SUPPLEMENTAL DATA

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Supplemental methods

Data collection and search strategy

The Gilead Global Safety Database, which includes safety data from both clinical trial and postauthorization settings, was searched for events of subsequent malignancies of T-cell origin that matched 77 preferred terms, listed below, from version 26.1 of the Medical Dictionary for Regulatory Activities. Events that were reported after treatment with axicabtagene ciloleucel (axi-cel) or brexucabtagene autoleucel (brexu-cel) were captured cumulatively up to March 5, 2024. Each event was reviewed for potential association with the chimeric antigen receptor (CAR) T-cell therapy. Of note, Kite-sponsored clinical trials require reporting of subsequent malignancies; in contrast, the reporting that occurs in the postauthorization setting, including in postauthorization studies, is largely voluntary. Median time to onset was calculated with duplicate cases removed (case 3 and 13, both with time to onset of 18.9 months). The duplication was confirmed after the cumulative review had been completed. Event outcome and survival status were reviewed again after the cumulative review had been completed, based on case information in the Gilead Global Safety Database on April 23, 2024.

Complete list of preferred terms searched in the Gilead Global Safety Database
Adult T-cell lymphoma/leukaemia
Adult T-cell lymphoma/leukaemia recurrent
Adult T-cell lymphoma/leukaemia refractory
Adult T-cell lymphoma/leukaemia stage I
Adult T-cell lymphoma/leukaemia stage II
Adult T-cell lymphoma/leukaemia stage III
Adult T-cell lymphoma/leukaemia stage IV
Anaplastic large cell lymphoma T- and null-cell types
Anaplastic large cell lymphoma T- and null-cell types recurrent
Anaplastic large cell lymphoma T- and null-cell types refractory
Anaplastic large cell lymphoma T- and null-cell types stage I
Anaplastic large cell lymphoma T- and null-cell types stage II
Anaplastic large cell lymphoma T- and null-cell types stage III
Anaplastic large cell lymphoma T- and null-cell types stage IV
Angiocentric lymphoma
Angiocentric lymphoma recurrent

Angiocentric lymphoma refractory
Angiocentric lymphoma stage I
Angiocentric lymphoma stage II
Angiocentric lymphoma stage III
Angiocentric lymphoma stage IV
Angioimmunoblastic T-cell lymphoma
Angioimmunoblastic T-cell lymphoma recurrent
Angioimmunoblastic T-cell lymphoma refractory
Angioimmunoblastic T-cell lymphoma stage I
Angioimmunoblastic T-cell lymphoma stage II
Angioimmunoblastic T-cell lymphoma stage III
Angioimmunoblastic T-cell lymphoma stage IV
Cutaneous T-cell lymphoma
Cutaneous T-cell lymphoma recurrent
Cutaneous T-cell lymphoma refractory
Cutaneous T-cell lymphoma stage I
Cutaneous T-cell lymphoma stage II
Cutaneous T-cell lymphoma stage III
Cutaneous T-cell lymphoma stage IV
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Intestinal T-cell lymphoma recurrent
Intestinal T-cell lymphoma refractory
Intestinal T-cell lymphoma stage I
Intestinal T-cell lymphoma stage II
Intestinal T-cell lymphoma stage III
Intestinal T-cell lymphoma stage IV
Large granular lymphocytosis
Lymphocytic leukaemia
Lymphomatoid papulosis
Lymphoproliferative disorder
Natural killer-cell leukaemia
Natural killer-cell lymphoblastic lymphoma
Peripheral T-cell lymphoma unspecified

Peripheral T-cell lymphoma unspecified recurrent
Peripheral T-cell lymphoma unspecified refractory
Peripheral T-cell lymphoma unspecified stage I
Peripheral T-cell lymphoma unspecified stage II
Peripheral T-cell lymphoma unspecified stage III
Peripheral T-cell lymphoma unspecified stage IV
Precursor T-lymphoblastic leukaemia acute
Precursor T-lymphoblastic lymphoma/leukaemia
Precursor T-lymphoblastic lymphoma/leukaemia recurrent
Precursor T-lymphoblastic lymphoma/leukaemia refractory
Precursor T-lymphoblastic lymphoma/leukaemia stage I
Precursor T-lymphoblastic lymphoma/leukaemia stage II
Precursor T-lymphoblastic lymphoma/leukaemia stage III
Precursor T-lymphoblastic lymphoma/leukaemia stage IV
T-cell chronic lymphocytic leukaemia
T-cell lymphoma
T-cell lymphoma recurrent
T-cell lymphoma refractory
T-cell lymphoma stage I
T-cell lymphoma stage II
T-cell lymphoma stage III
T-cell lymphoma stage IV
T-cell lymphoma unclassifiable
T-cell prolymphocytic leukaemia
T-cell type acute leukaemia
T-cell unclassifiable lymphoma high grade
T-cell unclassifiable lymphoma low grade

