Check for updates

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

Second Primary Malignancies After Commercial CAR T Cell Therapy: Analysis of FDA Adverse Events Reporting System (FAERS)

Tracking no: BLD-2024-024166R1

Magdi Elsallab (Harvard Medical School, United States) Moataz Ellithi (University of Nebraska Medical Center, United States) Matthew Lunning (Fred and Pamela Buffett Cancer Center at the University of Nebraska Medical Center, United States) Christopher D'Angelo (University of Nebraska Medical Center, United States) Jihyun MA (Department of Biostatistics, University of Nebraska Medical Center, United States) Miguel-Angel Perales (Memorial Sloan Kettering Cancer Center, United States) Matthew Frigault (Massachusetts General Hospital, United States) Marcela Maus (Massachusetts General Hospital, Harvard Medical School, United States)

Abstract:
Second primary malignancies (SPMs) were reported in 536 out of 12,394 (4.3%) adverse event reports following CAR T cell therapies in the FDA Adverse Event Reporting System (FAERS). Myeloid and T-cell neoplasms were disproportionately more frequently reported, warranting further follow-up.

Conflict of interest: COI declared - see note

COI notes: M. Lunning reports research support by BMS and consultancy for AbbVie, AZ, BMS, Caribou, Diachi Sankyo, Fate Therapeutics, Genentech, Genmab, Ipsen, Janssen, Kite, Loxo, Nurix, Recordati, Regeneron, SeaGen, Takeda, ViTToria C. D'Angelo reports being on the advisory boards of Seagen, BMS, Abbvie, Ono Pharma. He received research funding from Ono Pharma, BMS, Fate Therapeutics, Curis Inc, Beigene and has provided consultation to Abbvie. M. Perales reports honoraria from Adicet, Allogene, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, ImmPACT Bio, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Sanofi, Syncopation, VectivBio AG, and Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of Nexlmmune. He has ownership interests in Nexlmmune, Omeros and OrcaBio. He has received institutional research support for clinical trials from Allogene, Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis. M. J. Frigault reports consultancy for BMS, Novartis, Kite, Arcellx, Iovance, Cytoagents. M.V. Maus is an inventor on patents related to adoptive cell therapies, held by Massachusetts General Hospital (some licensed to Promab) and University of Pennsylvania (some licensed to Novartis). M.V.M. holds equity in 2SeventyBio, Century Therapeutics, Neximmune, Oncternal, and TCR2 and has served as a consultant for multiple companies involved in cell therapies. M.V.M. is on the Board of Directors of 2Seventy Bio. M.V.M. has received grant/research support from CRISPR Therapeutics, Kite Pharma, Servier, and Novartis. All other authors declare no competing interests.

Preprint server: No;

Author contributions and disclosures: ME and MOE contributed to study conception and design, data analysis and interpretation, figure creation, and draft manuscript preparation. JM contributed to the data compilation and curation. ML, CD, MF, MP, and MM contributed to data interpretation, manuscript drafting and editing. All authors reviewed the results and approved the final version of the manuscript.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: For original data, please contact MVMAUS@mgh.harvard.edu

Clinical trial registration information (if any):

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

Title: Second Primary Malignancies After Commercial CAR T Cell Therapy: Analysis of FDA Adverse Events Reporting System (FAERS)

Running title: Second Primary Malignancies After CAR T Therapy

Authors:

Magdi Elsallab, MD, PhD [1,2,*]; Moataz Ellithi, MD [3,*]; Matthew A. Lunning, DO [3]; Christopher D'Angelo, MD [3]; Jihyun Ma, MS., MA.[4]; Miguel-Angel Perales, MD [5,6]; Matthew Frigault, MD [2]; Marcela V. Maus, MD, PhD [2]

Affiliations:

1. Harvard-MIT Center for Regulatory Science, Harvard Medical School, Boston, MA, USA.
2. Cellular Immunotherapy Program, Mass General Cancer Center, and Department of Medicine, Harvard Medical School, Boston, MA, USA.
3. Fred and Pamela Buffet Cancer Center, University of Nebraska Medical Center, Omaha, NE, USA.
4. Department of Biostatistics, University of Nebraska Medical Center, Omaha, NE, USA.
5. Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
6. Department of Medicine, Weill Cornell Medical College, New York, NY, USA.

* These authors have contributed equally.

