NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

ONCOLOGY AND HAEMATOLOGY EXPERT ADVISORY GROUP/CLINICAL TRIALS, BIOLOGICALS AND VACCINES EXPERT ADVISORY GROUP

Title of paper: Signal assessment of the development of secondary T-cell malignancies following CAR T cell therapy

Type of paper: For advice

Active(s) rINN	idecabtagene vicleucel lisocabtagene maraleucel ciltacabtagene autoleucel tisagenlecleucel brexucabtagene autoleucel axicabtagene ciloleucel
Product name(s)	Abecma Breyanzi Carvykti Kymriah Tecartus Yescarta
Marketing Authorisation Holder(s)	Abecma and Breyanzi: Bristol-Myers Squibb Pharma EEIG Carvykti: Janssen-Cilag Limited Kymriah: Novartis Pharmaceuticals UK Limited Tecartus and Yescarta: Gilead Sciences Ltd
Legal status	POM
Therapeutic classification (ATC code)	Abecma: Antineoplastic agents (L01) Breyanzi: Antineoplastic cell and gene therapy (L01XL) Carvykti, Kymriah and Yescarta: Other antineoplastic agents (L01XX) Tecartus: Other antineoplastic agents (L01X)
Previous assessments	This signal has not been assessed previously
Assessor	**Assessor(s)** [redacted]

Summary

Key Words	CAR T cell therapy, secondary malignancy, T cell malignancy
Issue	There have been reports of the development of T cell malignancies following the use of CAR T cell therapies in both clinical trial and post marketing sessions. The FDA began a review into this possible signal in 2023, which led other regulators to also investigate this signal.
Data sources considered	Exposure data, Company case reports, UK ADR reports, background rates of disease (epidemiological data and literature articles, Literature articles
Principal findings	The approximate total exposure to all CAR T cell products in a post marketing setting was [redacted] patients. A total of 27 cases of T cell malignancy following CAR T cell therapy were reported. 13 had not enough information to assess causality, 8 cases were assessed as not related to CAR T cell therapy, 3 were assessed as possibly related to CAR T cell therapy and 3 were assessed as related to CAR T cell therapy. There is not currently enough evidence to definitively state there is a causal relationship between the development of T cell malignancies and CAR T cell therapy, however there is enough evidence for a reasonable suspicion of a causal relationship. The mechanism by which CAR T cell therapies lead to the development of T cell malignancies is not currently fully understood. Given the seriousness of T cell malignancies, the reasonable suspicion of a causal relationship warrants action to be taken to address this.
Recommendations/ Regulatory implications	The recommendations proposed by PRAC are appropriate and should be followed in the UK. The actions are summarised below: • Update section 4.4 and 4.8 of the SmPC with current information to explain that T-cell malignancies have been reported and include secondary malignancy of T cell origin as a possible side effect • Update the PIL with current information • A common DHPC should be distributed to highlight the risk and call for increased reporting and testing • Update the RMP to add secondary malignancy of T-cell origin as an important identified risk • Update the key messages for the educational materials for healthcare professionals in Annex 6 of the RMP to reflect the safety concern • Update the RMP with the proposed testing recommendations in the event of secondary malignancy • MAHs to provide follow up information on individual case safety reports with further testing

Questions for the committee	1. Does the EAG/commission agree that, although not all products in the class had reports of T cell malignancies, that the development of T cell malignancies should be considered a class effect? 2. Does the EAG/commission agree with the recommendations outlined by the assessor? Are there any further actions that should be considered? To Oncology and Haematology EAG only: 3. Is the EAG aware of any barriers in the healthcare system that may lead to difficulties in providing patient samples to MAHs for further analysis?

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1. LIST OF ABBREVIATIONS

AE	adverse event
ADR	adverse drug reaction
ALL	acute lymphoblastic leukemia
CAR	chimeric antigen receptor
CCDS	core company data sheets
CHM	Commission on Human Medicine
CI	confidence interval
CIBMTR	Center for International Blood and Marrow Transplant Research
CIS	common integration site
ddPCR	droplet digital polymerase chain reaction
DHPC	Direct Healthcare professional Communication
DLBCL	diffuse large B-cell lymphoma
EAG	Expert Advisory Group
ECDRP	European Commission Decision Reliance Procedure
EMA	European Medicines Agency
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FL	follicular lymphoma
GMCT	gene modified cell therapy
GRV	gamma retroviral vector
HCP	health care professional
HGBL	high-grade B-cell lymphoma
ICF	informed consent form
ICSR	individual case safety report
IEC	immune effector cells
IHC	immunohistochemistry
IPMD	International Post-market Surveillance teleconference
IS	integration site
ISA	insertional site analysis
ISH	in-situ hybridisation
LGL	large granular lymphocyte
LISA	lentivirus insertion site analysis
MAH	Marketing Authorization Holder
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome

NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NK	natural killer
PAC	patient alert card
PASS	post authorisation safety study
PBMC	peripheral blood mononuclear cells
PET	positron emission tomography
PIL	Patient Information Leaflet
PMBCL	primary mediastinal B-cell lymphoma
PRAC	Pharmacovigilance Risk Assessment Committee
PT	preferred term
PTCL	peripheral T-cell lymphoma
PY	person years
RCL	replication competent lentivirus
RCL	replication competent retrovirus
RMM	risk minimisation measures
RMP	Risk Management Plan
RR	reference range
RUO	research use only
SAE	severe adverse event
SEER	Surveillance, Epidemiology and End Results
SIR	standardised incidence ratio
SmPC	Summary of Product Characteristics
SPM	second primary malignancy
TSS	transcription start site
UTR	untranslated region
VCN	vector copy number
VST	virus-specfic T lymphocytes
WBC	white blood cell
WGS	whole genome sequencing

2. INTRODUCTION

2.1. Issue

On the 28 November 2023 the FDA published on their website that they are investigating the serious risk of T-cell malignancy following use of BCMA-directed or CD-19 directed autologous CAR T-cell immunotherapies.

The announcement states that the FDA has received reports of T-cell malignancies, including CAR-positive lymphoma. Reports were received from clinical trials and/or post marketing adverse event data sources. FDA has determined that the possible risk of T-cell malignancies is applicable to all currently approved BCMA-directed and CD19-directed genetically modified autologous CAR T-cell immunotherapies. T-cell malignancies have occurred in patients treated with several products in the class. The FDA is investigating the identified risk of T-cell malignancy with serious outcomes, including hospitalization and death, and is evaluating the need for regulatory action. The FDA stated that the benefit risk ratio remains positive.

Following this FDA announcement, the signal was discussed at the MHRA Signal Management Review meeting on 6th December 2023 and a signal folder was subsequently opened based on the data available internationally (SA 25996219). The signal was assigned a priority rating of increased.

The MHRA contacted other regulators via the International Post-market Surveillance Teleconference (IPMS) in order to clarify the scope of the FDA review and to ask other regulators if they were investigating the signal. In January 2024 responses were received from regulators.

[redacted]

[redacted] the European Medicines Agency (EMA) validated a signal of secondary malignancy of T cell origin with CAR T cell products. The initial evidence for this signal was the review by the FDA and 23 cases of secondary T-cell malignancy found via a search of Eudravigilance. The signal was discussed at the January 2024 meeting of the Pharmacovigilance Risk Assessment Committee (PRAC). The MAHs for each CAR T cell product was requested to submit data (the list of questions sent to MAHs is available in Annex 1) from a cumulative review to the EMA by 7 February 2024.

The MHRA also requested that each MAH for CAR T cell products provide the data they submitted for the PRAC review by February 2024. This data forms the basis of this assessment report.

This signal was briefly discussed at the Commission on Human Medine (CHM) January and February meetings during the PRAC highlight agenda item. Commissioners advised that the signal be presented at the Oncology and Haematology EAG and the Clinical Trials, Biologicals and Vaccines EAG.

Since the FDA announcement MHRA has received several queries regarding this issue. This includes queries from a HCP and a group with a research interest in CAR T cell therapies. There has been press coverage of the FDA announcement both nationally and internationally.

2.2. Background

2.2.1. Drug mechanism of action

CAR T cell therapies are autologous, immunocellular therapies which involves harvesting a patient's own T cells and genetically engineering them ex vivo by transduction with a transgene encoding a chimeric antigen receptor (CAR). The patient then receives a transfusion of these cells. The CAR identifies and eliminates cells that express either CD19 or BCMA. Upon binding to the target cell the CAR promotes T cell activation, expansion and elimination of the target cell. Breyanzi, Kymriah, Tecartus and Yescarta target CD19. Abecma and Carvykti target BCMA. CAR T cell therapies are one off treatments. CAR T cell therapies utilise vectors to transduce T-cells; Tecartus and Yescarta use retroviral vectors and Breyanzi, Kymriah, Abecma and Carvykti use lentiviral vectors. CAR T cell therapies are administered following lymphodepleting chemotherapy.

2.2.2. Licencing history

Currently 6 CAR T cell products are licenced in the UK; Abecma, Breyanzi, Carvykti, Kymriah, Tecartus and Yescarta.

Abecma, Breyanzi and Carvykti were licenced nationally via the European Commission Decision Reliance Procedure (ECDRP). Kymriah, Tecartus and Yescarta are 'grandfathered' centrally authorised products.

All 6 products are under additional monitoring.

2.2.3. Indication

CAR T cell products are indicated for a variety of haematological malignancies, including B-cell leukaemia, B-cell lymphoma, follicular lymphoma, multiple myeloma and mantle cell lymphoma. The current licenced indications for each product are outlined below.

<u>Abecma:</u>

Adult patients with relapsed and refractory multiple myeloma who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti CD38 antibody and have demonstrated disease progression on the last therapy.

<u>Breyanzi:</u>

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

<u>Carvykti:</u>

Adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

<u>Kymriah:</u>

Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

<u>Tecartus:</u>

Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

Adult patients 26 years of age and above with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

Yescarta:

Adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Adult patients with relapsed or refractory (r/r) DLBCL and primary mediastinal large B cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Adult patients with r/r follicular lymphoma (FL) after three or more lines of systemic therapy.

2.2.4. Summary of Product Characteristics (SmPC)

Section 4.4 of the SmPC for all products contains a warning regarding the possibility of secondary malignancies developing. It states patients should be monitored life-long for secondary malignancy and if these develop the company should be contacted to arrange collection of patient samples for testing. The Carvykti SmPC mentions a case of CAR-positive T-cell lymphoma in a study. The exact wording included in section 4.4 for each product is below.

Abecma and Breyanzi: *"Patients treated with XXXX may develop secondary malignancies. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy of T cell origin occurs, the company should be contacted to obtain instructions on the collection of patient samples for testing."*

Carvykti: *"Patients treated with CARVYKTI may develop secondary malignancies. A case of CAR-positive T cell lymphoma has been reported in an ongoing study. Patient should be monitored life-long for secondary malignancies. In the event a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing."*

Kymriah: *"Patients treated with Kymriah may develop secondary malignancies or recurrence of their cancer. They should be monitored life long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing."*

Tecartus and Yescarta: *"Patients treated with XXXX may develop secondary malignancies. Patients should be monitored life long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing."*

2.2.5. Risk Management Plan (RMP)

Secondary malignancies are included as an important potential risk in the RMPs of all six products.

The exact wording of the safety concern in the RMP for each product is '*Secondary malignancies*' (Abecma), '*Secondary malignancies/insertional oncogenesis*' (Breyanzi), '*Second primary malignancy*' (Carvykti), '*Secondary malignancy*' (Tecartus, Yescarta) and '*Secondary malignancies (including vector insertion site oligo/monoclonality)*' (Kymriah).

Post authorisation Safety Studies (PASS) to follow up patients for 15 years following treatment are included in the RMP for all six products.

2.2.6. Secondary T-cell malignancy

A secondary malignancy is the development of a new malignancy suspected to be possibly related to previous treatment with radiation therapy, chemotherapy or gene-modified cell therapy. This signal relates to the development of secondary T-cell malignancy.

2.2.7. Usage

[redacted]

Exposure data is included in the data for consideration.

3. DATA FOR CONSIDERATION

3.1. Exposure data

Cumulative exposure data was requested from the MAHs for each product. A summary of the available exposure data is below.

Abecma

The estimated cumulative exposure to Abecma in BMS-sponsored clinical trials is [redacted] subjects as of 15 January 2024. [redacted] patients were in the UK.

