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Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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To:	Karin Knudson, PhD Chair, Review Committee Cell Therapy Branch 2 (CTB2), Div of Cell Therapy 1 (DCT1) Office of Cellular Therapy and Human Tissue CMC (OCTHT) Office of Therapeutic Products (OTP)
Through:	Christopher Jason, MD Branch Chief, PB2 DPV, OBPV Meghna Alimchandani, MD Deputy Director DPV, OBPV
Subject:	Review of Pharmacovigilance Plan
Applicant:	Iovance Biotherapeutics, Inc.
Product:	AMTAGVI (lifileucel)
STN Number:	125773/0
Proposed Indication:	*Treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor*[1].
Submission Date:	BLA: March 27, 2023
Action Due Date:	February 23, 2024

[1] Except for Reviewer's Comments and subheadings, italicized statements in this memorandum indicate language quoted directly from Applicant materials. Acronyms: PD-1: programmed cell death protein-1; BRAF: proto-oncogene B-Raf; MEK: mitogen-activated extracellular signal-regulated kinase.

1 Objective and Scope

The purpose of this review is to assess the Applicant's proposed pharmacovigilance plan (PVP) for lifileucel (AMTAGVI) received March 27, 2023, submitted under BLA 125773/0/2. The BLA proposes a single course regimen to treat unresectable or metastatic melanoma which failed specific prior treatments. The regimen includes nonmyeloablative lymphodepletion (NMA-LD) followed by lifileucel (LN-144) and then up to six doses of aldesleukin (IL-2). This review provides recommendations for post-authorization safety monitoring for the use of lifileucel, should this product be approved.

2 Product Information[2]

2.1 Product Description

AMTAGVI (lifileucel) is a tumor-derived autologous T cell immunotherapy [autologous tumor infiltrating lymphocytes(TIL); LN-144] is a preparation of autologous, non-genetically modified tumor-derived autologous T cell immunotherapy that is in development for the immunotherapy of melanoma and other solid tumors. The product is an Advanced Therapy Medicinal Product (ATMP) that is classified as an autologous somatic cell therapy. Lifileucel is composed primarily of (b) (4) *lymphocytes obtained from resected tumor material and expanded ex vivo in the presence of the cytokine interleukin-2 (IL-2), anti-CD3 (OKT3) antibody, and* (b) (4) *feeder cells. The final product is a cryopreserved suspension of* (b) (4) *autologous TIL that is formulated for intravenous infusion.*

2.2 Proposed Indication and Dosing Regimen

AMTAGVI(lifileucel) is a tumor-derived autologous T cell immunotherapy indicated for the treatment of adult patients with unresectable or metastatic melanoma previously treated with a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor. AMTAGVI is provided as a single dose for infusion containing a suspension of tumor-derived T cells. The dose is supplied in (b) (4) to 4 patient specific IV infusion bags in individual protective metal cassettes. Each dose contains (b) (4) viable cells.

The lifileucel regimen consists of:

1) Nonmyeloablative lymphodepletion (NMA-LD) (cyclophosphamide 60 mg/kg intravenously [IV] with mesna daily for 2 days then fludarabine 25 mg/m^2 IV daily for 5 days). (The use of NMA-LD is intended to eliminate suppressive influences and provide an optimal environment to support expansion, engraftment, and antitumor cytotoxicity of the transferred TIL.)
2) Lifileucel (LN-144) infusion as soon as possible after 24 hours (but no more than 4 days) have elapsed following the last dose of fludarabine.
3) At 3 to 24 hours after lifileucel infusion, begin IL-2 infusion at 600,000 IU/kg every 8 to 12 hours up to a maximum of 6 doses to support cell expansion in

[2] This information is based on recent draft labeling. See the final approved U.S. Prescribing Information (USPI) for approved indications and dosing and product description.

vivo. (The IL-2 infusion increases the therapeutic potency of the TIL.)

The Applicant indicated the NMA-LD and IL-2 components of the regimen are based on a regimen developed and tested by the (b) (4)

3 Background

Melanoma makes up 5% of all new cancer cases in the U.S. and is responsible for 1.3% of all cancer deaths [1]. Although there have been recent advances in treatment and the overall 5-year relative survival is 93.5%, the 5-year relative survival with distant metastasis is only 35.1% [1]. The Applicant summarized current therapies for metastatic disease as including immune checkpoint inhibitors (ICI) (cytotoxic T lymphocyte antigen-4 [CTLA-4], programmed cell death protein-1 (PD-1), and programmed death-ligand 1 [PD-L1] blocking antibodies), targeted therapies (including BRAF and MEK inhibitors), and other therapies (such as fixed-dose combination of nivolumab/relatlimab (PD-1 blocking antibody/lymphocyte activation gene-3 [LAG-3] blocking antibody). They also cited several publications indicating patients often do not achieve long-term benefit from these therapies and have limited options.