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

***Correspondence to:**

Marcela V Maus

Massachusetts General Hospital Cancer Center

149 13th Street

Room 3.216

Charlestown MA 02129

email: MVMAUS@mgh.harvard.edu

Keywords: CAR T; Safety; Second primary neoplasm; T-cell Lymphoma; Lymphoma; Leukemia; Myeloma; Myeloid neoplasm; Myelodysplastic syndrome

Data sharing statement: For original data, please contact MVMAUS@mgh.harvard.edu

Abstract word count: 40

Text word count: 1194

Number of figures and tables: 2

Number of references: 24

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

ABSTRACT

Second primary malignancies (SPMs) were reported in 536 out of 12,394 (4.3%) adverse event reports following CAR T cell therapies in the FDA Adverse Event Reporting System (FAERS). Myeloid and T-cell neoplasms were disproportionately more frequently reported, warranting further follow-up.

TO THE EDITOR:

Chimeric antigen receptor T cell therapies (CAR T) have emerged as groundbreaking treatments for different hematologic malignancies [1]. To date, the Food and Drug Administration (FDA) has approved six CAR T products for relapsed or refractory B cell acute lymphoblastic leukemia, diffuse large B cell lymphoma, mantle cell lymphoma, follicular lymphoma, and multiple myeloma. CAR T-eligible patients are often heavily pretreated with a higher risk of treatment-related adverse events (AEs), including second primary malignancies (SPMs) [2,3]. Recently, the FDA received reports of CAR-positive lymphomas in patients treated with CAR T products [4]. Such concerns highlight the need for better characterization of SPM risk after CAR T cell therapy. Herein, we analyzed the FDA AE Reporting System (FAERS) database to quantify the CAR T reports with SPMs. Detailed methods can be found in the supplementary appendix.

We identified 12,394 unique CAR T AE reports, of which 2,225 were associated with the System Organ Class "Neoplasms benign, malignant and unspecified". After applying exclusion criteria, 536/12,394 (4.3%) SPM reports were included. Axicabtagene ciloleucel (Axi-cel) and

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

tisagenlecleucel (tisa-cel) comprised most of the reports (277/536, 51.7% and 177/536, 33.0%, respectively). Characteristics of the AE reports are detailed in **Table 1**.

The most frequent SPMs by High-level Group Term (HLGT) were leukemias (333/536, 62.1%) representing 2.7% (333/12,394) of all CAR T reports. Leukemias included myelodysplastic syndromes (MDS) (208/536, 38.8%; 208/12,394, 1.7%), acute myeloid leukemias (106/536, 19.8%; 106/12,394, 0.9%), and 2 cases of T-cell large granular lymphocytic leukemia. Skin neoplasms were the second most frequent SPM (54/536, 10.1%; 54/12,394, 0.4%) which included non-melanoma skin neoplasms (42/536, 7.8%, 42/12,394, 0.3%) and skin melanomas (12/536, 2.2%; 12/12,394, 0.1%). Hematopoietic neoplasms excluding leukemias and lymphomas were reported in (26/536, 4.9%; 26/12,394, 0.2%) including lymphoproliferative disorder NEC (n=15), myeloproliferative neoplasms (n=7), and histiocytoses (n=4). Nervous system tumors were reported in (21/536, 3.9%; 21/12,394, 0.2%), while respiratory neoplasms were reported in (20/536, 3.7%; 20/12,394, 0.2%). (**Figure 1; Tables S6-S11).**

T-cell non-Hodgkin lymphomas were identified in 17/536 (3.2%) reports, representing 0.1% (17/12,394) of all CAR T reports. These included 12 anaplastic large T-cell lymphomas (7 in tisa-cel and 3 in axi-cel, and 2 in ciltacabtagene autoleucel [cilta-cel]), 3 peripheral T-cell lymphoma (1 in tisa-cel, 1 in cilta-cel, and 1 in lisocabtagene maraleucel [liso-cel]), one angioimmunoblastic T-cell lymphoma (axi-cel), and one enteropathy associated T-cell lymphoma (cilta-cel). **(Figure 1a)**. Most cases were reported from the United States (n=9). Out of the 17 cases, 8 reported death, 4 reported hypogammaglobulinemia, 3 reported cytokine release syndrome, 2 reported hemophagocytic lymphohistiocytosis, and 2 reported neurotoxicity.

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

The enteropathy-associated T-cell lymphoma case also had immune-mediated enterocolitis. Two cases reported out-of-specification manufacturing without additional information (**Tables S13**).