The estimated cumulative commercial exposure to Abecma as of 11 January 2024 is [redacted] patients. [redacted] patients were in the UK.

Breyanzi

The estimated cumulative exposure for Breyanzi in clinical trials through to 17 January 2024 is [redacted] patients were in the UK.

The estimated worldwide number of commercially exposed patients from to 17 January 2024, [redacted] provided to BMS was [redacted] patients. [redacted] patients were in the UK.

Carvykti

As of 31 December 2023, the cumulative clinical trial subject exposure to Carvykti in all ongoing and completed clinical trials was [redacted]). The MAH did not provide a country breakdown for clinical trial exposure.

The estimated cumulative exposure to Carvykti from launch to 31 December 2023 is an estimated [redacted] patients. [redacted] patients were in the UK.

Kymriah

In total [redacted] patients have been exposed to Kymriah in the commercial setting, to 11 January 2024. [redacted] patients were in the UK.

Tecartus

The cumulative exposure to Tecartus as of 11 January 2024 is approximately [redacted] participants or patients. [redacted] participants from clinical trials and [redacted] patients from the post marketing setting. [redacted]. [redacted] patients in the post marketing setting were in the UK.

Yescarta

The cumulative exposure to Yescarta as of 11 January 2024 is approximately [redacted] participants or patients.

Estimated cumulative interventional clinical trial exposure to Yescarta is [redacted]
The total cumulative exposure in [redacted]) is [redacted] clinical trial patients were in the UK.

The exposure to Yescarta is approximately [redacted] patients from the post marketing setting. [redacted] patients were in the UK.

Assessor's comment

The assessor notes that MAHs used slightly different data lock points and methodologies for estimating exposure data. Therefore, when comparing exposure between products they should be considered approximate.

The approximate total exposure to all CAR T cell product in a post marketing setting was [redacted] patients. [redacted] of these patients were in the UK.

3.2. T-cell malignancy cases

The MAHs were requested to provide a summary of cases of T-cell malignancy from clinical studies, any observational study or registry source, as well as spontaneously reported cases from all relevant sources. A summary of cases for each product is included below.

Abecma

A comprehensive search of the BMS Corporate Safety Database through 11 January 2024 was performed to identify cases from all sources (clinical trial, solicited, literature and spontaneous) in which Abecma was considered as a suspect or interacting drug.

The search identified 1 case describing T-cell malignancy [redacted] This case was from a clinical trial and was a [redacted]-year-old [redacted] with onset [redacted] after CAR T cell therapy; [redacted] The MAH has assessed the causality as not related.

Assessor's comment

The assessor notes that the case has a short time to onset, [redacted] However, the sample analysis suggesting [redacted] seem to suggest a lack of causal association.

Breyanzi

A cumulative search of the corporate safety database from to 17 January 2024 was conducted for T-cell malignancies. The search identified a total of 3 cases reporting 3 severe adverse events suggestive of T-cell malignancies.

The first case was a post marketing case of peripheral T-cell lymphoma (PTCL) unspecified in a [redacted] year-old [redacted] The onset was [redacted] post CAR T cell treatment, and the case had a fatal outcome. Testing for CAR expression has not been performed by the MAH. However, the MAH notes that the treating institution performed [redacted] for the presence of CAR protein expression [redacted] was assessed at the treating institution as negative for CAR expression [redacted]. In addition, [redacted] or detection of CAR transgene expression was also assessed at the treating institution as negative. The MAH assessed the case as not related to Breyanzi.

The second case was a clinical trial case of [redacted] peripheral T-cell lymphoma unspecified in a [redacted]-year-old [redacted] The onset was [redacted] post CAR T cell treatment. [redacted] The combined evidence above suggested the peripheral T-cell lymphoma was not derived from a CAR T

cell, and that the [redacted] was due to residual non-malignant CAR T cells from the original Breyanzi infusion. The MAH assessed the case as not related to Breyanzi.

The third case was a clinical trial case of cutaneous T-cell lymphoma unspecified in a [redacted]-year-old [redacted]. The onset was [redacted] post CAR T cell treatment. [redacted] No insertional site analysis was performed [redacted] The MAH assessed the case as not related to Breyanzi.

Assessor's comment

For the first and third case the assessor agrees with the MAHs assessment that [redacted] there does not seem to be a causal association between the T-cell lymphoma and CAR T cell therapy. It is noted however that in the first case, testing for transgene expression was done by the treating institution rather than the MAH, so testing will not have been via a standardised protocol.

Regarding the second case the assessor is in agreement with the MAH and [redacted] suggests there may not be a causal relationship between Breyanzi and the peripheral T-cell lymphoma.

Carvykti

5 total cases were identified by the MAH through clinical trials and the GMS Global Safety Database.

The first case was a clinical trial case of peripheral T-cell lymphoma unspecified in a [redacted] year-old [redacted] The onset was [redacted] post CAR T cell treatment. The subject presented with [redacted] The subject was diagnosed with CAR-T associated peripheral T-cell lymphoma unspecified and treated with [redacted] The subject later [redacted]

The MAH assessed the case as related to treatment with Carvykti.

The second case was a clinical trial case of peripheral T-cell lymphoma unspecified in a [redacted] year-old [redacted]. The onset was approximately [redacted] following CAR T cell treatment. [redacted] Additionally, this subject experienced [redacted] or the duration of follow-up post treatment. Further testing is pending. The MAH assessed the case as related to treatment with Carvykti.

The third case was from the post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma, approximately [redacted] post treatment with Carvykti. [redacted] The MAH assessed the case as not related to treatment with Carvykti.

The fourth case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma approximately [redacted] post CAR T cell treatment. The patient presented with [redacted] The MAH assessed the case as related to treatment with Carvykti.

The fifth case was from the post marketing setting and was a [redacted]-year-old who developed T-cell lymphoma approximately [redacted] after CAR T cell treatment. The case was 'late breaking' and came in after the data lock point, so details are sparse. [redacted] CAR sequencing is pending. The MAH assessed the event as related to Carvykti at this time, pending further testing.

Assessor's comment

The assessor suggests that the first and fourth case suggest a causal relationship between the development of T-cell lymphomas and treatment with Carvykti. The first case contains strong evidence, with the patient experiencing [redacted] The first case also [redacted] It has been suggested that [redacted] may lead to tumorigenesis.

The assessor suggest that the second case could be related to Carvykti, however not enough detail was given on testing and levels of CAR transgene to fully assess causality.

The assessor agrees, given the [redacted], that the third case is likely not related to CAR T cell treatment.

The assessor agrees with the MAH regarding the fifth case does not have enough information to assess causality.

<u>Kymriah</u>

A cumulative search was conducted in the Novartis global safety database up to 11 January 2024. Initially 9 cases were retrieved. 1 case was a duplicate. 1 case reporting [redacted] the event was coded as symptom of the underlying disease progression [redacted]). Therefore, this case was not considered a second primary malignancy. Therefore, the total number of cases of secondary T-cell malignancy received for Kymriah was 7.

The first case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma on [redacted] after CAR T cell treatment. The case had a fatal outcome. It was unknown if the autopsy was performed or not [redacted] The MAH assessed the causality as not suspected.

The second case was from a post marketing setting and was a [redacted] year-old [redacted] who developed peripheral T-cell lymphoma unspecified [redacted] after CAR T cell treatment. The patient was [redacted] The clinical diagnosis was peripheral T-cell lymphoma (not otherwise specified). The case had a fatal outcome. It was reported that an autopsy was not performed. No CAR transgene testing was performed. The MAH assessed the causality as not suspected.

The third case was from a post marketing setting and was a [redacted] year-old [redacted] who developed T-cell lymphoma [redacted] after CAR T cell treatment. The final diagnosis of mature T-cell lymphoma was [redacted] The patient passed away, with cause of death not reported. [redacted] Therefore, no additional analyses were recommended at this time. [redacted] The MAH assessed the causality as not suspected.

The fourth case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma [redacted] after CAR T cell treatment. The patient developed a [redacted] suspicion of T-cell lymphoma. [redacted]

[redacted]

[redacted] The case had a fatal outcome. The MAH assessed the causality as not suspected.

The fifth case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma [redacted] after CAR T cell treatment. In [redacted] the patient presented with [redacted]. The patient was diagnosed with anaplastic T-cell lymphoma [redacted] The MAH assessed the causality as not suspected.

The sixth case was from a post marketing setting who developed T-cell lymphoma after CAR T cell treatment. Age and sex were unknown. [redacted] The MAH assessed the causality as not suspected.

The seventh case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed large granular lymphocytosis [redacted] after CAR T cell treatment. [redacted] The MAH assessed the causality as not assessable.

Assessor's comment

Regarding the first, second, fifth and seventh case, as no samples were available for CAR transgene testing, the assessor suggests there is not enough information to assess causality.

As the third case had sample tested by the MAH and [redacted] the assessor suggests there does not appear to be a causal relationship with the development of T-cell lymphoma and Kymriah in this case.

Regarding the fourth cases, [redacted] The company suggest that there is not a causal relationship, [redacted] The assessor suggest that a causal relationship should not be ruled out [redacted]

The assessor suggests that for the sixth case given [redacted] the development of T-cell lymphoma does not seem to be related to Kymriah in this case.

Tecartus

The MAH reported that the cumulative search of the Gilead Global Safety Database up to 24 January 2024 retrieved no T-cell malignancy events reported for [redacted] participants or patients after Tecartus infusion.

Yescarta

The cumulative search of the Global Safety Database up to 24 January 2024 using PTs in the search strategy retrieved 11 new T-cell malignancy cases after Yescarta infusion.

The first case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma [redacted] after CAR T cell treatment. The case had a fatal outcome. The patient experienced [redacted] The MAH stated there was not enough information to assess causality.

The second case was from a post marketing setting and was a [redacted] year-old [redacted] who developed lymphocytic leukaemia/lymphoproliferative disorder [redacted] after CAR T cell treatment. Notable past medical history includes [redacted] the reporter noted a diagnosis of large cell lymphoma/post-transplant lymphoproliferative disease. [redacted] The MAH state the information provided does not support causality; [redacted]

The third case was from a post marketing setting and was a [redacted] year-old [redacted] who developed large granular lymphocytosis [redacted] after CAR T cell treatment. [redacted]

[redacted]. The MAH stated there was not enough information to assess causality.

The fourth case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma [redacted] after CAR T cell treatment. [redacted] The MAH states testing results do not support causality.

The fifth case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed lymphoproliferative disorder [redacted] after CAR T cell treatment. The MAH stated there was not enough information to assess causality.

The sixth case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma [redacted] after CAR T cell treatment. A [redacted] with pathology suggesting T-cell malignancy, however, further follow up is awaited. The MAH stated there was not enough information to assess causality.

The seventh case was from a clinical trial and was a [redacted]-year-old [redacted] who developed large granular lymphocytosis [redacted] after CAR T cell treatment. [redacted]

[redacted] The MAH suggests that data do not support a causal relationship between T-LGL and Yescarta treatment.

The eighth case was from a post marketing setting who developed angioimmunoblastic T-cell lymphoma after CAR T cell treatment. This was a literature case, and the MAH was unable to gather further details. The MAH stated there was not enough information to assess causality.

The ninth case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma after CAR T cell treatment. The case was reported to the MAH in [redacted] so follow-up is ongoing. The MAH stated there was not enough information to assess causality.

The tenth case was from a post marketing setting and was a [redacted] year-old [redacted] who developed T-cell lymphoma [redacted] after CAR T cell treatment. The case had a fatal outcome. The MAH stated there was not enough information to assess causality.

The eleventh case was from a post marketing setting and was a [redacted]-year-old [redacted] who developed T-cell lymphoma [redacted] after CAR T cell treatment [redacted] The MAH suggests that testing results provided by the reporter do not support causality with Yescarta.

Assessor's comment

The assessor agrees with the MAH regarding the first, third, fifth, sixth, eighth, ninth and tenth cases, that there is not enough information of assess causality. Without CAR transgene testing it is difficult to assess causality given patients have multiple other confounding factors including previous treatment and underlying conditions

For the second case, the assessor agrees with the MAH that although no CAR transgene testing is available, past medical history suggests that the patient's lymphoproliferative disorder is not related to Yescarta.

