blood advances

TO THE EDITOR:

T-cell malignancies with anti-CD19 chimeric antigen receptor T-cell therapy

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On 28 November 2023, the US Food and Drug Administration announced an investigation into the risk of T-cell malignancies after autologous chimeric antigen receptor (CAR) T-cell therapies.[1] Among those, the CD19-directed therapies axicabtagene ciloleucel (axi-cel) and brexucabtagene autoleucel (brexu-cel) are 2 of the earliest approved CAR T-cell therapies. Axi-cel and brexu-cel have demonstrated clinically meaningful long-term efficacy along with manageable safety profiles in patients with B-cell malignancies.[2,3] Notably, epidemiological studies demonstrate there is an increased risk of T-cell malignancies occurring among patients with malignancies of B-cell origin compared with the general population (supplemental Table 1).[4] The cumulative incidence of T-cell malignancies occurring after B-cell malignancies is dependent on the initial diagnosis (supplemental Tables 2-4). To characterize the specific risk of T-cell malignancies after the administration of axi-cel or brexu-cel, we reviewed events reported in the Gilead Global Safety Database, which includes safety data from clinical trials, postauthorization studies, and spontaneous reports to the database (supplemental Methods).

As of 16 February 2024, 17 578 patients had received axi-cel and 3336 had received brexu-cel (Table 1). Upon review of the Gilead Global Safety Database cumulative to 5 March 2024, there were 13 subsequent malignancies of T-cell origin among patients who received axi-cel, for an overall reporting rate of 0.07% (n = 13/17 578; Tables 1-2). This rate was consistent with the clinical trial incidence of T-cell malignancies reported after axi-cel, namely 0.1% (n = 1/905; Table 1). The median time to onset of these subsequent T-cell malignancies was 12.2 months (range, 1.8-58.5). No T-cell malignancies were reported among patients who received brexu-cel (Table 1). Four of the 13 cases of T-cell malignancies had sufficient tumor biopsy and/or blood sample availability for molecular analysis, including the detection of the CAR transgene. None of the cases demonstrated causality, with CAR detected at frequencies near or below the limit of detection in each case (Table 2).

Overall, T-cell malignancies reported after axi-cel were rare (none reported with brexu-cel), and the reporting rate was consistent with the background risk among patients with B-cell malignancies. At present, a causal relationship between T-cell malignancies and treatment with axi-cel or brexu-cel is not established. The benefit-risk profile for both therapies in their respective approved indications continues to be positive.

Underestimation of subsequent malignancies is possible because of variable reporting in the postauthorization setting. Ongoing reporting of any new T-cell malignancy after CAR T-cell therapy and access to tumor biopsy samples can help ensure an accurate and appropriate risk assessment.

Most of the data reported here are from the postauthorization setting (ie, institutional review board study approval is not applicable). For data reported in the context of clinical trials, the studies were approved by the institutional review board at each study site, and all patients treated in that setting provided written informed consent.

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Kite is committed to sharing clinical trial data with external medical experts and scientific researchers in the interest of advancing public health, and access can be requested by contacting medinfo@kitepharma.com. Data for cases 11 to 13 reported in the Gilead Global Safety Database have been reported previously (doi: https://doi.org/10.1038/s41591-024-02826-w; doi: https://doi.org/10.1016/j.jtct.2024.02.009; and doi: https://doi.org/10.1016/j.jtct.2023.12.228).

The full-text version of this article contains a data supplement.

Table 1. Malignancies of T-cell origin after treatment with axi-cel or brexu-cel reported in the Gilead Global Safety Database

	Postauthorization setting	Kite-sponsored clinical trial setting	Gilead Global Safety Database total
Patients treated with axi-cel, N	16 623	905	17 578*
Reporting rate of patients with subsequent malignancies of T-cell origin, n (%)†	12 (0.072)	1 (0.110)	13 (0.074)
MedDRA high-level group term‡			
Non-Hodgkin lymphomas of T-cell origin	7 (0.042)	0	7 (0.04)
Leukemias	4 (0.024)	1 (0.110)	5 (0.028)§
Hematopoietic neoplasm (excluding leukemias and lymphomas)	2 (0.012)	0	2 (0.011)§
Patients treated with brexu-cel, N	2940	396	3336
Reported number of patients with subsequent malignancies of T-cell origin, n	0	0	0

Cases reported cumulatively up to 5 March 2024.
MedDRA, Medical Dictionary for Regulatory Activities.
*Includes 50 patients from a non–Kite-sponsored interventional clinical trial in China (not included in the Kite–sponsored clinical trial setting).
†The percentage is derived from the number of patients reporting at least 1 event among the total treated with the CAR T-cell therapy in that setting.
‡The Gilead Global Safety Database was searched for events of subsequent malignancies of T-cell origin that matched 77 preferred terms from MedDRA version 26.1 (supplemental Methods).
§In 1 case, the preferred terms lymphocytic leukemia and lymphoproliferative disorder were reported for the same condition.