Analysis of SPMs disproportionality in the CAR reports showed a significantly higher reporting odds ratio (ROR) for myelodysplastic syndrome in axi-cel (ROR = 3.5 [95% CI 2.9; 4.2]), tis-cel (ROR = 1.3 [95% CI 1-1.8]), liso-cel (ROR = 4.6 [95% CI 2.4; 8.5]), ide-cel (ROR = 2.8 [95% CI 1.2;6.7]), and cilta-cel (ROR = 6.7 [95% CI 3.3; 13.5]) **(Figure 1c)**. Tisa-cel and cilta-cel were associated with higher ROR for acute myeloid leukemia (ROR= 1.5 [95% CI 1.2;2.0]; and 4.1 [95% CI 1.3; 12.8], respectively). Anaplastic large T-cell lymphomas were disproportionately more reported in tisa-cel (ROR= 7.4 [95% CI 3.1;17.4]) **(Figure 1c).**

SPMs have been extensively documented in survivors of hematologic malignancies [2,3]. However, fewer studies have reported on SPM incidence after CAR T therapies. Six out of the 8 pivotal trials reported the incidence of SPMs. SPMs after Tisa-cel were reported in 3/137 (2.2%) in the acute lymphoblastic leukemia trials (ELIANA and ENSIGN)[5], while no SPMs were reported in the large B cell lymphoma trial (JULIET) [6]. ZUMA-1 and ZUMA-7 trials reported incidence of SPMs after axi-cel of <1% and 4.7%, respectively [7,8]. No SPMs were reported after brexucabtagene autoleucel (brexu-cel) ZUMA-3 trial [9]. The incidences of SPMs after liso-cel were 8.1% and 3.3% in the TRANSCEND NHL and the TRANSFORM trials, respectively [10,11]. While CARTITUDE-1 reported SPMs of 25.8% after cilta-cel [12], the KarMMa-1 trial did not report on SPMs after ide-cel [13]. SPM incidence of 3.6% after commercial CD19 and BCMA CAR T products was reported by Ghilardi and colleagues [14]. Other reports on commercial CAR T cells indicated an SPM incidence between 3.9 and 4.5% [15,16]. While SPMs

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

represented 4.3% of the total submitted FAERS CAR T AE reports, this percentage only reflects the likelihood of reporting SPMs to the FDA.

ROR of myeloid neoplasms was elevated in 5/6 of the CAR-T products. Myeloid neoplasms after CAR T were reported in the pivotal trials with SPM data as well as other investigational studies [7,8,13,17,1]. A recent study reported a shorter onset of myeloid neoplasms after CAR T compared to their development following stem cell transplantation [1,17]. Additionally, cytogenetic and clonal abnormalities were frequently present in patients before receiving CAR T therapies suggesting a clonal evolution of existing treatment-related clonal hematopoiesis [17,18].

The FDA indicated that 22 cases of T-cell malignancies were reported to be associated with five of the six CAR-T products[19]. Genetic sequencing was performed for three cases with the CAR transgene identified in the malignant clones[19]. We identified 19 cases of T-cell malignancies (17 T-cell non-Hodgkin lymphomas and two T-cell large granular lymphocytic leukemia). Details on two cases associated with cilta-cel and liso-cel were previously published [20,21]. CAR transgene integration into the 3' UTR of the PBX2 gene was detected in the cilta-cel case. However, the evidence was inconclusive as to whether the CAR integration was a driver of the malignant transformation, given the presence of pre-existing genetic mutations unrelated to CAR T infusion. Ghilardi et. al. identified a case of peripheral T cell lymphoma developed three months after receiving axi-cel[14]. The CAR transgene copies in the tumor biopsy were very low. NGS analysis revealed that the population giving rise to the malignant clone predated the CAR T infusion. However, they did not rule out CAR T manufacturing or induced inflammation as contributors to lymphoma development. Finally, additional studies have reported viral

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

integrations into key hematopoiesis regulatory genes, such as TET2 and CBL, resulting in clonal expansion in 2 responding CAR T patients with no malignant transformation reported to date [22,23].

The FAERS database remains a valuable resource for identifying adverse events (AEs) not captured during clinical studies, however, it has limitations such as duplicate report submissions, missing information, inability to establish causal relationships, and underreporting or overreporting based on AE severity. Additionally, the absence of a denominator reflecting the total number of prescribed products limits the ability to establish AE incidence. Finally, the quarterly release of raw data may delay independent analysis and public information dissemination.

In conclusion, SPMs after CAR T represented a small fraction of the AE reports in FAERS. The disproportionality analysis suggests an increased risk of reporting certain SPMs, notably myeloid and T-cell malignancies. The low numbers do not provide conclusive evidence of the risk of SPMs after CAR T therapy. Dedicated registries to study SPMs post CAR T can offer valuable insights for patient care and future development. This becomes pertinent as CAR T therapies expand to nonmalignant conditions [24]. Finally, the primary cause of mortality in relapses or refractory hematologic malignancies remains the primary disease.