The fourth case had [redacted], suggesting that Yescarta is not implicated in the development of T-cell lymphoma in this case. Additionally, the assessor is not clear if the diagnosis of T-cell lymphoma not otherwise specified was ever confirmed.

Regarding the seventh case, although a [redacted] he assessor does not feel this case provides evidence of a causal relationship between the development of T-cell malignancies and Yescarta.

Regarding the eleventh case, the MAH states that due to [redacted] the evidence does not support causality with Yescarta. The assessor agrees with this assessment.

Summary of cases

A total of 27 events of T-cell malignancy were reported for the current licenced CAR T cell products. Cases were reported for all products except Tecartus. 6 cases were from clinical trials and 21 cases were in a post marketing setting. The most common reported PT was related to T-cell lymphoma, with 21 cases reporting these PTs (T-cell lymphoma (14), peripheral T-cell lymphoma unspecified (5), cutaneous T-cell lymphoma (1), angioimmunoblastic T-cell lymphoma (1)). Other reported PTs were large granular lymphocytosis (3), lymphoproliferative disorder (1), lymphcytic leukemia (1) and T-cell large granular lymphocyte leukemia/ large granular lymphocytosis (1).

13 cases had no testing for CAR transgene or replication competent lentivirus. 14 cases had some form of testing for CAR transgene or replication competent lentivirus. Testing methods and sample type varied. 5 cases were considered negative for the presence of CAR T. 3 cases had very low levels of CAR transgene detected, which suggested the CAR T treatment was not involved in the development of the secondary malignancy.

6 cases had either high levels of transgene or levels that allowed for further analysis to be completed. The finding for testing in each of the 6 cases are briefly summarised below.

- For one case who received Abecma, insertional site analysis [redacted]
- For one case who was treated with Breyanzi, [redacted]
- For one case who received Carvykti [redacted]
- A case who received Carvykti [redacted] Further testing results are pending.
- CAR sequencing from a patient who received Carvykti [redacted]
- One case which was treated with Kymriah had [redacted]

Assessor's comment

A total of 27 cases of T-cell malignancy following CAR T cell therapy were reported. 13 had not enough information to assess causality, 8 cases were assessed as not related to CAR T cell therapy, 3 were assessed as possibly related to CAR T cell therapy and 3 were assessed as related to CAR T cell therapy.

Insertional site analysis for the Abecma and Breyanzi cases suggest integration of the CAR transgene did not have a causative role in the development of T-cell malignancy, however this cannot be completely ruled out due to limitations in testing.

The assessor suggest that it is not possible to fully rule out that the Kymriah case had a causal relationship, [redacted]

One of the Carvykti cases could have a causal association, [redacted] and follow up testing is required before a determination on causality can be made.

The other two Carvykti cases provide the strongest evidence of a causal relationship between the development of T-cell malignancy following CAR T cell treatment. [redacted]

3.3. UK ADR data

A search of the MHRA's database of UK Adverse Drug Reaction reports was completed on the 13 March 2024. One case of T-cell malignancy for patients treated with a CAR T cell therapy was identified. To note this case was reported after the MAHs deadline to report data for this review, so is an additional case to the cases described in section 2.2. [redacted]

The patient was a [redacted]-year-old [redacted] who received Breyanzi as part of a clinical trial. Approximately [redacted] after CAR T cell infusion, the patient was hospitalised with [redacted]. [redacted]

[redacted] The investigator assessed [redacted] T-cell lymphoma as related to Breyanzi.

The company has requested biopsy samples for transgene testing. The company states at time of reporting there is insufficient information to determine a casual association.

Assessor's comment

[redacted]

Without CAR transgene testing it is difficult to determine causality. The assessor notes the patient [redacted] after CAR T cell infusion. The assessor also notes that the patient has [redacted]

3.4. Background occurrence of T-cell malignancies

MAHs were asked to provide information on the background occurrence of T-cell lymphoma/leukemia/lymphoproliferative disorder, where possible by indication. A brief summary of the information is presented below.

Overall (in general population)

Data from the US registry Surveillance, Epidemiology and End Results (SEER) was used by several MAHs. The estimated the crude incidence rate (per 100,000 person-years) of T-cell malignancy (overall) was 2.25. The crude incidence rate for peripheral T-cell lymphomas was 1.15.

The world-age standardized incidence rate of T-cell lymphomas was 2.2 per 100,000 in the period 1997-2003 in Modena, Italy (Luminari et al., 2007); and the European-standardized incidence rate was 1.9 per 100,000 in 2010-2015 in Reggio Emilia, Italy (Mangone et al., 2023).

Patients with multiple myeloma

Data from the Optum claims database, which is a US claims database, was used to estimate the cumulative incidence of secondary T-cell malignancies at 1, 2, 3, 4, and 5 years from the index date. The cumulative incidence proportion of developing T-cell lymphoma among patients with multiple myeloma is 0.18% by 1 year, which increases to 0.45% by 5 years.

US based registry data estimated the crude incidence rate (per 100,000 person-years) for T-cell malignancy (overall) in patients with a prior multiple myeloma diagnosis was 10.96.

Janssen used various databases to estimate the incidence of T-cell lymphoma for the multiple myeloma population. In patients with newly diagnosed multiple myeloma, the incidence rate of T-cell lymphoma ranges from approximately 76 per 100,000 person years in both the MDCD and Pharmetrics databases to 147 per 100,000 person years in CCAE. Among multiple myeloma patients initiating an agent in each of the drug classes for the first time ever, the incidence of T-cell lymphoma ranges from 46 per 100,000 person years to 88 per 100,000 person years for IMiDs (e.g. lenalidomide), 52 per 100,000 PY to 131 per 100,000 person years for proteasome inhibitors, and 60 per 100,000 person years to 114 per 100,000 for anti-CD38 mAbs. In patients receiving first ever haematopoietic stem cell transplant for multiple myeloma, the incidence of T-cell lymphoma was estimated to be 173 per 100,000 persons years in CCAE and 179 per 100,000 person years in Optum DOD. Finally, there were too few incident cases of T-cell lymphoma among patients with triple-class exposed multiple myeloma in any of the databases to produce stable incidence rates.

Patients with large B-cell lymphoma

Data from the Optum claims database was used to estimate the cumulative incidence of secondary T-cell malignancies at 1, 2, 3, 4, and 5 years from the index date. The cumulative incidence proportion of developing T-cell lymphoma among patients with large B-cell lymphoma is 1.72% by 1 year, which increases to 3.16% by 5 years (n = 19,331).

A study based on the US SEER registry identified patients diagnosed between 2000 and 2016 with a first primary B-cell lymphoma. The study included 80,155 patients with diffuse large B-cell lymphoma (DLBCL), with a mean follow up of 4.5 person years at risk. For DLBCL 0.12% of patients present a T-cell primary lymphoma after a primary DLBCL which is an incidence rate of 26.6 per 100,000 person-years, and patients have a 5.5-fold risk of presenting a T-cell primary lymphoma compared to the general population. Of note, the increase in risk of presenting with a T-cell lymphoma after a B-cell lymphoma appears to have increased over time: the standardised incidence ratio (95% CI) was 3.6 (3.0-4.3) for 2000-2005, 5.3 (4. -6.2) for 2006-2011, and 6.4 (5.0-8.0) for 2012-2016 (Chihara et al., 2021).

The incidence proportion of 0.14% for non-Hodgkin lymphoma (NHL) and 0.16% for Hodgkin lymphoma as second primary malignancies among a cohort of patients with DLBCL or primary mediastinal large B-cell lymphoma (PMBCL) (N=6,205 and 190, respectively) over a median follow up of 56.8 months in Israel (Neeman et al., 2020). A study found the incidence proportion of 0.74% for NHL and 0.17% for Hodgkin lymphoma among a cohort of patients with DLBCL (N=34,254). The average follow-up interval for this study population is not reported, however median duration from DLBCL diagnosis to Hodgkin lymphoma as secondary malignancy was 61 months. Reported SIR were as follows (Jiang et al., 2020):

- NHL: 1.9 (95% CI 1.7-2.1)
- Hodgkin lymphoma: 7.2 (95% CI 5.5-9.3)

Patient with acute lymphoblastic leukaemia

Data from the Optum claims database was used to estimate the cumulative incidence of secondary T-cell malignancies at 1, 2, 3, 4, and 5 years from the index date. The cumulative incidence proportion of developing T-cell lymphoma among patients with acute lymphoblastic leukaemia is 2.04% by 1 year, which increases to 3.03% by 5 years.

Six studies described the incidence or frequency of lymphoproliferative disorders in adult or children with acute lymphoblastic leukaemia. Incidence proportions of non-Hodgkin's lymphoma were:

Children:

- Great Britain: 0.04% over a follow-up of ≤ 5 years (Stiller et al., 2023)
- US and Canada: 0.05% over a mean follow-up of 20.5 years (Turcotte et al., 2017)
- Japan: 0.07% over a median follow-up of 9.5 years (Ishida et al., 2014)
- EU, North America, and Asia: 0.10% over an unknown follow-up (Schmiegelow et al., 2013)

Adults

- Sweden: 0.44% over a median follow-up of 3 years (Zheng et al., 2019)
- US: 0.09% over a median follow-up of 6.4 years (Ghimire and Shah, 2014)

Incidence proportions of Hodgkin's lymphoma were:

Children

- Great Britain: 0.03% over a follow-up of ≤ 5 years (Stiller et al., 2023)
- US and Canada: 0.03% over a mean follow-up of 20.5 years (Turcotte et al., 2017)
- EU, North America, and Asia: 0.05% over an unknown follow-up (Schmiegelow et al., 2013)

Adults

- Sweden: 0.20% over a median FU of 3 years (Zheng et al., 2019)

The standardised incidence ratio of 13.2 (95% CI 4.9-28.7) for NHL (including Burkitt lymphoma) and Hodgkin lymphoma and miscellaneous lymphoreticular neoplasms in 14,361 patients with lymphoblastic leukemia diagnosed before age 15 years in the Great Britain (Stiller et al., 2023). The relative risk for NHL and Hodgkin lymphoma in 2,474 adult (>20 years) patients with ALL in Sweden. The relative risk for NHL and Hodgkin lymphoma were 4.9 (95% CI 2.7-8.9) and 14.6 (95%

CI 6.1-35.2), respectively (Zheng et al., 2019). A standardised incidence ratio of 36 (95% CI 19-62) and incidence rate of 7.3 per 100,000 PY for NHL was reported among 2,807 newly diagnosed children with ALL aged 1-15 years (who successfully achieved complete remission and survived at least 2 months) in Japan (Ishida et al., 2014).

Patient with follicular lymphoma

Data from the Optum claims database was used to estimate the cumulative incidence of secondary T-cell malignancies at 1, 2, 3, 4, and 5 years from the index date. The cumulative incidence proportion of developing T-cell lymphoma among patients with follicular lymphoma is 0.88% by 1 year, which increases to 1.79% by 5 years.

One study noted 39 T-cell lymphomas in 42,360 patients with follicular lymphoma with a mean follow-up of 6.4 person-years at risk (incidence proportion: 0.09%; incidence rate: 14.4 per 100,000 person-years) (Chihara et al., 2021). In follicular lymphoma patients, the standardized incidence ratios (and 95% CI) by type of T-cell malignancy were as follows:

- T-cell lymphoma: 3.0 (95% CI 2.1-4.1)
- Mycosis fungoides/Sezary syndrome: 2.4 (95% CI 1.0-4.6)
- Peripheral T-cell lymphoma-not otherwise specified: 2.2 (95% CI 0.9-4.6)
- Angioimmunoblastic T-cell lymphoma: 1.5 (95% CI 0.2-5.5)
- Anaplastic large cell lymphoma: 4.4 (95% CI 1.4-10.3)
- Cutaneous T-cell lymphoma: 4.4 (95% CI 2.1-8.0)

One study reported the frequency of mature T- and NK-cell neoplasm among 8,028 adults (≥18 years) FL patients (grades 1-3B). Reported incidence proportion was 0.05% over a median follow up of 7.1 years (Dinnessen et al., 2020).