Table 2. Subsequent malignancies of T-cell origin reported after axi-cel

	Patient information			T-cell malignancy		
Patient	Age, y	Reported indication for CAR T-cell therapy	Prior lines of therapy, n	Preferred term	Time to onset from axi-cel infusion, mo	Event outcome as reported (survival status)*
1	68	DLBCL	Not reported	T-cell lymphoma	1.9	Fatal
2	29	Large cell lymphoma	2	Lymphoproliferative disorder	6.7	Not resolved (alive at last follow-up 3.7 y after event onset date)
				Lymphocytic leukemia	6.7	Not reported
3†	62	DLBCL	2	Large granular lymphocytosis	18.9	Not resolved (alive at last follow-up 3.0 y after event onset date)
4	63	DLBCL	5	Large granular lymphocytosis	15.4	Not reported (alive at last follow-up 3.6 y after event onset date)
5	59	DLBCL	2	T-cell lymphoma	19.6	Not resolved (survival status unknown)
6	59	DLBCL	2	Lymphoproliferative disorder	8.9	Resolving (survival status unknown)
7	80	TFL	4	T-cell lymphoma	30	Not reported (survival status unknown)
8‡	63	DLBCL	1	Large granular lymphocytosis	58.5	Not resolved (alive at last follow-up 9.5 mo after event onset date)
9	30	Unknown indication§	1	T-cell lymphoma	<7‖	Not resolved (survival status unknown)
10	68	DLBCL	3	Angioimmunoblastic T-cell lymphoma	37.6	Fatal
11	64	B-cell lymphoma	2	T-cell lymphoma	3	Not reported (death due to non–small cell lung cancer)
12	59	Large B-cell lymphoma	2	T-cell lymphoma	1.8	Fatal
13†	62	DLBCL	2	Large granular lymphocytosis	18.9	Not resolved (alive at last follow-up 3.0 y after event onset date)

BCR, B-cell receptor; BM, bone marrow; CAPP-seq, cancer personalized profiling by deep sequencing; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; FFPE, formalin-fixed paraffin-embedded; LN, lymph node; N/A, not applicable; PB, peripheral blood; qPCR, quantitative polymerase chain reaction; RCR, replication-competent retrovirus; scDNA-seq, single-cell DNA sequencing; scRNA-seq, single-cell RNA sequencing; TCL, T-cell lymphoma; TCR, T-cell receptor; TCR-seq, T-cell receptor sequencing; TFL, transformed follicular lymphoma; T-LGL, T-cell large granular lymphocytosis.
*Event outcome and survival status was reported with Global Safety Database case information as of 23 April 2024, after the cumulative review on 5 March 2024.
†After the review of the Global Safety Database cases, case 3 was determined to be a duplicate of case 13 and the cases were merged.
‡Patient was enrolled in the ZUMA-7 clinical trial (ClinicalTrials.gov identifier: NCT03391466) and the T-cell malignancy event occurred after the data cutoff date of the primary overall survival analysis.[2]
§A follow-up to the case reported: "The initial diagnosis of DLBCL might not be accurate. The indication and current condition of B-cell lymphoma was removed (pending clarification)." As of 23 April 2024, Kite has not received clarification regarding the indication.
‖Specifically reported as shortly after axi-cel infusion. The time from infusion to the case reported to the Gilead Global Safety Database was within 7 months.

Table 2 (continued)