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

Authorship contribution

ME and MOE contributed to study conception and design, data analysis and interpretation, figure creation, and draft manuscript preparation. JM contributed to the data compilation and curation. ML, CD, MF, MP, and MM contributed to data interpretation, manuscript drafting and editing. All authors reviewed the results and approved the final version of the manuscript.

Conflict-of-Interest Statements

M. Lunning reports research support by BMS and consultancy for AbbVie, AZ, BMS, Caribou, Diachi Sankyo, Fate Therapeutics, Genentech, Genmab, Ipsen, Janssen, Kite, Loxo, Nurix, Recordati, Regeneron, SeaGen, Takeda, ViTToria **C. D'Angelo** reports being on the advisory boards of Seagen, BMS, Abbvie, Ono Pharma. He received research funding from Ono Pharma, BMS, Fate Therapeutics, Curis Inc, Beigene and has provided consultation to Abbvie. **M. Perales** reports honoraria from Adicet, Allogene, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, ImmPACT Bio, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Sanofi,

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

Syncopation, VectivBio AG, and Vor Biopharma. He serves on DSMBs for Cidara Therapeutics, Medigene, and Sellas Life Sciences, and the scientific advisory board of Nexlmmune. He has ownership interests in Nexlmmune, Omeros and OrcaBio. He has received institutional research support for clinical trials from Allogene, Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis. **M. J. Frigault** reports consultancy for BMS, Novartis, Kite, Arcellx, Iovance, Cytoagents. **M.V. Maus** is an inventor on patents related to adoptive cell therapies, held by Massachusetts General Hospital (some licensed to Promab) and University of Pennsylvania (some licensed to Novartis). M.V.M. holds equity in 2SeventyBio, Century Therapeutics, Neximmune, Oncternal, and TCR2 and has served as a consultant for multiple companies involved in cell therapies. M.V.M. is on the Board of Directors of 2Seventy Bio. M.V.M. has received grant/research support from CRISPR Therapeutics, Kite Pharma, Servier, and Novartis. All other authors declare no competing interests.

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

References:

1. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. *Nat Rev Clin Oncol*. 2023;20(6):359-371. doi:10.1038/s41571-023-00754-1

2. Miret M, Anderson A, Hindocha P, et al. Incidence of second primary malignancies in relapsed/refractory B-cell non-Hodgkin's lymphoma patients in England. *Leuk Res*. 2023;127:107042. doi:10.1016/j.leukres.2023.107042

3. Musto P, Anderson KC, Attal M, et al. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. *Ann Oncol*. 2017;28(2):228-245. doi:10.1093/annonc/mdw606

4. Levine BL, Pasquini MC, Connolly JE, et al. Unanswered questions following reports of secondary malignancies after CAR-T cell therapy. *Nat Med*. Published online January 9, 2024:1-4. doi:10.1038/s41591-023-02767-w

5. Levine JE, Grupp SA, Pulsipher MA, et al. Pooled safety analysis of tisagenlecleucel in children and young adults with B cell acute lymphoblastic leukemia. *J Immunother Cancer*. 2021;9(8):e002287. doi:10.1136/jitc-2020-002287

6. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. *Lancet Oncol*. 2021;22(10):1403-1415. doi:10.1016/S1470-2045(21)00375-2

7. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. *Blood*. 2023;141(19):2307-2315. doi:10.1182/blood.2022018893

8. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with Axicabtagene Ciloleucel in Large B-Cell Lymphoma. *N Engl J Med*. 2023;389(2):148-157. doi:10.1056/NEJMoa2301665

9. Shah BD, Ghobadi A, Oluwole OO, et al. Two-year follow-up of KTE-X19 in patients with relapsed or refractory adult B-cell acute lymphoblastic leukemia in ZUMA-3 and its contextualization with SCHOLAR-3, an external historical control study. *J Hematol OncolJ Hematol Oncol*. 2022;15(1):170. doi:10.1186/s13045-022-01379-0

10. Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. *Blood*. 2023;141(14):1675-1684. doi:10.1182/blood.2022018730

11. Abramson JS, Palomba ML, Gordon LI, et al. Two-year follow-up of lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in TRANSCEND NHL 001. *Blood*. Published online October 27, 2023:blood.2023020854. doi:10.1182/blood.2023020854

12. Munshi N, Martin T, Usmani SZ, et al. S202: CARTITUDE-1 FINAL RESULTS: PHASE 1B/2 STUDY OF CILTACABTAGENE AUTOLEUCEL IN HEAVILY PRETREATED PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA. *HemaSphere*. 2023;7(Suppl):e6102468. doi:10.1097/01.HS9.0000967720.61024.68