The frequency of indolent NHL and Hodgkin lymphoma as secondary malignancies among a cohort of adult patients (≥18 years) with FL (N=8,028) was reported in a study in the Netherlands. The incidence proportions of indolent NHL and Hodgkin lymphoma over a median follow-up of 7.1 years were 0.10% and 0.24%, respectively (Dinnessen et al., 2020). A study reported the frequency, observed/expected ratio and incidence rate of Hodgkin lymphoma as second primary malignancies among a cohort of patients with follicular lymphoma (N=15,517) in the US. The incidence proportion of Hodgkin lymphoma over a median follow-up of 71 months were 0.14% (incidence rate: 20.7 per 100,000 person years) and reported observed/expected ratio was 5.9 (95% CI 3.6-8.9) (Giri et al., 2017). A study reported the frequency and incidence rate of Hodgkin lymphoma as secondary malignancies among a cohort of patients with follicular lymphoma (N=655) in Spain. The incidence proportion of Hodgkin lymphoma over a median follow-up of 12 years was 0.15% (incidence rate: 13.2 per 100,000 person years) (Jiménez-Ubieto et al., 2018).

Mantle cell lymphoma

Data from the Optum claims database was used to estimate the cumulative incidence of secondary T-cell malignancies at 1, 2, 3, 4, and 5 years from the index date. The cumulative incidence proportion of developing T-cell lymphoma among patients with mantle cell lymphoma is 0.78% by 1 year, which increases to 1.66% by 5 years.

Assessor's comment

The MAHs provide a variety of data on background incidence of T-cell malignancies, varying from data from published literature to crude epidemiological analysis of claims data. Methodologies, follow up time and cohort size varied between data sources, limiting the ability to directly compare between different data sources. Claims data has various limitations including completeness of the data and biases in terms of who receives treatment, and a crude analysis does not adjust for these factors.

From the available data, acknowledging limitations, the development of T-cell malignancies in the general population is rare. Taking the data as a whole, those who have had a previous haematological malignancy appear to be at a higher risk of developing T-cell malignancies compared to the general population, however, estimates of incidence vary across studies.

The crude epidemiological analysis of claims data by Gilead Sciences Ltd. provides a useful comparison of T-cell malignancy incidence rates between the different background indications. It suggests that those with multiple myeloma have a lower cumulative incidence of T-cell lymphoma, compared to those with large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma and acute lymphoblastic leukaemia.

3.5. Literature

Relevant publications in the literature are summarised below. Some publications were case reports of secondary T-cell malignancy which on review by the assessor seemed to match the narrative of individual cases that have already been described in this report. Therefore, those publications will not be discussed in this section.

In a clinical report by Bishop et al. that discussed the phase 1, first-in-human administration of HLA-matched sibling donor-derived CAR19 T cells using the piggyBac transposon system, the authors reported 2 out of 10 treated patients developed CAR T cell-derived lymphoma based on identification of a new mass composed of monoclonal CAR19 T cells (according to TCR beta chain analysis) and other abnormal phenotypes. Before these 2 cases, secondary T-cell malignancy derived from CAR T cells had not been previously documented following administration of CAR T cell products (Bishop et al., 2021).

In another related article by Micklethwaite et al., there was a discussion on the 2 CAR-positive T cell malignancies that developed after receiving piggyBac transposon-derived CAR T cells. The authors mentioned the detailed mechanistic studies revealing a high transgene copy number in the malignant CAR T cells, but no evidence of insertional mutagenesis. This suggested that the vector design and production methodology used in these piggyBac transposon-derived CAR T cell products was the predominant factor in malignant transformation (characterized by significant changes in somatic structural variation, gene copy number, and global gene expression) for the occurrence of the 2 CAR T-cell malignancies (Micklethwaite et al., 2021)

FDA officials Verdun and Marks published a Perspective article summarizing the current Agency view on secondary cancers from clinical trial and commercial use of CAR T products, mentioning 3 cases of T-cell malignancies for which genetic sequencing was performed and CAR transgene was detected in the malignant clone, indicating that the CAR T product was most likely involved in the development of the T-cell cancer. The authors concluded that secondary T-cell cancers occurring after the use of CAR T cells for the treatment of relapsed or refractory hematologic cancers appear to be relatively rare adverse events. Appropriate product labelling will be a resource that can help clinicians manage conversations with patients about the benefits and risks associated with treatment options.

A paper discussing challenges when manufacturing CAR-T for T-cell neoplasm state, "…the generation of autologous CAR-Ts from the peripheral blood mononuclear cells (PBMC) of patients with T-cell neoplasms is very problematic since malignant and normal T cells are isolated together in the process of leukapheresis. In this case, the autologous CAR-T product might contain engineered T cells generated from malignant T lymphocytes." For non T-cell neoplasms the authors state, "Moreover, in the case of malignancies other than T-cell neoplasms, for the aim of generating autologous CAR-Ts, T cells are isolated from the patient and are genetically engineered to express CARs. But in the case of T-cell malignancies, isolating only healthy non-malignant T cells is almost impossible and rather problematical since malignant T cells and normal T cells are isolated simultaneously from such patients." The authors present a case where a leukemic B cell was unintentionally genetically modified to express CD19 redirected CAR as follows, "Generating

autologous CAR-Ts from patients with T-cell malignancies is challenging since during the process of T-cell isolation, both normal and malignant T cells are isolated. Therefore, after the CAR transgene introduction process, the CAR-T product population will contain malignant T cells as well as normal ones. In 2018, Ruella et al. reported that during the generation process of CD19-redirected CAR-Ts, one leukemic B cell was unintentionally-genetically manipulated to express the CD19 redirected CAR. This contamination resulted in the binding of the CD19-redirected CAR to the CD19 antigen; therefore, the target antigen was no longer recognizable by the administered CD19-redirected CAR-Ts. Even though this incidence is rare in the case of B-cell malignancies, it has a higher occurrence possibility when generating autologous CAR-Ts from patients with T-cell malignancies (especially in T-cell leukaemia patients whose number of circulating malignant T cells are high)." (Safarzadeh Kozani et al., 2021).

A report describes the results from a multicentre trial of ARI-0001 cell therapy in patients with CD19+relapsed/refractory malignancies. The only grade ≥3 malignancy observed in the study was myelodysplasia in a 7-year-old girl diagnosed with ALL who had already received 6 lines of therapy, including immunotherapy and allo HCT (Ortíz-Maldonado et al., 2021).

A study analysed a sample of 340 adult and paediatric patients who, over a 30 year period at a single centre, received γ-retroviral vector (GRV) transduced genetically modified immune effector cells (IECs) in 1 of 5 classes of therapeutics: donor-derived gene-marked virus-specific T lymphocytes (VSTs), autologous gene-marked VSTs, donor T cells transduced with an inducible caspase 9 suicide gene, dominant-negative tumour necrosis factor-b receptor-transduced VSTs, or CAR T cells with 7 distinct target antigens. Out of these patients, 16 cases of second primary malignancies were observed in 13 patients (3 of the 13 patients had more than 1 subsequent malignancy), with 1 case of T-cell lymphoma occurring 36 months after the administration of HER2 CAR T therapy for glioblastoma. The latter patient had a pre-existing diagnosis of constitutional mismatch repair deficiency syndrome, which "put him at increased risk for hematologic malignancies," including T-cell lymphomas. No IEC trans-gene was detected in the lymphoma biopsy, and replication-competent retroviruses (RCR) testing was negative at all time points before and after infusion. The authors state that "there is no evidence to date of subsequent resulting from GRV modification in T cells, as demonstrated by multiple groups" (Steffin et al., 2022).

A case report described a 72-year-old man with refractory DLBCL originally diagnosed more than 10 years ago and treated with fludarabine-based chemoimmunotherapy. He had multiple relapses and then was given CD19-targeted CAR T-cells and, within 1 week, he developed a growing mass on his shin at the site of his known lymphoma. The biopsy showed a diffuse, sheet-like infiltrate composed of medium-to-large atypical cells. Stains showed that the infiltrate was negative for B-cell markers, including PAX5, and positive for CD3 with predominately CD4 compared with CD8. The authors reported that "the infiltrate lacked BCL2 (not shown), which is suggestive of T-cell lymphoma. However, 15 days after the biopsy, this lesion completely resolved without intervention, and the positron emission tomography scan confirmed complete remission. This likely represented the CAR T cells that were homing to this particular site but eventually dissipated. These can mimic persistent disease or even a T-cell lymphoma and should be evaluated with caution." (Song and Herrera, 2019).

Assessor's comment

Literature articles did not provide any new or significant information related to this signal.

The assessor does note case reports of T-cell malignancies developing following treatment with CAR T cell products other than the 6 licenced products.

4. DISCUSSION

4.1. Strength of the evidence

4.1.1. 3.1.1 Assessment of causality

In terms of cases reports there is strong evidence of causality in two of the Carvykti cases. One of the Kymriah cases may have a causal association. For other cases, causality was ruled out or causality could not be assessed due to lack of information. In terms of the hierarchy of evidence, the evidence for causality is based on individual case reports. Events reported in trials were in very low numbers making any calculation of frequency unreliable. Evaluation of causality based on individual cases is challenging when there is a background risk of T-cell malignancy, albeit rare and the evaluation relies largely on result of genetic tests of individual patient samples which was missing in many cases.

A crude calculation of the rate of T-cell malignancy in those treated with the 6 licenced CAR T cell product is approximately 66 per 100,000. This is a crude estimate and does not consider whether reports are assessed as related to CAR T cell therapy or not and does not consider the likely underreporting. This is not a higher rate of T-cell malignancy than would be expected in patients with the licenced indications.

It is known that patients with a primary malignancy are at increased risk of developing a secondary malignancy. This is supported by the data on background incidence rate that has been presented. There are multiple confounding factors observed with each case and these need to be considered when assessing causality. Confounding factors are discussed in section 3.1.3.

Based on the available data the event of secondary T-cell malignancy following CAR T cell therapy appears to be rare. The assessor suggests that although there is a low number of cases reported, the limitation of post marketing surveillance make it likely that there is underreporting. The assessor notes that 7 of the 27 reported cases (25.9%) were reported to the MAHs in the 2.5 months between the FDA initial announcement of the investigation and the MAHs submitting data for this assessment. Increase in reporting may well be due to increased awareness of the issue, due to the attention received of the FDA review.

Variation in exposure between different products in the class make it difficult to look at association with individual product. The number of reports of secondary T-cell malignancy for an individual product was not proportional to the exposure for that product.

4.1.2. Possible mechanisms

Insertional mutagenesis could potentially lead to oncogenesis, by disrupting normal gene regulation. Potential mechanisms by which insertional mutagenesis could lead to malignancy include vector enhancer-mediated activation of down-stream gene expression, insertional gene inactivation and gene activation by 3’end truncation (Bushman, 2020). It is noted that design of vectors can consider these issues, such as designing vectors to be self-inactivating. If insertional mutagenesis occurs it could lead to cell immortalisation, transformation, and subsequent tumorigenesis. The vectors used in current licenced CAR T cell products are replication defective, so integration into the genome can only happen once per viral vector. Multiple integrations into the same cell is possible, but can be reduced by minimising the number of vector copies per cell when the product is manufactured.

Reactivation of replication-competent retroviruses or lentiviral vectors is another possible mechanism which could lead to the development of malignancies; however, this does seem less likely than insertional mutagenesis. Reactivation of replication competent retroviruses or lentiviruses could occur due to homologous or nonhomologous recombination events of viral components, reassembly, and amplification, which could lead to malignant transformation. If such recombination events were to occur and result in a functional replication competent retrovirus/lentivirus, they would likely be confined to T cells, as they are the only cell type with cell surface receptors that allow integration of the specific replication competent retrovirus/lentivirus used in production. The

transgene could theoretically insert into a chromosomal region that activates an oncogene or disrupts a tumour suppressor gene leading to a transformation event.

Another possible mechanism is that a pre-existing malignant or pre-malignant clone was present at the time of apheresis, and then infused back into the patient. Recent viral infections can trigger proliferation of these malignant clones and it may also be possible that CAR T cell therapy may play a role in triggering proliferation of these clones.

It is also important to consider that patients who receive CAR T cell therapy are lymphodepleted and experience immunosuppression, which in itself could potentially accelerate the onset of malignancy due to pre-existing malignant mutations.

There is a possibility that epigenetic changes during the manufacturing process could also play a role.