		Molecular analysis results			
Patient	**T-cell malignancy**	**Tumor sample received by Kite**	**Method for transgene testing**	**Sample test result details**	**Assessment**
1	T-cell lymphoma	Not received	N/A	N/A	N/A
2	Lymphoproliferative disorder/lymphocytic leukemia	Not received	N/A	N/A	N/A
3†	Large granular lymphocytosis	Not received	N/A	N/A	N/A
4	Large granular lymphocytosis	Not received	N/A	N/A	N/A
5	T-cell lymphoma	PB and BM aspirate	ddPCR for CAR transgene in blood; flow cytometric analysis of CAR T cells from BM aspirate	CD19 CAR transgene was detectable at low levels in the diagnostic BM aspirate by flow cytometry, at the lower limit of detection, and at low levels in peripheral blood samples by ddPCR; neither frequency of CAR-positive cells nor levels of CAR transgene indicated a pronounced CAR T-cell presence above the limit of detection. Disease involvement was restricted to BM. Combined with the lack of T lymphoblasts detected in the BM diagnostic sample, these data did not indicate presence of CAR-positive cells outside the normal immune cell repertoire.	Molecular analysis results do not support causality
6	Lymphoproliferative disorder	Not received	N/A	N/A	N/A
7	T-cell lymphoma	Not received	N/A	N/A	N/A
8‡	Large granular lymphocytosis	PB and BM biopsy (FFPE)	ddPCR for CAR transgene in blood and BM; qPCR for RCR in blood	CD19 CAR transgene was detected near the lower limit of quantification by ddPCR in the blood, and the CAR transgene was not detected by ddPCR in a diagnostic BM biopsy. RCR was undetected in blood	Molecular analysis results do not support causality
9	T-cell lymphoma	Not received	N/A	N/A	N/A
10	Angioimmunoblastic T-cell lymphoma	Not received	N/A	N/A	N/A
11	T-cell lymphoma	Not received; analysis performed by primary medical team	qPCR for CAR transgene	Molecular testing performed was previously reported.[5] The lymph node tumor was reported to have 8 CAR transgene copies per microgram of DNA by qPCR, corresponding to 0.005% of cells analyzed. The reporter concluded that the very low level of CAR signal was more likely to be due to infiltrating CAR T cells than the TCL harboring the CAR transgene. The T-cell population from which the neoplastic T-cell clone arose was preexisting and present at the time of axi-cel infusion and, likely, at the time of apheresis (day −28).	Molecular analysis results do not support causality

BCR, B-cell receptor; BM, bone marrow; CAPP-seq, cancer personalized profiling by deep sequencing; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; FFPE, formalin-fixed paraffin-embedded; LN, lymph node; N/A, not applicable; PB, peripheral blood; qPCR, quantitative polymerase chain reaction; RCR, replication-competent retrovirus; scDNA-seq, single-cell DNA sequencing; scRNA-seq, single-cell RNA sequencing; TCL, T-cell lymphoma; TCR, T-cell receptor; TCR-seq, T-cell receptor sequencing; TFL, transformed follicular lymphoma; T-LGL, T-cell large granular lymphocytosis.

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‡Patient was enrolled in the ZUMA-7 clinical trial (ClinicalTrials.gov identifier: NCT03391466) and the T-cell malignancy event occurred after the data cutoff date of the primary overall survival analysis.[2]

§A follow-up to the case reported: "The initial diagnosis of DLBCL might not be accurate. The indication and current condition of B-cell lymphoma was removed (pending clarification)." As of 23 April 2024, Kite has not received clarification regarding the indication.

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Table 2 (continued)

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12	T-cell lymphoma	Not received; analysis performed by primary medical team	Peripheral blood:flow cytometry and qPCR for CAR transgene, BCR clonoSEQ (ctDNA), CAPP-seq (ctDNA), TCR-seq (ctDNA), and EBV titer. BM-derived TCL: qPCR for CAR transgene, CAR vector capture sequencing, CAPP-seq, scRNA-seq, scDNA-seq DLBCL: CAPP-seq	Deep molecular characterization of the EBV^+ TCL at the bulk and single-cell level with longitudinal analysis in blood and original DLBCL. Bulk flow cytometric analysis of the TCL demonstrated absence of CAR-positive T cells. qPCR of the TCL showed CAR transgene is below the limit of detection; vector capture sequencing also showed absence of CAR transgene. Results at the single-cell level demonstrated no CAR transgene RNA expression or DNA integration in the TCL cells. Dominant TCRβ clone in TCL was detectable in LN DLBCL and blood before axi-cel infusion. EBV expression and clonal hematopoiesis *DNMT3A* and *TET2* mutations detected at high frequency (91.4%) in the TCL also preexisted in the DLBCL tumor before CAR infusion.[6]	Molecular analysis results do not support causality
13†	Large granular lymphocytosis	Not received; analysis performed by primary medical team	Flow cytometric analysis of CAR frequency in BM	A preliminary report of the case was described.[7] CAR positivity in the peripheral blood of a patient harboring a population of TCRγ rearranged, potentially oligoclonal T granular lymphocytes. Approximately, 1%-2% $CD8^+CD57^+$CAR T cells were detected among total viable blood cells by flow cytometry. Clear identification of T-LGL cells was not established because limited markers (CD3, CD8, CD57 and CD5) were available to demarcate the T-LGL cells and distinguish from normal persisting CAR T-cell presence in the BM.	Insufficient molecular analysis to determine relation to CAR

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