13. Munshi NC, Anderson LD, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N Engl J Med*. 2021;384(8):705-716. doi:10.1056/NEJMoa2024850

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

14. Ghilardi G, Fraietta JA, Gerson JN, et al. T-cell Lymphoma and Secondary Primary Malignancy Risk After Commercial CAR T-cell Therapy. *Nat Med*. Published online January 24, 2024. doi:10.1038/s41591-024-02826-w

15. Jacobson CA, Locke FL, Ma L, et al. Real-World Evidence of Axicabtagene Ciloleucel for the Treatment of Large B Cell Lymphoma in the United States. *Transplant Cell Ther*. 2022;28(9):581.e1-581.e8. doi:10.1016/j.jtct.2022.05.026

16. Sidana S, Ahmed N, Akhtar OS, et al. Real World Outcomes with Idecabtagene Vicleucel (Ide-Cel) CAR-T Cell Therapy for Relapsed/Refractory Multiple Myeloma. *Blood*. 2023;142:1027. doi:10.1182/blood-2023-181762

17. Alkhateeb HB, Mohty R, Greipp P, et al. Therapy-related myeloid neoplasms following chimeric antigen receptor T-cell therapy for Non-Hodgkin Lymphoma. *Blood Cancer J*. 2022;12(7):113. doi:10.1038/s41408-022-00707-4

18. Miller PG, Sperling AS, Brea EJ, et al. Clonal hematopoiesis in patients receiving chimeric antigen receptor T-cell therapy. *Blood Adv*. 2021;5(15):2982-2986. doi:10.1182/bloodadvances.2021004554

19. Verdun N, Marks P. Secondary Cancers after Chimeric Antigen Receptor T-Cell Therapy. *N Engl J Med*. 2024;0(0):null. doi:10.1056/NEJMp2400209

20. Harrison SJ, Nguyen T, Rahman M, et al. CAR+ T-Cell Lymphoma Post Ciltacabtagene Autoleucel Therapy for Relapsed Refractory Multiple Myeloma. *Blood*. 2023;142:6939. doi:10.1182/blood-2023-178806

21. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet Lond Engl*. 2020;396(10254):839-852. doi:10.1016/S0140-6736(20)31366-0

22. Shah NN, Qin H, Yates B, et al. Clonal expansion of CAR T cells harboring lentivector integration in the CBL gene following anti-CD22 CAR T-cell therapy. *Blood Adv*. 2019;3(15):2317-2322. doi:10.1182/bloodadvances.2019000219

23. Fraietta JA, Nobles CL, Sammons MA, et al. Disruption of TET2 promotes the therapeutic efficacy of CD19-targeted T cells. *Nature*. 2018;558(7709):307-312. doi:10.1038/s41586-018-0178-z

24. Mackensen A, Müller F, Mougiakakos D, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. *Nat Med*. 2022;28(10):2124-2132. doi:10.1038/s41591-022-02017-5

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

Tables:

Table.1 Characteristics of FAERS CAR T reports

	All CAR T reports	All SPM CAR T reports	Axi-cel SPM reports	Tisa-cel SPM reports	Brexu-cel SPM reports	Liso-cel SPM reports	Ide-cel SPM reports	Cilta-cel SPM reports
N (%)	12394 (100)	536 (100)	277 (100)	177 (100)	20 (100)	23 (100)	15 (100)	24 (100)
Age, years								
Mean (SD)	53.8 (20.5)	58.7 (18.2)	61.3 (11.1)	50.1 (26.2)	58.4 (18.8)	69.4 (9.9)	65.0 (8.3)	68.5 (7.8)
Median (IQR)	60.0 (45.0, 68.0)	63.0 (56.0, 70.0)	62.0 (56.0, 68.0)	62.0 (20.0, 70.8)	62.0 (60.3, 70.3)	71.0 (67.0, 76.0)	66.5 (56.0, 70.0)	71.0 (63.0, 75.0)
Missing	3884	131	62	55	6	2	3	3
Sex (%)								
Female	3813 (38.1)	181 (36.8)	91 (34.5)	68 (44.2)	3 (16.7)	10 (45.5)	3 (23.1)	6 (28.6)
Male	6182 (61.9)	311 (63.2)	173 (65.5)	86 (55.8)	15 (83.3)	12 (54.5)	10 (76.9)	15 (71.4)
Missing	2399	44	13	23	2	1	2	3
Weight, kg								
Mean (SD)	75.78 (24.6)	74.21 (24.1)	75.73 (18.9)	68.73 (28.4)	74.5 (23.9)	84.5 (27.1)	78.9 (8.8)	76.9 (17.0)
Reporter								
Consumer	1274 (11.4)	24 (4.6)	10 (3.7)	13 (7.5)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
Healthcare practitioner	4844 (43.2)	220 (42.3)	153 (56.9)	53 (30.8)	9 (50.0)	3 (13.6)	0 (0.0)	2 (8.3)
Physician	5075 (45.3)	276 (53.1)	106 (39.4)	106 (61.6)	9 (50.0)	19 (86.4)	14 (93.3)	22 (91.7)
Missing	1201	16	8	5	2	1	0	0
Reporting region								
North America	7530 (60.8)	346 (64.6)	201 (72.6)	95 (53.7)	11 (55.0)	16 (69.6)	7 (46.7)	16 (66.7)
Europe	2890 (23.3)	151 (28.2)	70 (25.2)	62 (35.0)	6 (30.0)	1 (4.4)	7 (46.7)	5 (20.8)