4.1.3. Confounding factors

Current licenced CAR T cell therapies are not first line treatment and are approved for indications where haematological malignancies are relapsed and refractory. Therefore, patient receiving CAR T cell therapies will have had multiple previous lines of therapy. Many of the lines of therapy for the approved indication are known to be genotoxic and can contribute to a raised risk of new malignancies of individuals receiving CAR T cell therapies. Prior lines of therapies that could contribute to the development of new malignancies include alkylating agents, nucleoside analogs, topoisomerase inhibitors, immunomodulatory drugs, radiation therapy and stem cell transplants.

Genetic predisposition can also play a contributory role in the development of secondary malignancies.

As seen in data on background occurrence of T-cell malignancies, individuals who have had a previous haematological malignancy are at increased risk of developing T-cell malignancies compared to the general population.

Environmental and behavioural factors can also contribute to raised risk of developing new malignancies.

4.1.4. Conclusion on causality

The assessor suggests that there is not currently enough evidence to definitively state there is a causal relationship between the development of T-cell malignancies and CAR T cell therapy, however there is enough evidence for a reasonable suspicion of a causal relationship.

4.2. Benefit risk

The assessor suggests that given the remaining uncertainty surrounding a causal association between CAR T cell therapy and development of secondary T-cell malignancy, as presented in this assessment report, there is no impact on the benefit-risk profile of the 6 licenced products. Furthermore, the assessor suggests, given the seriousness of all the currently approved indications, if a causal association was confirmed, given the events seemingly being rare, the benefit risk balance would remain positive for the current approved indication.

The assessor suggests that the possibility of the development of secondary T-cell malignancies will need to be considered, in the context of the benefit risk balance, in future applications for marketing authorisations of new CAR T cell products and for any application for extension of indication for the currently licenced products.

The assessor notes that there are a wide range of advances in CAR T cell technology currently in development, including the universal CAR T and use of CRISPR and base editing technology. It is not clear if these advances will impact the risk of developing secondary malignancies.

4.3. MAHs proposed actions

4.3.1. MAH suggested actions relating to product information and risk minimisation measures

Each MAH was asked to propose actions based on the data they have provided.

Summary of Product Characteristics and Patient Information Leaflet

The MAHs for Abecma, Breyanzi and Kymriah propose no changes to the current SmPC and PIL.

The MAH for Carvykti proposes to add Hematologic malignancy, which includes T-cell lymphoma, as an ADR in SmPC Section 4.8 Undesirable Effects. This will include updates to the ADR table, and the Description of Selected Adverse Reactions section will include a brief summary of T-cell lymphomas observed in clinical trials.

The MAH for Tecartus and Yescarta concludes that the language in the SmPC for Yescarta sufficiently describes the risk and intends to align the SmPC for Tecartus with the same language. The wording is: "*Patients treated with Yescarta may develop secondary malignancies. Patients are to be monitored lifelong for secondary malignancies. In the event that a secondary malignancy of T-cell origin occurs, the company is to be contacted to obtain instructions on patient samples to collect for testing*.".

Direct Healthcare Professional Communication (DHPC)

No MAH has proposed a DHPC to communicate this safety issue to healthcare professionals.

Risk Management Plan (RMP) and educational materials

The MAHs for Abecma, Breyanzi and Kymriah do not propose any changes to the current RMPs or educational materials.

The MAH for Carvykti proposes to update the RMP to add "Hematologic Malignancies of T-cell origin" as an important identified risk for the product. "Second Primary Malignancy (other than hematologic malignancies of T-cell origin)" will remain an Important Potential Risk.

The MAH for Tecartus and Yescarta proposes changing the important potential risk to 'secondary malignancies of Tcell origin' in both products' RMPs. The current wording of the important potential risks are 'secondary malignancy' and 'RCR (Replication competent retrovirus)in the Tecartus RMP and 'secondary haematologic malignancy (including replication competent retrovirus [RCR])' in the Yescarta RMP. In addition, the MAH proposes an update to the Patient Alert Card (PAC) to inform patients and their treating physicians about sample collection and testing. The proposed text included in the PAC is as follows:

"*If you were diagnosed with new blood cancer after being treated with Yescarta/Tecartus, please have your physician contact Kite at [telephone number] to obtain instructions on further testing.*

This card should be retained lifelong."

4.3.2. Current practices for follow-up of cases

The MAHs were asked to comment on the current practices for receiving a case report of secondary malignancy.

Abecma and Breyanzi

All individual case safety reports (ICSRs) received by BMS are entered into the BMS Corporate Safety Database and processed based on standard operating procedures. Medical assessment is provided for all serious ICSRs, including reports of secondary malignancies. The medical assessment is based on information available at the time of case processing. Any missing information is requested via the specific targeted questionnaire for secondary malignancies in accordance with the Annex 4 of EU RMP for Abecma/Breyanzi. Request for tumor samples and transgene testing of the SPM samples is described below.

For commercial patients, the Company has developed a global non-interventional laboratory testing protocol, protocol number CA082-085, describing the process of collection and associated transgene assay testing service of tumor tissue from patients who have received a BMS-manufactured Gene Modified Cell Therapy (GMCT) and have reported a spontaneous serious adverse event (SAE) of secondary malignancy to the Company.

Existing tumor samples of these patients will be eligible for testing if the patient has received a BMS-manufactured GMCT and has been diagnosed with a qualifying secondary malignancy suspected of T-cell origin, or if the patient has been diagnosed with a secondary malignancy which the Company safety team has further qualified for investigation.

Protocol requirements for the testing include an available secondary malignancy tumor sample for testing, accompanied by a pathology report, local ethics committee (EC)/institutional review board (IRB) approval of the protocol in the healthcare institution where the secondary malignancy has been diagnosed and SAE reported to the Company, informed consent from the patient or authorized representatives, and a contract concluded between the healthcare institution and the Company.

Tumor samples from hospitals will be sent through a central biosample vendor to contracted specialty laboratories for transgene testing by RNA-scope in-situ hybridization (ISH) method. If the transgene is detected by ISH, additional tumor samples will be tested for insertion site analysis [redacted] The results of the test will be shared with the safety organization of the Company for further evaluation and reporting to health authorities, as well as with the treating physician who reported the SAE, provided the tumor sample for testing, and requested to receive the results.

For clinical trials, all SPMs reported as SAEs follow a workflow outlining the steps for the collection, review, analysis and reporting of SPMs in accordance with the clinical study requirements. Upon receipt of a SAE report for a SPM diagnosed in a clinical trial subject, the clinical site enters all relevant SAE data into the electronic case report form (eCRF) and the BMS Medical Monitor responsible for the clinical trial in which the SPM was reported enters the relevant information into an SPM tracker. Once the information is entered into the tracker, BMS Clinical Operations personnel request relevant tissue and peripheral blood from the investigative site, with directions for sample collection, including requisition forms, lab kits and shipment information to ensure adequate sample stability. If tissue and/or peripheral blood are not available, this is documented in the site/study electronic trial master file (eTMF).

If tissue and/or peripheral blood are available, personnel from BMS Biospecimen Lead are notified regarding the availability of incoming sample(s). Once the samples are received, they are sent for testing for the presence of transgene by a validated RNA-scope in-situ hybridization (ISH) or qPCR/droplet digital (dd) PCR method. If insufficient or damaged specimens are provided by the investigative site, additional samples are requested by BMS Clinical Operations and the process repeated. After test results are obtained, they are reviewed and discussed by the BMS Translational Scientist and Medical Monitor. This discussion results in a decision regarding whether testing concludes (if results are negative for transgene detection) or if downstream insertional site analysis (ISA) analysis is needed. Once all relevant test results are received, the transgene investigation is considered completed and routine testing and analysis per the protocol is subsequently performed through end of study.

<u>Carvykti</u>

The MAH diligently strives to obtain tissue samples from providers reporting second primary malignancies (SPMs) in patients treated with cilta-cel in clinical trials and in the commercial setting globally. Upon receipt of a new SPM case report, the MAH ensures timely case processing and expedited reporting of this event to applicable health authorities. Concurrently, the MAH proactively sends to the HCP or other reporter the MAH's Targeted Follow-Up Questionnaire for SPMs, which includes additional questions about the patient and event.

Depending on the type of SPM, the MAH requests providers to submit tissue samples such as:

- Two entire dedicated FFPE blocks from excisional (preferred) or diagnostic blocks. If an entire block is not available, 20-5 μm sections mounted on positively charged slides are desired. The number of slides should be scaled up if the specimen area is smaller than 1 cm x 1 cm and/or the tumor content is less than 60%.
- 4 mL of bone marrow aspirate (clinical trial only, if applicable), and/or
- 4 mL of blood

However, tissue samples are ultimately submitted at providers' discretion. The MAH cannot guarantee samples will be obtained in a timely manner, nor the quality or quantity of samples to sufficiently analyze SPMs. In clinical trials, one of the challenges is that the MAH needs to operate across multiple countries and adhere to a multitude of international regulations regarding consent and sample export requirements. This challenge of obtaining samples is amplified in the commercial setting, because the MAH is heavily dependent on providers to report SPM cases and subsequently submit samples after obtaining patient consent. This not only compromises the feasibility of testing when samples are not provided, but also could result in a delay when limited material is provided, because the MAH must carefully allocate samples across a battery of assays delineated below, in the core testing algorithm for post-infusion SPM assessments as per the FDA guidance. Vector sequences are detected by qPCR and the presence of WPRE+/CD3+ and/or anticamelid+ cells is assessed by ISH/IHC in a patient's tumor FFPE samples. If at least 1% of cells in tumor samples are positive for vector sequences, NGS-based vector integration site analysis will be conducted. Based on sample availability, the MAH will test concurrently across qPCR and ISH/IHC assays to help accelerate timelines. Because of potential pathogenicity of replication competent lentivirus (RCL), the MAH will also test if RCL is present in the patient from CAR T cell production using a qPCR assay against the lentivirus vesicular stomatitis virus-G gene in blood.

Once final test results following the completion of the testing algorithm are received (or any new information obtained either through the Questionnaire or otherwise spontaneously received), the new information is sent in a timely manner for global case processing of this follow-up information and reported as relevant to applicable health authorities.

Of note, the assessment of CAR presence and lentiviral integration pattern may not be sufficient to evaluate the causal relationship of cilta-cel and the development of SPM. Additional assays will be needed to address causality, including assessment of somatic/germline mutations and/or identification of malignant clone(s) and evaluation of clonal evolution over time. In the commercial setting, the feasibility of such testing is significantly limited as compared to clinical trials due to the additional efforts required by providers and the voluntary consent of patients for this testing. Attaining consent for research use only (RUO) assays which may include genetic testing is operationally difficult in the commercial setting. While these assays are needed for safety, they raise questions of whether a clinical research protocol is needed. Moreover, as assays for core testing (qPCR, IHC, LIA, and RCL) and additional assays to evaluate causality are RUO, there is difficulty conveying results to physicians. These test results are complex and require expertise to assure appropriate interpretation. While the presence of CAR T cells may be confirmed, these tests are unlikely to be sufficient for the determination of causality. Clinically, providers may mischaracterize/misinterpret such results if not very familiar with the rationale for testing and assays used.

The MAH is diligently working to conduct the above tests to comply with regulatory guidance and perform scientific evaluation of causality, aligned with the recently published NEJM position paper. Considering the challenges mentioned above, it is important to implement an industry-wide standard and practice of tumor sampling collection and molecular analyses to generate robust information on the risk for, and the nature of, secondary cancers post-infusion of CAR-T therapies to provide additional mechanistic insights.

<u>Kymriah</u>

Novartis has developed a testing algorithm detailing the course of actions to assess reports of secondary malignancies in patients previously treated with Novartis CART compounds.

For tisagenlecleucel, secondary malignancy cases can be reported from clinical trials or from the post-marketing setting through various sources (spontaneous reports, literature, POP, MAPs, quarterly PASS CCTL019B2401 registry transfer, etc.). The sequential actions taken when a case is reported are presented below.

For clinical trial patients, including patients in the long-term follow-up study CTL019A2205B which follows patients treated with a Novartis CAR-T therapy in haematological indications, the Investigator is advised to report any new second primary malignancy as a Serious Adverse Event. For all events related to second primary malignancies, the clinical trial medical lead will contact the Investigator to arrange testing as per protocol requirements including coordination of kit shipment for tumor and/or blood sample collection. Once the investigator agrees to send samples for testing, a dedicated team manages the evaluation of second primary malignancies. Of note, the patient signs an inform consent form (ICF) at protocol entry that includes consent for testing of secondary cancer.