Data collection for tumor biopsy and blood biospecimens

In the cases reported to Kite for which biospecimens were obtained with patient consent (including peripheral blood and a relevant tumor biopsy, as clinically feasible), molecular assessment for the CD19 CAR transgene and/or replication-competent retrovirus (RCR) was subsequently performed.[1] The presence of CAR and RCR were tested by droplet digital polymerase chain reaction and quantitative polymerase chain reaction, respectively. In one

case, T-cell immunophenotyping was also performed on a bone marrow aspirate by flow cytometric analysis to assess the frequency of CAR-positive cells. For other cases, additional patient data and sample analyses results were retrieved from prior reports and recent publications.

Real-world evidence

An epidemiologic study was conducted by Kite to assess the incidence of subsequent malignancies of T-cell origin, using the same 77 search terms as in the review of the Gilead Global Safety Database, in patients with large B-cell lymphoma (LBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), acute lymphoblastic leukemia (ALL), and multiple myeloma (MM) using data from the Optum claims database of commercially insured patients in the United States. Patients with at least 2 billable visits with an LBCL, FL, MCL, ALL, or MM diagnosis since 2017 were identified and followed up from identification (date of second diagnosis) until death or disenrollment. A minimum of 6 months of continuous enrollment with medical and pharmacy benefits before follow-up was required. Patients with a T-cell malignancy diagnosis any time prior to follow-up were excluded.

Occurrence of T-cell malignancy during follow-up was defined first by at least 1 diagnosis from a physician encounter and second by at least 2 diagnoses on different days to increase specificity of the outcome definition. Cumulative incidence was defined as the proportion of patients who had a subsequent malignancy of T-cell origin during follow up year 1, 2, 3, 4, or 5 and was calculated using the Kaplan-Meier (KM) method (1-KM estimator).

Supplementary results

Table S1. Incidence of T-cell malignancies

Category	Incidence in literature
Overall	T-cell lymphomas are rare cancers. Per the GLOBOCAN Global Cancer Observatory data, the incidence of newly diagnosed cases of NHL was estimated to be 509,600 in 2018.[2] Of these, T-cell lymphomas were estimated to account for 10-15% of new diagnoses,[2] or approximately 50,960 to 76,440 new cases globally. In the United States, approximately 80,000 cases of NHL are reported annually.[3] Of these, T-cell lymphomas are estimated to account for up to 6-10% of cases (5600 to 8000).[3,4]
Patients with B-cell NHL	The literature supports that patients with B-cell lymphoma are at risk of developing a subsequent T-cell malignancy. Using the United States-specific SEER database, it was demonstrated that patients with B-cell lymphoma have nearly 5-fold increased risk of developing a subsequent T-cell lymphoma compared with the general population.[5] Certain subtypes of NHL were associated with even greater risk of secondary T-cell lymphoma, including DLBCL.[5] The incidence of a new T-cell lymphoma diagnosis among patients with DLBCL or MM (diagnosed between 2018 and 2022) was estimated by Kaur et al. using the Komodo Healthcare Map™ as a real-world data source.[6] The incidence of T-cell lymphoma was 2.73% and 0.24% after an initial DLBCL and MM diagnosis, respectively, using methods that required ≥1 T-cell lymphoma-related billable interaction at any time after the initial DLBCL or MM claim through 2023. When more stringent criteria were applied, namely the requirement for ≥5 T-cell lymphoma-related billable interactions, the incidence of T-cell lymphoma was 0.62% and 0.06% after an initial DLBCL and MM diagnosis.[6] These data suggest that the incidence of subsequent T-cell malignancy varies based on initial hematologic malignancy diagnosis. This difference in background rates of T-cell malignancies is further supported by an epidemiologic study conducted by Kite to assess the incidence of subsequent malignancies of T-cell origin in patients with LBCL, FL, MCL, ALL, and