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

Asia	613 (5.0)	17 (3.2)	1 (0.4)	14 (7.9)	0 (0.0)	2 (8.7)	0 (0.0)	0 (0.0)
Africa	1 (0.01)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Others	261 (2.1)	8 (1.5)	1 (0.4)	5 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)
Missing	1099	14	4	1	3	4	1	1
Report Year								
2017 (Oct-Dec)	72 (0.6)	1 (0.2)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2018	833 (6.7)	22 (4.1)	9 (3.3)	12 (6.8)	0 (0.0)	1 (4.4)	0 (0.0)	0 (0.0)
2019	1652 (13.3)	43 (8.0)	17 (6.1)	26 (14.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2020	1752 (14.1)	80 (14.9)	52 (18.8)	22 (12.4)	0 (0.0)	4 (17.4)	2 (13.3)	0 (0.0)
2021	1927 (15.6)	114 (21.3)	59 (21.3)	41 (23.2)	4 (20.0)	9 (39.1)	1 (6.7)	0 (0.0)
2022	2611 (21.1)	129 (24.1)	80 (28.9)	22 (12.4)	5 (25.0)	5 (21.7)	6 (40.0)	11 (45.8)
2023	3547 (28.6)	147 (27.4)	60 (21.7)	53 (30.0)	11 (55.0)	4 (17.4)	6 (40.0)	13 (54.2)
Outcome Specified as serious	11571 (93.4%)	530 (98.9)	276 (99.6)	176 (99.4)	19 (95.0)	23 (100.0)	15 (100.0)	21 (87.50)
Outcome								
Death	2861 (24.7)	207 (39.1)	124 (44.9)	67 (38.1)	6 (31.6)	4 (17.4)	4 (26.7)	2 (9.52)
Disability	94 (0.8)	17 (3.2)	4 (1.5)	11 (6.3)	0 (0.0)	0 (0.0)	1 (6.7)	1 (4.76)
Hospitalization	1860 (16.1)	37 (7.0)	14 (5.1)	13 (7.4)	5 (26.3)	0 (0.0)	2 (13.3)	3 (14.29)
Life threatening	673 (5.8)	15 (2.8)	4 (1.5)	9 (5.1)	0 (0.0)	0 (0.0)	1 (6.7)	1 (4.76)
Required intervention	28 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other serious	6055 (52.3)	254 (47.9)	130 (47.1)	76 (43.2)	8 (42.1)	19 (82.6)	7 (46.7)	14 (66.67)
Missing	823	6	1	1	1	0	0	3

SPM: Second Primary Malignancy; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Brexu-cel: brexucabtagene autoleucel; Liso-cel: lisocabtagene maraleucel; Ide-cel: idecabtagene vicleucel; Cilta-cel: ciltacabtagene autoleucel.