For patients receiving commercial Kymriah, including patients in the PASS CCTL019B2401 using data from CIBMTR and EBMT, upon receipt of a case report of a secondary malignancy, Novartis will attempt to contact the reporting physician to encourage archived tissue sample and/or fresh blood collection for testing. Of note, follow-up on secondary malignancy cases can only be initiated if there is an identifiable reporter of the case and an identifiable patient using the unique identifier (de-identified for any patient identifying information) or patient's Batch ID. The Kymriah batch ID is used to identify the reporting physician contact information through the Kymriah ordering system. Any spontaneously reported case to Novartis, for which the primary reporter has refused further contact, is considered as lost to follow-up for secondary malignancy sample collection. In the post-marketing setting, the requirements for an additional ICF allowing for testing of in case of the occurrence of a secondary malignancy varies by country / region. Once the physician confirms that the ICF has been signed as required by local regulations prior to the sample(s) collection, shipment and analysis will be initiated. Novartis attempts to collect appropriate specimens (i.e., archived tissue block and/or unstained slides) as well as fresh peripheral blood (if feasible and patient provides appropriate consent) and secondary malignancy tissue samples (including bone marrow aspirate) when available and applicable.

Once samples are received, CTL019 CAR transgene levels will be quantified using the quantitative polymerase chain reaction (qPCR) method. Based on the clinical trial experience, qPCR data were observed to be more robust than flow cytometry data to quantify the relative number of CAR-T positive cells. Therefore, as a first step, the transgene levels are quantified using the qPCR method.

If CAR transgene can be detected in peripheral blood and/or secondary malignancy tissue, the transgene levels will be compared to the corresponding time point or visit with the average levels observed in peripheral blood and/or bone marrow aspirate in the pivotal clinical studies to estimate the fold-change in transgene expression. Of note, no robust reference data are available from clinical studies to understand the trafficking of CAR T cells in lymph nodes or other tissues outside blood and bone marrow aspirate or CSF (cerebrospinal fluid). It is hypothesized that in case of a CAR-positive secondary malignancy, all secondary malignancy cells will contain the CAR transgene and therefore the qPCR signal will be significantly above average blood levels at that time point post Kymriah infusion. Peripheral blood and/or secondary malignancy archived biopsy samples will be tested for the presence of replication-competent lentivirus (RCL) using the VSVg qPCR assay, in line with the FDA Guidance for Industry.

Once testing results for transgene and/or RCL become available, a decision will be made at the Novartis Safety Management Team (SMT), composed by a multidisciplinary team, for the need of additional analyses [redacted] Additional analyses may include

immunophenotyping, in situ hybridization, LISA, analyses of collected-apheresis cells (prior to manufacturing) and/or manufactured product characterization.

It is important to emphasize that the detailed analyses to be performed for the follow-up assessment are prioritized and strongly dependent on availability of archived specimen and/or fresh blood from the patient and adapted as needed to the specimens provided.

- Pathology review: Slides are reviewed by a board-certified pathologist at Novartis laboratory to determine whether the tissue specimen is involved with at least 20% of the reported secondary malignancy. The formal pathology report is also obtained from the clinical site for reference and details included in Novartis patient summaries (PDF that is redacted is also saved in the safety reporting system)
- Immunophenotyping: detection of cells by targeting cell surface markers (CD markers or CAR) with labelled monoclonal antibodies. This can be conducted by flow cytometry for cell suspensions (e.g., blood preparations or bone marrow aspirate) or by immunohistochemistry on previous frozen tissue sections (unstained slides) from biopsies (for some antibodies use of paraffin-fixed sections is also possible). Detection antibodies are usually labelled with fluorescence molecules.
- In situ hybridization: A mRNA probe matching the sequence of the CAR transgene is used to detect the transgene in a tissue (e.g., tumor biopsy). In contrast to qPCR, this method can localize the transgene in specific parts of a histopathologic tissue specimen, in particular, this can differentiate between blood cells in the vasculature of tissues and the tissue itself as locus of the transgene. Co-staining for CD3 (T cells), CD19 (B cells) and PAX5 (a transcription factor expressed throughout B cell maturation and detected in most B-cell neoplasms, including those that lack expression of mature B cell markers, such as BALL and B-cell lymphomas) are done concomitantly to help differentiate the location of the mRNA for CAR transgene.
- Lentivirus Insertion Site Analysis (LISA): LISA is a PCR-based method to identify the genomic integration sites of e.g., a CAR transgene. In addition, the distribution of integration sites and the relative position to known genes can be determined. For a given individual cell or tissue sample, it also reports the accumulation of insertions near genes coding for e.g., oncogenes or proteins controlling transcription of genes involved in regulation of cell growth. This distribution pattern can be compared with insertion site pattern known from other viral vectors with clinical background data or from HIV infections and thereby support the risk assessment for derailed cell growth control potentially leading to malignant transformation. Such additional genetic testing may require specific patient consent and specific local approvals pending clinical site / country.

<u>Tecartus and Yescarta</u>

Kite may receive reports of secondary malignancies in clinical trial participants (via clinical trial investigators or via E2B gateway transmission to the global safety database or via fax or email using the paper serious adverse event [SAE] report form to Patient Safety) or in commercially treated patients (eg, via spontaneous reports, Medical Science Liaisons [MSLs], Kite MedInfo, or as part of the United States Center for International Blood and Marrow Transplant Research [CIBMTR] Registry-based studies, KTE-C19-110 [Yescarta] and KTUS-472-5655 [Tecartus].

When a request for secondary malignancy testing is received from a clinical trial investigator, the request receiver informs the Medical Monitor, Clinical Operations (CO) Study Lead, Safety and Pharmacovigilance (PV) team, and Translational Medicine (TM) team. TM then routes a request form for testing patient samples to the study investigator via the CO Study Lead, who emails the request to the study investigator to provide a description of the new malignancy, clinical justification for the request, and available pathology reports. Upon receipt of a completed request form, TM may recommend testing of patient samples per the testing algorithm (see Response to Request 2.d.iii). If additional samples are needed (eg, biopsy and/or blood collection), a request will be sent to the

study investigator via the CO Study Lead. Once samples are obtained, TM requests testing from the appropriate specialty lab.

Upon medical review of spontaneous Individual Case Safety Reports that include a preferred term describing a potential secondary malignancy, Kite sends the reporter a Targeted Questionnaire (TQ) specific to collecting information on the secondary malignancy. Kite may send a version of the TQ translated in local language if necessary. This query for additional information is contingent on the reporter providing Kite with contact information as well as the reporter not declining further contact. The questionnaire instructs the reporter to contact Kite at [redacted] to obtain instructions on patient samples to collect for testing in the event of a new malignancy. Three attempts are made to deliver this TQ to the reporting HCP with the initial attempt within 12 to 15 calendar days from receipt of safety information.

The following steps are implemented to attempt to obtain patient samples. The receiver of the requests informs the country/region contact, for example the Kite Medical Science Liaison or other country medical lead, as well as the Kite Safety & PV and TM Departments. Based on information provided, including any necessary additional information requested from the local receiver, TM determines if sample collection and testing is recommended per the testing algorithm (see Response to Request 2.d.iii). The country/region contact provides the reporting healthcare professional with an informed consent form for secondary malignancy sample collection to be signed by the patient. If the patient provides consent, the reporting healthcare professional is provided with a link to order a sampling kit directly from the central laboratory vendor. The Kite TM Department manages all sample requests with the central laboratory vendor and informs Safety & PV regarding results before informing the requestor of the results.

Assessor's comment

All of the MAHs have global procedures or protocols in place for additional testing of samples from patients who have developed a secondary malignancy following CAR T cell therapy.

All MAHs make efforts to obtain relevant patient samples for testing. All MAHs evaluate the samples for the presence of vector specific sequences, above a certain level. Samples which are positive undergo insertional site analysis.

Exact testing methods vary by MAH. Some MAHs use qPCR and others use digital droplet PCR. In situ hybridization and in situ immunochemistry are conducted by some MAHs and not others. Some MAHs also test for replication competent lentivirus or replication competent retrovirus as part of their procedures. A variety of methods are also used for insertional site analysis, including PCR based methods and next generation sequencing. The assessor acknowledges that a variety of aspects, such as product particulars and sample type/volume, need to be considered when determining testing methodology, so it may not be practical to align methods across MAHs.

The assessor notes that the MAHs have differing criteria to assess whether insertional site analysis, or other further testing should be completed. Some of the criteria are vague or seem to be arbitrary. The assessor suggests that MAHs need to clearly define their decision criteria.

The assessor notes that the PRAC have, in their preliminary assessment report for this signal, outlined recommendations for consideration in the development of testing procedures for CAR T cell therapies. The assessor suggests that the recommendations by PRAC are reasonable and should be considered by MAHs in the development of their testing procedure. The list of recommendations is included later in this report in section 4.4.2.

4.3.3. Barriers to testing

MAHs provided justifications for lack of testing carried out in cases of T-cell malignancies. Some barriers to testing which were highlighted include different health authority requirements, no consent being obtained for testing, no response for request for samples being received from the reporting physician, [redacted], fatal outcomes so no samples obtained, patient location, and a limited amount of sample being received.

Barriers are greater in the post marketing setting than the clinical trial setting.

Assessor's comment

As no UK cases were known at the time MAHs provided data for this assessment, the barriers to testing as described by the MAHs in their responses may or may not be reflective of the UK context. The assessor plans to ask the Oncology and Haematology EAG if there are any barriers that may be an issue in the context of the UK healthcare system.

4.3.4. Improvement to follow up

MAHs were asked to propose further actions to improve follow up of cases.

Abecma and Breyanzi

The Company developed the non-interventional transgene assay testing protocol (CA082-085 Protocol for Transgene Service Assay) according to the Abecma and Breyanzi RMPs as Category 3 additional risk minimization activity to standardize and accelerate the transgene testing of secondary tumor samples in the post marketing setting. The protocol, the informed consent and additional study specific documents and procedures (tumor sample requisition form, laboratory manual, kits with component for specimen collection and preparation and shipping materials for refrigerated shipment, site contract template) are shared with the healthcare institutions reporting the SAE and submitted to EC/IRB for notification or approval, as required by local regulations. Contracts are established with testing laboratories and operational support is provided to facilitate sample logistics, aiming to minimize the time between SAE reporting and the availability of test results. [redacted]

RNA-scope in situ hybridization (ISH) is a valuable method for detection of transgene due to its compatibility with formalin fixed and paraffin embedded (FFPE) tissue which enables rapid investigation in a wide range of clinical samples. [redacted]

T-cell malignancies represent a broad, highly heterogeneous group of malignancies. Diagnosis requires integration of clinical findings along with morphological assessments, immunophenotyping, cytogenetic, and molecular analysis of the peripheral blood, bone marrow, and tissue presenting unique challenges to obtain the appropriate sample at time of diagnosis for transgene testing.

Obtaining samples for transgene testing works effectively when a tumor tissue biopsy is collected for diagnosis because standard practice is to formalin fix and paraffin embed (FFPE) tumor biopsies. These FFPE tissue blocks provide residual preserved tumor tissue specimen, in which diagnosis confirmed presence of neoplastic cells, for transgene testing by RNA Scope in-situ hybridization (ISH).

For cases of T-cell malignancies where diagnosis is made from blood and or bone marrow samples in absence of tissue biopsy, close engagement with the treating institution is required to review the pathology reports conducted for the diagnosis and request the relevant sample(s) for transgene testing. In these cases, blood and or bone marrow aspirate will be requested for transgene testing by PCR. However limited availability of preserved blood and or bone marrow aspirate collected at time of diagnosis may require a patient to consent to additional sample collection after the diagnosis at which time the patient may have received immunosuppressive or anti-cancer therapy. If fresh blood and or bone marrow aspirate are collected after diagnosis, close communication with the treating institution is important to confirm active status of the T-cell malignancy and obtain relevant pathology reports to aid in interpretation of the transgene levels and clonality if CAR positive cells are detected.

An RNA Scope in-situ hybridization (ISH) assay has been validated to detect transgene in FFPE tissue, and ddPCR assay has been validated to detect transgene in DNA extracted from blood and or bone marrow to enable transgene testing on multiple sample types depending on sample availability.