One example is the phase II LEAP-004 study which evaluated the combination of the multikinase inhibitor lenvatinib and the PD-1 inhibitor pembrolizumab in patients with melanoma that progressed on inhibitors of programmed cell death protein-1 (PD-1) or its ligand (PD-L1) given alone or with other therapies [2]. The phase I/IIa, open-label RELATIVITY-020 trial part D assessed efficacy and safety of the PD-1 inhibitor nivolumab and lymphocyte activation gene-3 (LAG-3) blocking antibody relatlimab in advanced melanoma with progression during, or within 3 months of treatment with one or more anti–PD-(L)1-containing regimens [3]. A summary of results of these studies demonstrating the limitations is shown in Table 1.

Table 1: Results of recent trials of therapy following advanced melanoma with progression after use of PD-1/PD-L1 inhibitors.

TRIAL	N (subjects)	ORR	Median PFS (months)	Median OS (months)	TRAEs Grade 3-5
LEAP-004	103	21.4%	4.2	14.0	45.6%
RELATIVITY-020	518	9.2 to 12%	2.1 to 3.2	14.7 to 17.1	12.8 to 15%

ORR=objective response rate; PFS=progression free survival; OS=overall survival; TRAEs=treatment related adverse events

Mechanism of Action

Tumor Infiltrating Lymphocytes (TIL) include cytotoxic and helper T cells and other immune cells that infiltrate tumors as part of a patient's immune response to cancer [4-6]. In Adoptive Cell Therapy (ACT), TIL are recovered from a patient's tumor, expanded ex vivo, and then re-infused to migrate to and target tumor-specific neoantigens (mutated antigens) [7, 8]. The interaction with neoantigens triggers a series of events mediating tumor cell lysis [9-11].

The Applicant summarized the advantages of adoptive cell therapy (ACT) with TIL compared to other current therapies as including: 1) a well characterized and manageable safety profile; 2) clinical benefit with durable tumor responses after only a single treatment regimen in even highly pretreated patients; and 3) recognition of neoantigens derived from mutated genes expressed in tumors cells, thereby endowing TIL therapy with a unique tumor specificity unmatched by other current T-cell therapies.

Reviewer Comment: The Applicant refers to the product as TIL and the class is referred to as TIL in the literature, however per FDA Chemistry Manufacturing and Controls (CMC) review, the Established Pharmacologic Class (EPC) will be referred to as "tumor derived autologous T cell immunotherapy". Please refer to the CMC review memo for further discussion. Note that for purposes of this review memorandum, "TIL" may be used interchangeably with "tumor derived autologous T cell immunotherapy."

4 Clinical Studies

4.1 Overview

The primary study in support of the application is Study C-144-01, an ongoing Phase 2, prospective, interventional, multicenter study evaluating the efficacy and safety of treatment with lifileucel (LN-144) (i.e., adoptive cell therapy [ACT] with autologous TIL). The study enrolled adult patients with unresectable or metastatic melanoma who were previously treated with, and progressed on, at least 1 systemic therapy, including a programmed cell death protein-1 (PD-1) blocking antibody and, if proto-oncogene B-Raf (BRAF) V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor with a mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor.

Clinical studies providing safety data for the application are summarized in Table 2. Primary safety data is from Study C-144-01 (lifileucel treatment of advanced melanoma) for Cohorts 2 and 4 (data cutoff date of 15 Sep 2021). Additional supporting safety data from studies of LN-145 used in treating other cancers (data cutoff date: 30 Jun 2022) was provided for:

- Cervical cancer: Study C-145-04 Cohorts 1, 2, and 4
- Non-small cell lung cancer (NSCLC):
  - Study IOV-LUN-202 Cohorts 1 and 2
  - Study IOV-COM-202 Cohort 3B
- Head-and-neck squamous cell carcinoma (HNSCC): Study C-145-03 Cohort 2