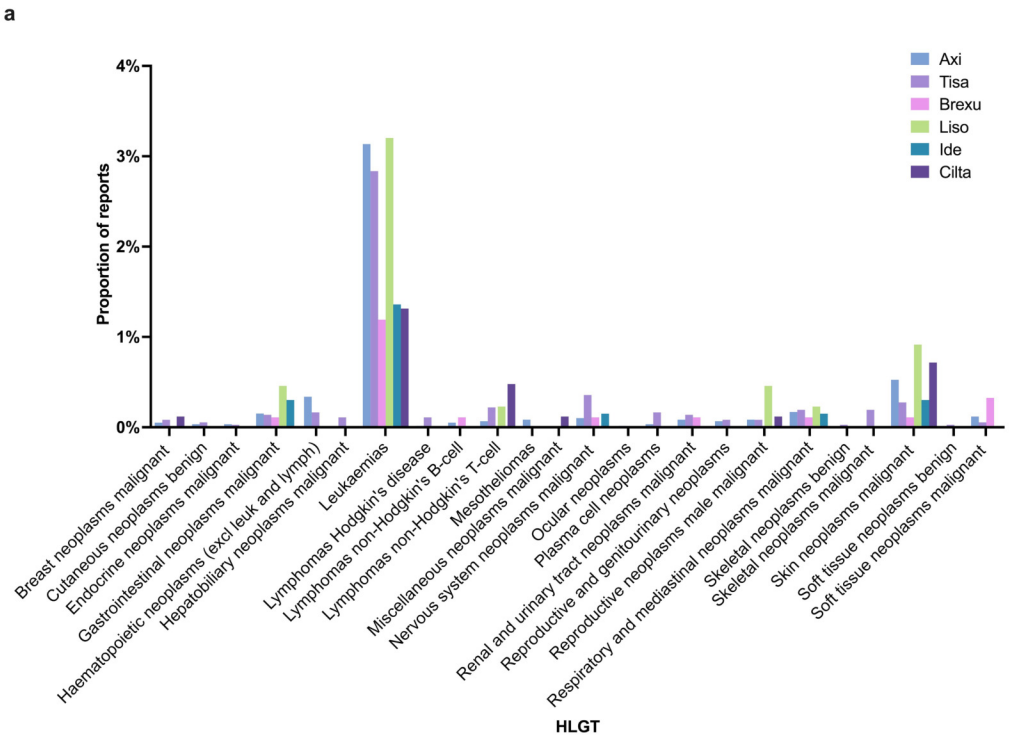
Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218201/blood.2024024166.pdf by guest on 17 May 2024