Carvykti

As evident from the adopted PRAC signal assessment report, the MAH has a rigorous process in place for testing of SPMs following cilta-cel infusion in both clinical trials and commercial setting (total of 4 cases identified for CARVYKTI, in 3 cases CAR transgene analysis was performed and analysis of the last case is pending sample availability).

No further actions for cilta-cel have been identified. The MAH is taking every effort to conduct the above tests to meet regulatory guidelines and to perform scientific evaluation of causality, aligned with the recently published NEJM position paper (Verdun 2024). However, as mentioned above, the MAH cannot guarantee samples or sufficient quality/quantity of samples will be obtained at all or in a timely manner. Considering the aforementioned challenges, it is important to implement an industry-wide tumor sampling collection and testing standard and practice to generate robust information on the risk for, and the nature of, secondary cancers post-infusion of CAR-T therapies to provide additional mechanistic insights.

Kymriah

From Novartis' perspective the main hurdle resides in obtaining reporting physician's response and patient or family's consent for sharing samples with Novartis. There is usually archived tissue available, but fresh blood from the patient may not be possible due to many reasons, including: patient deceased, patient living too far from the Kymriah infusion site to return for a blood draw, patient not able to or unwilling to provide consent, [redacted] Clinicians have been very motivated to report the T-cell secondary malignancies and to send tissue and/or fresh blood for testing. However, usually the patient is under the care of another clinician and site for the secondary malignancy and/or may live a considerable distance from the Kymriah clinical site. This may also affect the ability to obtain consent from the patient as well as delays in reporting and/or testing. For other secondary cancers such as MDS, lineage switch ALL to AML, recurrence of a pre-existing solid tumor (breast, lung etc) or a skin cancer, the clinician/PI may feel strongly that those are not a secondary cancer related to CTL019/Kymriah and therefore decline the testing.

Tecartus and Yescarta

Actions to improve the follow up of cases of secondary malignancies particularly those of T-cell origin, for tumour sample collection, pathology work-up and transgene analyses include the following:

1. The MAH proposes an update to the patient alert card (PAC) to improve sample collection and testing by involving the patient in the process for communicating directly with the HCP about options available to them for testing. The MAH proposes an update to the PAC to inform patients and their

treating physicians about sample collection and testing. The patients are instructed to carry the PAC at all times and show the PAC to their HCPs. Therefore, the PAC is the best vehicle to convey the information as it will precisely target the different HCPs that patients encounter during their lifetime. The proposed text included in the PAC is as follows: “If you were diagnosed with new blood cancer after being treated with Yescarta/Tecartus, please have your physician contact Kite at [telephone number] to obtain instructions on further testing. This card should be retained lifelong.”

2. Furthermore, Kite has recently further refined its process for collecting samples from patients who have developed a secondary malignancy after being treated with marketed axicabtagene ciloleucel or brexucabtagene autoleucel by providing detailed instructions needed to process any reports of secondary malignancy consistently and efficiently in a procedural document (PD).

The PD for collection of samples in the commercial setting describes the following actions and responsibilities:

- Who should be contacted after a Kite/Gilead employee receives a secondary malignancy report and request for sampling.
- Who should review the report, request additional information, and request informed consent from the patient.
- Following the patient's consent, who should be responsible for providing the HCP with the central laboratory vendor's contact information and confirming that the HCP contacted the lab and ordered a sampling kit.
- Who is responsible for ensuring the lab conducts the testing according to the testing algorithm (described below).
- Who should receive the results and who communicates the results to the HCP.

The PD also contains a testing algorithm to enable a systematic determination of which sample collection and testing is recommended based on information provided, including any necessary additional information requested from the local receiver of the secondary malignancy report.

A similar PD for MAH sponsored cell therapy clinical studies is in place to define the process for collection and testing patient samples related to potential secondary malignancies.

The TM department at Kite is the lead for testing of samples and has a PD that describes the process. Kite’s algorithm to assess reports of secondary malignancies employs molecular analysis to assess the possible relation between the T-cell malignancy and CAR T-cell therapy. Molecular analyses include polymerase chain reaction (PCR) testing for RCR or CAR transgene presence by droplet digital PCR (ddPCR); any samples positive for RCR or suggestive of substantial CAR presence in the tumor or in circulation will undergo further testing, including characterization of common mutations and vector integration sites.

The secondary malignancy testing algorithm serves as a guide for determining the need for sample collection and appropriate testing; however, in practice the context of each case is considered. There are several nuances for decision making at each step, including sample characteristics, study context in the case of a clinical trial participant, team discussion, and scientific judgment; and as such, departures from the algorithm may be implemented. Furthermore, sample availability may differ due to the collection of samples from earlier timepoints in clinical trial participants.

Relevant diagnostic tissue samples and blood are requested from consented patients who develop hematologic malignancies of T-cell origin after CAR T therapy. New solid tumors and hematologic malignancies of non-T cell origin may also be tested if the treating physician suspects CAR T involvement, requests testing, and the patient consents to collection and analyses of relevant biopsies and peripheral blood samples. Regardless of the new malignancy subtype, Kite advises that all new malignancies be reported as adverse events and monitored by the patient's physician, oncologist, or care team.

Molecular assessment of new malignancies naturally depends on the availability of tumor biopsy samples. Kite acknowledges the difficulty of obtaining samples for testing; in Kite’s experience,

tumor biopsy samples are largely unavailable or seldom consented to for further testing in the postmarketing setting. Without availability of biopsy samples, Kite is not able to further investigate the case.

If available, patient samples will be tested for the presence of RCR and for the CAR transgene by qPCR and ddPCR, respectively. Tests are performed by Kite using validated methodology. If a patient sample is positive for RCR and/or pronounced CAR presence is detected in the tumor or in the circulating immune cells (PBMCs) that is potentially suggestive of secondary CAR T-cell expansion, further testing and investigation involving collaboration with the patient's treating physician will occur. Available tumor and blood samples will be requested and evaluated for common hematologic mutations using next generation sequencing (NGS). If no preexisting (ie, before CAR T-cell infusion) cancer-associated hematologic mutations are identified by NGS, then vector integration site analysis is performed. Kite reviews all sample analysis results, which are then shared with the HCP. To date, no such results of RCR positivity or substantial CAR presence have occurred to warrant further testing of common mutations or vector integration sites.

The MAH has therefore standardized the way it is managing follow-up of secondary malignancy cases and sample request and collection. This process is also dependent on the willingness of treatment centers and treating HCPs to report these cases and contribute to the process of collecting samples and on the patients to consent to carry out further testing and procedures in relation with their secondary malignancy of T cell origin. The MAH is also proposing to update the PAC to involve the patient in the process for obtaining samples.

4.4. Outcome of reviews by other regulators

4.4.1. FDA

As discussed in the section 1.1 the FDA was the first regulator to initiate a review into the signal of secondary T-cell malignancy and CAR t cell therapies.

On the 19 January 2024 the FDA published a class label request for all FDA approved autologous CAR T cell products.

The labelling of all products was updated to the below:

"*1. Boxed Warning, Highlights Section of the Prescribing Information (PI)*

T cell malignancies have occurred following treatment with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including <XXXX>. (5.9)

2. Boxed Warning, Full Prescribing Information

T cell malignancies have occurred following treatment with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including <XXXX> [see WARNINGS AND PRECAUTIONS (5.9)].

3. WARNINGS AND PRECAUTIONS, Secondary Malignancies, Highlights Section of the PI

Secondary malignancies: T cell malignancies have occurred following treatment with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including <XXXX>. (5.9)

4. WARNINGS AND PRECAUTIONS, 5.9 Secondary Malignancies, Full Prescribing Information

T cell malignancies have occurred following treatment with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including <XXXX>. Mature T cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusion, and may include fatal outcomes. [See BOXED WARNING, ADVERSE REACTIONS (6.3), PATIENT COUNSELING INFORMATION (17).]

5. ADVERSE REACTIONS, 6.3 Postmarketing Experience

Because adverse events to marketed products are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to product exposure. The following adverse event has been identified during postmarketing use of <XXXX>.

Neoplasms: T cell malignancies

6. Section 17 PATIENT COUNSELING INFORMATION

Secondary Malignancies

Secondary malignancies, including T cell malignancies, have occurred [see BOXED WARNING, WARNINGS AND PRECAUTIONS (5.9), ADVERSE REACTIONS (6.3)]

7. MEDICATION GUIDE

<XXXX> can increase your risk of getting cancers including certain types of cancers of the immune system. Your provider should monitor you for this."

The wording for Tecartus varies slightly from the above, as no cases have been reported for this product.

Verdun and Marks, a perspective piece published in the NEJM, by two FDA employees stated "*At this time, we recommend that patients and clinical trial participants who receive treatment with these products be monitored for new cancers throughout their lives, since — owing to the relatively recent widespread introduction of CAR-T products into clinical care — we don't yet know how long after treatment people remain at risk for these adverse events*.".

The FDA review is currently ongoing.

Assessor's comment

Regarding the point from the FDA that patients should be monitored throughout their lives for new cancers, the assessor suggests this expectation is already cover by section 4.4 of the SmPC which states "*Patients should be monitored life-long for secondary malignancies*".

4.4.2. PRAC

The preliminary PRAC assessment report with the PRAC rapporteur proposed recommendations were available to the MHRA and are outlined below. At the time of this report the final assessment report and adoption of PRAC recommendations is still awaited and is anticipated on 11 April.

The recommendations were as follows:

1. A common update of the existing warning in section 4.4 of the SmPC to highlight that secondary malignancies of T cell origin have been reported with CAR-T products. The following wording is proposed for Abecma, Breyanzi, Carvykti and Yescarta:

[redacted]

2. Update of section 4.8 Undesirable effects, by including secondary malignancy of T-cell origin into the table of undesirable effect is proposed for Abecma, Breyanzi, Carvykti, Kymriah and Yescarta (SOC Neoplasm benign, malignant and unspecified (including cysts and polyps)).

[redacted]

3. Update the PIL in accordance with the SmPC updates as follows:

[redacted]

4. A common DHPC, with information on the increased risk for T-cell malignancies in line with the proposed update of the product information, and a summary of the background to this signal, should be sent to relevant HPCs. [redacted]
5. In Annex II D for all products, the HCP Education materials, should be updated to among the key messages, include the risk for T-cell malignancy; [redacted]
6. With respect to the RMP, secondary malignancy of T-cell origin should be added to the summary of safety concerns as an important identified risk. It requires both further characterization as well as additional RMMs, for all CAR T cell products.
7. Regarding follow up of secondary malignancies, particularly of T-cell origin, the following recommendations are considered applicable to all the CAR T cell products. The respective RMP should be updated accordingly:

- [redacted]

8. [redacted]
9. For all products, results from ongoing sample testing of any case of T-cell malignancy should be provided when available (at least time lines for this should be provided).

Assessor's comment

The assessor finds the PRACs recommendations to be reasonable given the current evidence and suggests that MHRA follow the same recommendations.

The wording proposed in the preliminary PRAC assessment is broadly acceptable. [redacted]

Final wording for the product information adopted at the PRAC April meeting will be provided to experts in due course.

Regarding point 5, the assessor highlights that Annex II D does not apply to GB licences, and the changes to the key messages in the educational materials should be completed in Annex 6 of the RMP instead.

4.4.3. Other regulators

[redacted]

Outcome of reviews by other regulators are not known.

5. CONCLUSIONS

The assessor suggests that there is not currently enough evidence to definitively state there is a causal relationship between the development of T-cell malignancies and CAR T cell therapy, however there is enough evidence for a reasonable suspicion of a causal relationship. The mechanism by which CAR T cell therapies lead to the development of T-cell malignancies is not currently fully understood.

Existing pharmacovigilance activities are in place to further characterise the risk of secondary malignancy, including post authorisation safety studies which follow up patients for 15 years.

The assessor is of the opinion that, given the seriousness of T-cell malignancies, the reasonable suspicion of a causal relationship warrants action to be taken to address this. The recommendations by PRAC seem appropriate to address this issue. MAHs should also have clear plans for follow up and sampling of cases of T-cell malignancy, as sample analysis will be vital in order to gather evidence to confirm a causal relationship of this signal.

Although not all of the products in the class saw reports of T-cell malignancy, the assessor suggests that it should be considered a class effect, however advice for expert committees will be sought regarding this point.