	MM using data from the Optum claims database of patients treated in the United States (**Table S2-S4**).
Patients treated with CAR T-cell therapy	As of December 31, 2023, the United States FDA reported 22 cases of T-cell malignancies among more than 27,000 patients treated with currently approved CAR T-cell therapies.[7,8] The overall risk of T-cell cancers among patients who receive CAR T-cell therapy is regarded to be very low, including among the reports from the FDA.[7,9-11]
Patients with CAR-positive T-cell malignancy	Based on the United States FDA report of the 22 cases of T-cell malignancies after CAR T-cell therapy, 3 cases with sequencing analysis performed were determined to be CAR-positive within the malignant clone.[7] Although the field recognizes the importance of investigating the involvement of CARs in subsequent T-cell malignancies, detailed molecular testing is limited by a lack of adequate samples for analysis.[7] Notably, a finding of CAR-positivity within a tumor sample warrants further molecular investigation to distinguish the presence of normal CAR T cells among tumor cells from a malignant T-cell clone or population harboring the CAR transgene. Additional etiology interrogation may include profiling of prevalent and preexisting mutations within the T-cell malignancy, CAR integration site analysis, clonal tracing, and deeper analyses of alternative etiologies including, but not limited to, clonal hematopoiesis. Increased awareness of these events and understanding of the risk of T-cell malignancy in patients with NHL may help oncologists facilitate biospecimen collection for comprehensive analysis, particularly in the postauthorization setting. In the event of a diagnosis of a subsequent malignancy after receipt of axi-cel or brexu-cel, we encourage clinicians to contact Kite using the telephone number on the label appropriate for their region.

ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FDA, US Food and Drug Administration; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; SEER, Surveillance, Epidemiology, and End Results.

Table S2. Patient demographics and follow-up by indication in the real-world evidence analysis

Patient characteristics	LBCL	FL	MCL	ALL	MM
Number of patients, n	19,331	13,116	2810	3126	28,461
Age					
Mean (SD)	70.7 (12.9)	69.78 (11.6)	72.1 (10.1)	49.3 (28.5)	72.6 (10.1)
Median (IQR)	73 (66-80)	71 (64-78)	73 (67-80)	60 (18-73)	73 (67-80)
Female, n (%)	8963 (46.4)	6686 (51.0)	894 (31.8)	1473 (47.1)	13,549 (47.6)
Median follow-up, years (IQR)	1.20 (0.41-2.79)	1.72 (0.70-3.41)	1.37 (0.53-2.96)	1.17 (0.41-2.71)	1.53 (0.56-3.15)

ALL, acute lymphoblastic leukemia; FL, follicular lymphoma; IQR, interquartile range; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; SD, standard deviation.

Table S3. Cumulative incidence of subsequent T-cell malignancies identified from ≥1 physician encounter by indication in the real-world analysis

Patient cohort	Cumulative incidence (95% CI)				
	At 1 year (%)	At 2 years (%)	At 3 years (%)	At 4 years (%)	At 5 years (%)
LBCL	1.72 (1.52-1.93)	2.22 (1.98-2.49)	2.70 (2.40-3.02)	3.02 (2.67-3.40)	3.16 (2.78-3.58)
FL	0.88 (0.72-1.06)	1.20 (1.00-1.43)	1.42 (1.19-1.69)	1.66 (1.38-1.98)	1.79 (1.48-2.15)
MCL	0.78 (0.47-1.24)	1.01 (0.63-1.55)	1.47 (0.93-2.22)	1.66 (1.03-2.54)	1.66 (1.03-2.54)
ALL	2.04 (1.54-2.66)	2.41 (1.82-3.11)	2.77 (2.08-3.62)	2.77 (2.08-3.62)	3.03 (2.21-4.04)
MM	0.18 (0.13-0.25)	0.24 (0.18-0.32)	0.31 (0.24-0.41)	0.34 (0.26-0.45)	0.45 (0.33-0.62)

ALL, acute lymphoblastic leukemia; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma.

Table S4. Cumulative incidence of subsequent T-cell malignancies identified from ≥2 physician encounters by indication in the real-world analysis

Patient cohort	Cumulative incidence (95% CI)				
	At 1 year (%)	At 2 years (%)	At 3 years (%)	At 4 years (%)	At 5 years (%)
LBCL	0.85 (0.72-1.01)	1.13 (0.96-1.33)	1.45 (1.23-1.69)	1.54 (1.30-1.81)	1.59 (1.33-1.88)
FL	0.43 (0.32-0.56)	0.63 (0.49-0.80)	0.69 (0.53-0.88)	0.87 (0.67-1.12)	0.91 (0.70-1.17)
MCL	0.32 (0.15-0.66)	0.41 (0.19-0.80)	0.50 (0.24-0.96)	0.50 (0.24-0.96)	0.50 (0.24- 0.96)
ALL	1.41 (1.00-1.94)	1.54 (1.10-2.10)	1.67 (1.18-2.31)	1.67 (1.18-2.31)	1.93 (1.28- 2.79)
MM	0.10 (0.07-0.15)	0.15 (0.10-0.21)	0.18 (0.12-0.25)	0.19 (0.13-0.27)	0.25 (0.16-0.38)

ALL, acute lymphoblastic leukemia; FL, follicular lymphoma; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma.

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