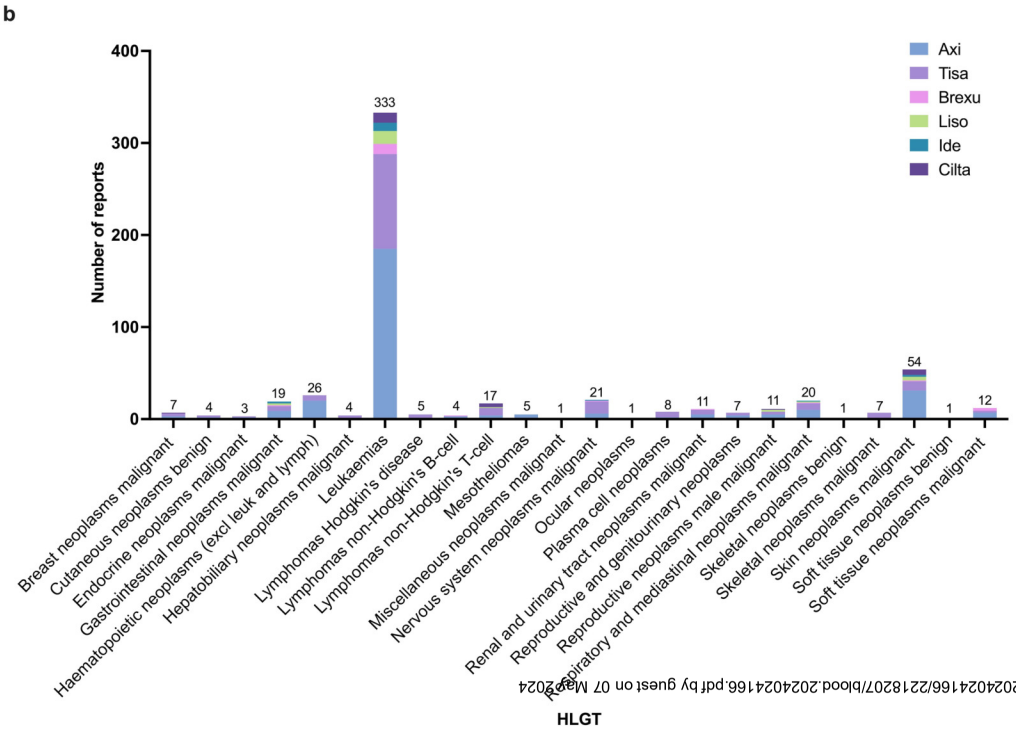
Figure Legend

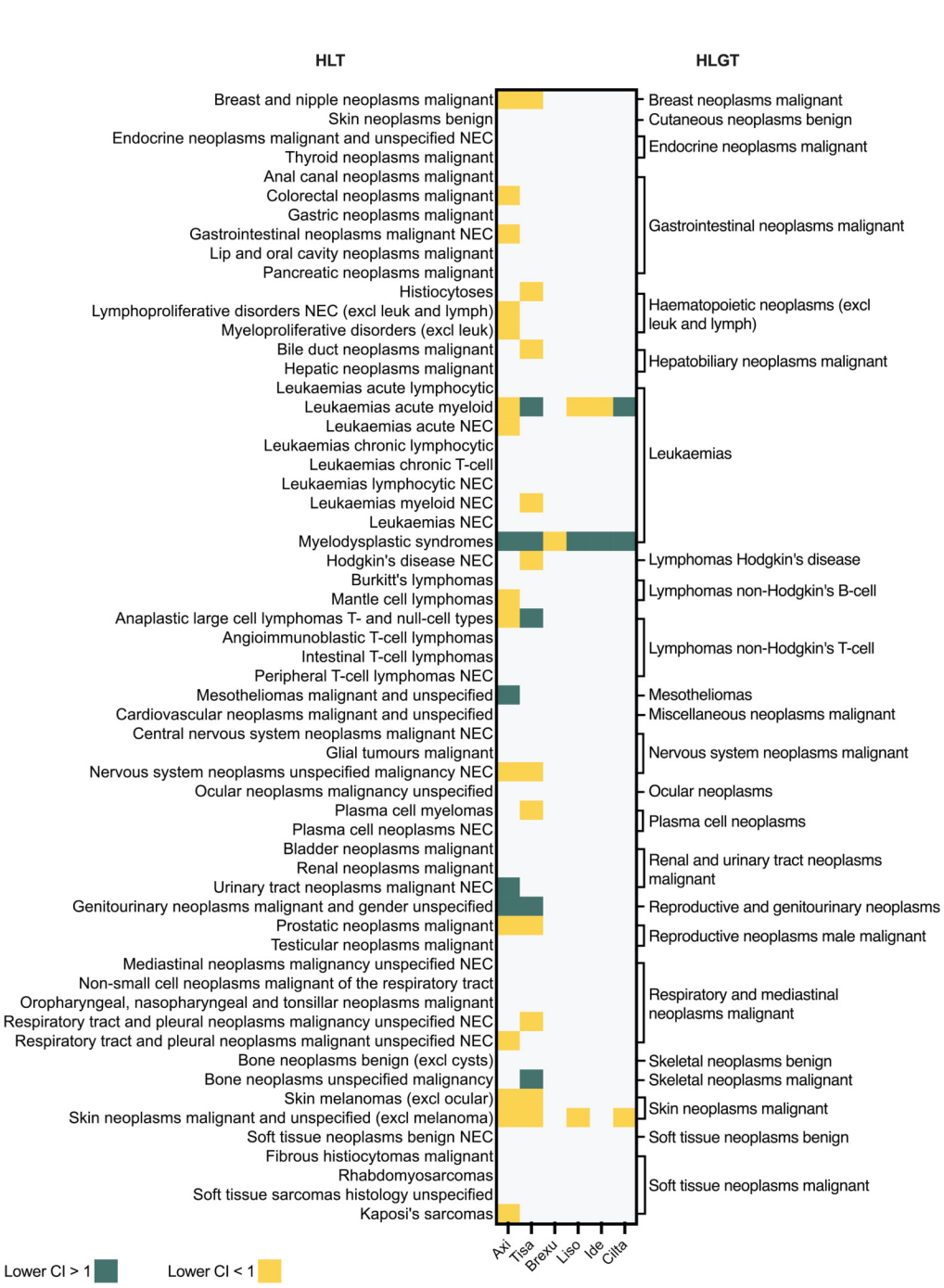
Figure 1. Frequency and disproportionality of reporting for second primary malignancies (SPMs) in different chimeric antigen receptor T-cell (CAR T) products. 1a. Proportion of reports of each SPM (in higher level group terms) in each product to the total number of AE reports associated with the corresponding CAR T product. 1b. Absolute number of reports for each SPM (in higher level group terms) in CAR T products. 1c. Disproportionality of reporting measured as the relative odds ratio (ROR), compared to the other non-CAR T drugs administered for the respective indication. Grey areas reflect insufficient number of reports (<3 reports) and thus ROR was not calculated. Green areas reflect significant ROR, defined as lower bound of the 95% confidence interval of greater than 1. Yellow areas reflect non-significant signal. Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Brexu-cel: brexucabtagene autoleucel; Liso-cel: lisocabtagene maraleucel; Ide-cel: idecabtagene vicleucel; Cilta-cel: ciltacabtagene autoleucel.

Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024

Figure 1







Downloaded from http://ashpublications.net/blood/article-pdf/doi/10.1182/blood.2024024166/2218207/blood.2024024166.pdf by guest on 07 May 2024