6. RECOMMENDATIONS

The recommendation proposed by PRAC are appropriate and should be followed in the UK. The actions are summarised below:

- Update section 4.4 and 4.8 of the SmPC with current information to explain that T-cell malignancies have been reported and include secondary malignancy of T cell origin as a possible side effect
- Update the PIL with current information. [redacted]
- A common DHPC should be distributed to highlight the risk and call for increased reporting and testing
- Update the RMP to add secondary malignancy of T cell origin as an important identified risk
- Update the key messages for the educational materials for healthcare professionals in Annex 6 of the RMP to reflect the safety concern
- Update the RMP with the proposed testing recommendations in the event of secondary malignancy
- MAHs to provide follow up information on individual case safety reports with further testing

7. ADVICE SOUGHT

1. Does the EAG/commission agree that, although not all products in the class had reports of T-cell malignancies, that the development of T-cell malignancies should be considered a class effect?
2. Does the EAG/commission agree with the recommendations outlined by the assessor? Are there any further actions that should be considered?

To Oncology and Haematology EAG only:

3. Is the EAG aware of any barriers in the healthcare system that may lead to difficulties in providing patient samples to MAHs for further analysis?

8. REFERENCES

Bishop, D.C., Clancy, L.E., Simms, R., Burgess, J., Mathew, G., Moezzi, L., Street, J.A., Sutrave, G., Atkins, E., McGuire, H.M., Gloss, B.S., Lee, K., Jiang, W., Maddock, K., McCaughan, G., Avdic, S., Antonenas, V., O'Brien, T.A., Shaw, P.J., Irving, D.O., Gottlieb, D.J., Blyth, E., Micklethwaite, K.P., 2021. Development of CAR T-cell lymphoma in 2 of 10 patients effectively treated with piggyBac-modified CD19 CAR T cells. Blood. https://doi.org/10.1182/blood.2021010813

Bushman, F.D., 2020. Retroviral Insertional Mutagenesis in Humans: Evidence for Four Genetic Mechanisms Promoting Expansion of Cell Clones. Molecular Therapy. https://doi.org/10.1016/j.ymthe.2019.12.009

Chihara, D., Dores, G.M., Flowers, C.R., Morton, L.M., 2021. The bidirectional increased risk of B-cell lymphoma and T-cell lymphoma. Blood 138. https://doi.org/10.1182/blood.2020010497

Dinnessen, M.A.W., Visser, O., Tonino, S.H., van der Poel, M.W.M., Blijlevens, N.M.A., Kersten, M.J., Lugtenburg, P.J., Dinmohamed, A.G., 2020. The impact of prior malignancies on the development of second malignancies and survival in follicular lymphoma: A population-based study. EJHaem 1. https://doi.org/10.1002/jha2.108

Ghimire, K.B., Shah, B.K., 2014. Second primary malignancies in adult acute lymphoblastic leukemia: A US population-based study. Blood. https://doi.org/10.1182/blood-2014-07-589911

Giri, S., Bhatt, V.R., Verma, V., Pathak, R., Bociek, R.G., Vose, J.M., Armitage, J.O., 2017. Risk of Second Primary Malignancies in Patients With Follicular Lymphoma: A United States Population-based Study, in: Clinical Lymphoma, Myeloma and Leukemia. https://doi.org/10.1016/j.clml.2017.06.028

Ishida, Y., Maeda, M., Urayama, K.Y., Kiyotani, C., Aoki, Y., Kato, Y., Goto, S., Sakaguchi, S., Sugita, K., Tokuyama, M., Nakadate, N., Ishii, E., Tsuchida, M., Ohara, A., 2014. Secondary cancers among children with acute lymphoblastic leukaemia treated by the Tokyo Children's Cancer Study Group protocols: A retrospective cohort study. Br J Haematol 164. https://doi.org/10.1111/bjh.12602

Jiang, S., Zhen, H., Jiang, H., 2020. Second primary malignancy in diffuse large B-cell lymphoma patients: A SEER database analysis. Curr Probl Cancer 44. https://doi.org/10.1016/j.currproblcancer.2019.100502

Jiménez-Ubieto, A., Grande, C., Caballero, D., Yáñez, L., Hernández-Garcia, M.T., Novelli, S., Arranz, R., Ferreiro, J.J., Bobillo, S., Mercadal, S., Galeo, A., Jiménez, J.L., Moraleda, J.M., Vallejo, C., Albo, C., Pérez, E., Marrero, C., Magnano, L., Palomera, L., Jarque, I., Martínez-Sánchez, P., Martín, A., Coria, E., López-Guillermo, A., Salar, A., Lahuerta, J.J., 2018. Secondary malignancies and survival outcomes after autologous stem cell transplantation for follicular lymphoma in the pre-rituximab and rituximab eras: A long-term follow-up analysis from the Spanish GELTAMO registry. Bone Marrow Transplant. https://doi.org/10.1038/s41409-018-0096-6

Luminari, S., Cesaretti, M., Rashid, I., Mammi, C., Montanini, A., Barbolini, E., Bellei, M., Pennese, E., Sirotti, M.A., Marcheselli, L., Partesotti, G., Bari, A., Maiorana, A., Bonacorsi, G., Federico, M., 2007. Incidence, clinical characteristics and survival of malignant lymphomas: A population-based study from a cancer registry in northern Italy. Hematol Oncol 25. https://doi.org/10.1002/hon.826

Mangone, L., Penna, D., Marinelli, F., Roncaglia, F., Bisceglia, I., Merli, F., Ruffini, A., Gamberi, B., Tieghi, A., Valli, R., Albertazzi, L., Iori, M., Giorgi Rossi, P., Vener, C., Morabito, F., Neri, A., Luminari, S., 2023. Incidence, mortality, and survival of hematological malignancies in Northern Italian patients: an update to 2020. Front Oncol 13. https://doi.org/10.3389/fonc.2023.1182971

Micklethwaite, K.P., Gowrishankar, K., Gloss, B.S., Li, Z., Street, J.A., Moezzi, L., Mach, M.A., Sutrave, G., Clancy, L.E., Bishop, D.C., Louie, R.H.Y., Cai, C., Foox, J., MacKay, M., Sedlazeck, F.J., Blombery, P., Mason, C.E., Luciani, F., Gottlieb, D.J., Blyth, E., 2021. Investigation of product-derived lymphoma following infusion of piggyBac-modified CD19 chimeric antigen receptor T cells. Blood 138. https://doi.org/10.1182/blood.2021010858

Neeman, Y., Perry, C., Silverman, B., Waintraub, N., Avivi, I., 2020. Rituximab is not associated with increased risk of second primary malignancies in Israeli patients with diffuse large B cell lymphoma treated with RCHOP regimen. Leuk Lymphoma 61. https://doi.org/10.1080/10428194.2020.1779257

Ortíz-Maldonado, V., Rives, S., Castellà, M., Alonso-Saladrigues, A., Benítez-Ribas, D., Caballero-Baños, M., Baumann, T., Cid, J., Garcia-Rey, E., Llanos, C., Torrebadell, M., Villamor, N., Giné, E., Díaz-Beyá, M., Guardia, L., Montoro, M., Català, A., Faura, A., González, E.A., Español-Rego, M., Klein-González, N., Alsina, L., Castro, P., Jordan, I., Fernández, S., Ramos, F., Suñé, G., Perpiñá, U., Canals, J.M., Lozano, M., Trias, E., Scalise, A., Varea, S., Sáez-Peñataro, J., Torres, F., Calvo, G., Esteve, J., Urbano-Ispizua, Á., Juan, M., Delgado, J., 2021. CART19-BE-01: A Multicenter Trial of ARI-0001 Cell Therapy in Patients with CD19+ Relapsed/Refractory Malignancies. Molecular Therapy 29. https://doi.org/10.1016/j.ymthe.2020.09.027

Safarzadeh Kozani, Pouya, Safarzadeh Kozani, Pooria, Rahbarizadeh, F., 2021. CAR-T cell therapy in T-cell malignancies: Is success a low-hanging fruit? Stem Cell Res Ther. https://doi.org/10.1186/s13287-021-02595-0

Schmiegelow, K., Levinsen, M.F., Attarbaschi, A., Baruchel, A., Devidas, M., Escherich, G., Gibson, B., Heydrich, C., Horibe, K., Ishida, Y., Liang, D.C., Locatelli, F., Michel, G., Pieters, R., Piette, C., Pui, C.H., Raimondi, S., Silverman, L., Stanulla, M., Stark, B., Winick, N., Valsecchi, M.G., 2013. Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. Journal of Clinical Oncology 31. https://doi.org/10.1200/JCO.2012.47.0500

Song, J.Y., Herrera, A.F., 2019. CAR T cells mimicking an aggressive lymphoma. Blood. https://doi.org/10.1182/BLOOD-2019-01-896753

Steffin, D.H.M., Muhsen, I.N., Hill, L.Q.C., Ramos, C.A., Ahmed, N., Hegde, M., Wang, T., Wu, M., Gottschalk, S., Whittle, S.B., Lulla, P.D., Mamonkin, M., Omer, B., Rouce, R.H., Heczey, A., Metelitsa, L.S., Grilley, B.J., Robertson, C., Torrano, V., Lapteva, N., Gee, A.P., Rooney, C.M., Brenner, M.K., Heslop, H.E., 2022. Long-term follow-up for the development of subsequent malignancies in patients treated with genetically modified IECs. Blood 140. https://doi.org/10.1182/blood.2022015728

Stiller, C.A., Bunch, K.J., Bayne, A.M., Stevens, M.C.G., Murphy, M.F.G., 2023. Subsequent cancers within 5 years from initial diagnosis of childhood cancer. Patterns and risks in the population of Great Britain. Pediatr Blood Cancer 70. https://doi.org/10.1002/pbc.30258

Turcotte, L.M., Liu, Q., Yasui, Y., Arnold, M.A., Hammond, S., Howell, R.M., Smith, S.A., Weathers, R.E., Henderson, T.O., Gibson, T.M., Leisenring, W., Armstrong, G.T., Robison, L.L., Neglia, J.P., 2017. Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970-2015. JAMA - Journal of the American Medical Association. https://doi.org/10.1001/jama.2017.0693

Zheng, G., Chattopadhyay, S., Sud, A., Sundquist, K., Sundquist, J., Försti, A., Houlston, R., Hemminki, A., Hemminki, K., 2019. Second primary cancers in patients with acute lymphoblastic, chronic lymphocytic and hairy cell leukaemia. Br J Haematol 185. https://doi.org/10.1111/bjh.15777

ANNEX 1 – PRAC QUESTIONS TO MAHs

This assessment report used data provided by the MAHs for each product in the class, based on their response to question sent to them as part of the PRAC assessment of this signal. The question the MAHs received are outlined below.

QUESTION 1

Specifically, for each CAR-T cell product, the responsible MAH should provide the following:

a) Cumulative exposure, broken down by region, and EU member state

b) A tabulated summary of cases of T-cell malignancy from clinical studies, any observational study or registry source, as well as spontaneously reported cases from all relevant sources. This should include causality assessment for each reported case. Please use the attached template for case presentation of T-cell malignancies. The completed Excel file should be submitted in Excel formal (file extension .xlsx). The headings in the Excel file should not be adjusted, no extra columns should be added.

Full case presentations/narratives should be appended.

c) Information on background occurrence of T-cell lymphoma / leukemia / lymphoproliferative disorder; preferably stratified by indications for which the CAR T-cell product is authorised.

d) An overall discussion on causality taking possible mechanisms into account, including risk for insertional mutagenesis and/or other mechanisms. This should include a literature review. Relevant non-clinical data should be commented, also covering potential process related risks.

QUESTION 2

Based on that, the need for the following should be addressed:

a) Updates to the product information, and if appropriate a proposal for wording for the SmPC and PIL

b) Other measures such as a DHPC

c) Updates of the RMP, and/or educational material

d) The MAHs are specifically asked to:

(i) present current practices if receiving a case report of a secondary malignancy,

(ii) provide a justification for all cases in which no adequate tumour samples were tested for transgene presence,

(iii) discuss and propose further actions to improve the follow-up of cases of secondary malignancies particularly those of T-cell origin; this includes but is not limited to tumour sample collection, pathology work-up and transgene analyses in a comprehensive and standardised manner.