Table 2: Clinical Studies

Study Number	**Study Design**	**Dose Regimen**	**No. of Patients**	**Population**
Primary Study				
C-144-01 US and Europe	Phase 2 prospective, interventional, multicenter efficacy/ safety	1) NMA-LD 2) TIL (lifileucel TN-144) 3) IL-2	Pooled Cohorts 2 and 4: Safety Population: N=160 Safety Analysis Set: N=156	Melanoma 53.8% male 46.2% female Median age: 56.0 years (20 to 79) Race: 95.5% White
Additional Supportive Safety Data				
C-145-03	Phase 2, prospective, interventional, multicenter	1) NMA-LD 2) TIL (TN-145) 3) IL-2	Cohort 2: Safety Population: N=18 Safety Analysis Set: N=17	Head-and-neck squamous cell carcinoma (HNSCC)
C-145-04	Phase 2, prospective, interventional, multicenter	1) NMA-LD 2) TIL (TN-145) 3) IL-2	Cohorts 1, 2, and 4: Safety Population: N=106 Safety Analysis Set: N=101	Cervical cancer
IOV-COM-202	Phase 2, prospective, interventional, multicenter	1) NMA-LD 2) TIL (TN-145) 3) IL-2	Cohort 3B: Safety Population: N=29 Safety Analysis Set: N=28	Non-small cell lung cancer (NSCLC)

IOV-LUN-202	Phase 2, prospective, interventional, multicenter	1) NMA-LD 2) TIL (TN-145) 3) IL-2	Cohorts 1 and 2: Safety Population: N=11 Safety Analysis Set: N=11	Non-small cell lung cancer (NSCLC)

Adapted from Tables 1 and 2, module 2.7.4 (STN125773/0.1)

4.2 Phase 2 Study C-144-01

The Applicant evaluated the efficacy and safety of lifileucel with this Phase 2, prospective, interventional, multicenter efficacy/safety study for the treatment of adult subjects with advanced melanoma that had progressed on prior therapies as noted above. The Applicant anticipated that toxicities or AEs observed during TIL immunotherapy would be primarily attributed to the NMA-LD preparative regimen or the IL-2 administration following TIL infusion based on a prior study using a similar regimen [12]. The primary, secondary, and exploratory objectives and endpoints are listed in Table 3.

Table 3: Primary and Secondary Efficacy/Safety Objectives/Endpoints for C-144-01

Primary	**Objectives**	**Endpoints**
Efficacy	Evaluate the efficacy of lifileucel in patients with unresectable or metastatic melanoma using the objective response rate (ORR), as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.	ORR
Secondary	**Objectives**	**Endpoints**
Efficacy	Evaluate the efficacy endpoints of duration of response (DOR), disease control rate (DCR), and PFS, as assessed by the IRC per RECIST v1.1	DOR, DCR, PFS
Efficacy	Further evaluate efficacy of lifileucel in patients with unresectable or metastatic melanoma by assessing ORR, DOR, DCR, and PFS, as assessed by the Investigator per RECIST v1.1	ORR, DOR, DCR, PFS
Efficacy	Evaluate overall survival (OS)	OS
Safety	Characterize the safety profile of lifileucel in patients with	Incidence, severity, seriousness, relationship to study treatment, and

	unresectable or metastatic melanoma	characteristics of treatment-emergent adverse events (TEAEs), including adverse events (AEs) leading to early discontinuation from treatment or withdrawal from the Assessment Period, and AEs resulting in deaths.
Exploratory	**Objectives**	**Endpoints**
Efficacy/Safety	Explore the persistence of lifileucel and potential immune correlates of response, outcome, and toxicity of the treatment	T-cell receptor (TCR) data and other biomarkers
Efficacy	Explore efficacy based on immune-related RECIST criteria (irRECIST), as assessed by the Investigator	Tumor responses (ORR, DOR, DCR, PFS)
Efficacy	Assess health-related quality of life (HRQoL)	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)

4.2.1 C-144-01 Study Design

Study C-144-01 consists of 4 cohorts. Cohort 1 included patients administered non-cryopreserved lifileucel product which is no longer in clinical use. Cohorts 2 and 4 received cryopreserved product. Cohort 3 patients were previously treated in Cohort 1, Cohort 2, or Cohort 4, had progressive disease (PD), and opted to be rescreened and retreated with the lifileucel regimen, using cryopreserved lifileucel product. The Applicant noted the study was designed without a control group because the heavily pretreated patient population has no alternative therapy options expected to have a meaningful benefit. In addition, they contend that any major tumor regression is presumed attributable to the investigational treatment regimen given the advanced, refractory disease.

