Transplant Research; SIE, Societa Italiana di Ematologia; UK, United Kingdom; US, United States.

- Rates of tocilizumab use in Europe vs US were 71% (95% CI, 67-74) vs 58% (95% CI, 55-61)
- Corticosteroid use was 45% (95% CI, 31-61) in Europe vs 48% (95% CI, 46-51) in the US (**Figure 5**)
- Tocilizumab use was consistent before and after December 2019 (70% [95% CI, 59-78] vs 72% [95% CI, 61-81]), while steroid use numerically increased (54% [95% CI, 41-67] vs 67% [95% CI, 56-77])
- Rates of intensive care unit admission were 20% (95% CI, 14-28) in Europe and 24% (95% CI, 15-37) in the US

CONCLUSIONS

- RWE of axi-cel in patients with R/R DLBCL and FL was robust, with a marked increase in quantity and quality from Europe since the prior analysis[9]
- Overall, safety was manageable and consistent between regions and with clinical trials[13-15]
- Evolving management in the real world may have correlated with improved safety over time

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- Full author disclosures are available through the Quick Response (QR) code

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