The null hypothesis for the study was that the primary efficacy endpoint for Cohort 4 of the study (ORR as assessed by the IRC per RECIST v1.1) was less than or equal to 10%. If the null hypothesis for Cohort 4 was rejected, a second hypothesis testing for the primary efficacy endpoint was performed on pooled data from Cohorts 2 and 4.

The study flow is as follows:

- **Screening**: Determine if patient meets inclusion/exclusion criteria within 28 days of completing informed consent form (ICF).
- **Enrollment**: Tumor resection (Manufacturing of TIL product: 22 days)
- **Baseline period**: Day -21 to Day -10
- **Treatment period**:
    - NMA-LD: Day -7 to Day -1

    - Lifileucel infusion: Day 0
    - IL-2 therapy: Day 0 up to Day 4
    - Through Day 28
- **Assessment Period**:
    - Every 6 weeks for 6 months
    - Every 3 months (6 months to 5 years)
    - End of Assessment (EOA): disease progression or start of a new anti-cancer therapy
- **Overall Survival (OS) follow-up period**:
    - Post EOA every 3 months up to 5 years (from enrollment)

Populations For Analysis

Three analysis sets were defined. The Full Analysis Set (FAS) was primary for analysis of efficacy based on patients who received lifileucel that met manufacturing specifications. The Safety Analysis Set was primary for analysis of safety and is based on patients who received any lifileucel infusion. Statistical analyses of efficacy and safety data were performed for Cohort 4, Cohort 2, Pooled Cohorts 2 and 4, and Cohort 1. The Applicant noted that pooled data allow a safety assessment in a larger pool of patients, provide greater confidence around the point estimate of the ORR, and provide a longer duration of follow up for the DOR. The Tumor Harvested (TH) Set (also referred to as Enrolled Set) is defined as the patients who had tumor resected for production of lifileucel whether they received lifileucel or not. There were 189 patients in the TH Set. Analysis of AEs and serious AEs (SAEs) were conducted on this set as well. The Safety Population was defined as patients who received any component of the TIL regimen (i.e., cyclophosphamide, fludarabine, TIL, or IL-2). There were 160 patients in the Safety Population and 156 of those received lifileucel to become part of the Safety Analysis Set.

Safety Assessments

Safety and tolerability are secondary endpoints assessed by AEs, clinical laboratory tests, physical examinations, and vital signs (including pulse oximetry during IL-2 administration) from Enrollment through the Assessment Periods.

Adverse Events

All AEs were collected during the Screening, Enrollment, and Treatment Periods. Only Grade 3/4 AEs and SAEs related to any study drug were reported from Day 30 through 6 months post-lifileucel infusion (or start of a new anti-cancer therapy). Only SAEs related to lifileucel were collected and reported after 6 months. Medically significant AEs considered related to lifileucel were reported and followed until resolved or resolved with sequelae. Safety events were recorded and graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Reviewer Comment: *The Phase 2 study design, safety objectives, endpoints, and assessment plan are acceptable.*

5 Summary of Applicant's Safety Database

OBPV defers to the product office on final review of the clinical safety database, which will inform the final language in the USPI. Below is our focused review of the Applicant data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125773/0 be approved. Please refer to the package insert for the final clinical safety data.

5.1 Adverse Events (AEs) from Phase 2 study (C-144-01).

5.1.1 Demographics and Other Characteristics of the Study Population

The Summary of Clinical Safety primarily presents data from the Safety Analysis Set which includes all patients who received any lifileucel infusion in the pooled Cohort 2 (n=67) and Cohort 4 (n=89).

Table 4: Safety Analysis Set Baseline Characteristics (Pooled: Cohort 2 and 4)

Characteristic	(N=156)
Median Age (years), (minimum, maximum)	56 (Min: 20, Max: 79)
Male/Female n (%)	84 (53.8%) / 72 (46.2%)
Race: White n (%)	149 (95.5%)
Patients who received full dose of lifileucel n (%)	145 (92.9%)

Adapted from Table 14.1.5.2.2 in module 5.3.5.2 (STN125773/0)

5.1.2 Adverse Event Analyses

Analyses of AEs were performed for the following study periods:

- Tumor Harvested (TH) Period: From tumor harvest up to start of NMA-LD or 30 days after tumor harvest if NMA-LD not received.
- NMA-LD Period: From start of NMA-LD to start of lifileucel infusion.
- Treatment-emergent Period: From start of lifileucel infusion (Day 0) up to 30 days after lifileucel infusion.
- Post-treatment-emergent Period: From 30 days after lifileucel infusion (Day 0) up to 6 months after lifileucel infusion (or start of new anticancer therapy)

This review will focus primarily on the safety analysis set. The Applicant noted that due to the uncontrolled, single-arm study design and multidrug treatment regimen, it was difficult to attribute specific treatment-emergent AEs (TEAEs) to lifileucel.

5.1.2.1 Treatment-Emergent AEs (TEAEs)

A summary of TEAEs is shown in Table 5. All 156 patients who received at least one dose of lifileucel experienced at least one TEAE, and most experienced at least one Grade 3/4 TEAE. The Applicant determined that 119 patients experienced at least one TEAE related (possibly, probably, and definitely) to lifileucel, and 57 patients had at least 1 TEAE related only to lifileucel. Of 54 patients with treatment-emergent SAEs, the Applicant determined 8 patients had at least 1 SAE related to lifileucel, and 4 patients had at least 1 SAE related only to lifileucel.

The incidence of AEs in Pooled Cohorts 2 and 4 peaked around the 3rd and 4th day of the NMA-LD regimen and gradually decreased until a second peak occurred following administration of IL-2 (the day after lifileucel infusion). The occurrence of TEAEs of all grades decreased rapidly over the two weeks following lifileucel infusion.

Table 5: Summary of TEAEs (Pooled Cohorts 2 and 4 Safety Analysis Set, N=156)

Number of patients with at least one of the following events	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
For the Safety Analysis Set TEAE	156 (100)	148 (94.9)	4 (2.6)
TEAE related to lifileucel	119 (76.3)	60 (38.5)	1 (0.6)
TEAE related to lifileucel only*	57 (36.5)	8 (5.1)	0
TEAE leading to lifileucel discontinuation	2 (1.3)	2 (1.3)	0
Post-Treatment-Emergent AE	97 (62.2)	37 (23.7)	6 (3.8)
Treatment-Emergent SAE	54 (34.6)	48	4 (
Treatment-Emergent SAE related to lifileucel	8 (5.1)	6 (3.8)	1 (0.6)
Treatment-Emergent SAE related to lifileucel only*	4 (2.6)	2 (1.3)	0
Post-Treatment-Emergent SAE	29 (18.6)	20 (12.8)	6 (3.8)

Adapted from Tables 21 and 14.3.2.1.2.2.1_R1 in module 5.3.5.2 (STN125773/0).
TEAEs include AEs that started from the lifileucel infusion to 30 days post lifileucel infusion. Post-Treatment-Emergent AEs refer to AEs that started 30 days post lifileucel infusion through 6 months after the lifileucel infusion or up to the start of a new anti-cancer therapy, whichever occurred first.
* Related to lifileucel only and not related to other components of the treatment regimen (i.e., cyclophosphamide, fludarabine, or IL-2).

Most Common TEAEs

TEAEs reported with an incidence greater than or equal to 20% in the pooled Cohorts 2 and 4 are shown in Table 6. Except for hypokalemia and hypophosphatemia, all the AEs listed are labeled adverse reactions or AEs observed in postmarketing experience with one or both NMA-LD agents (fludarabine, cyclophosphamide) and/or IL-2. Hypokalemia may result from vomiting and diarrhea [13] which are labeled adverse reactions for fludarabine, cyclophosphamide, and IL-2. Hypophosphatemia is common in cancer patients due to a number of factors [14] and one publication indicated potassium, calcium, magnesium and phosphorus levels commonly decrease with IL-2 infusion [15]. In addition, a 2014 guideline on best management practices noted a variety of electrolyte abnormalities may be observed with use of high dose IL-2 including hypomagnesemia, hypocalcemia, hypokalemia, hypophosphatemia, and hyponatremia [16].

Grade 3 or Higher TEAEs (Pooled Cohorts 2 and 4)

Most patients (94.9%) in pooled cohorts 2 and 4 experienced at least 1 grade 3 or 4 TEAE, and 4 patients died due to a TEAE. Table 6 shows TEAEs of any grade with an incidence greater than or equal to 20% along with all grade 3/4 TEAEs with an incidence of 10% or greater for pooled cohorts 2 and 4. There were no Grade 5 events reported with an incidence greater than 10%.

Table 6: TEAEs Reported at an Incidence of ≥ 20% Presented by SOC, PT, and Grade: Pooled Cohorts 2 and 4, Safety Analysis Set (N=156)

System Organ Class (SOC) Preferred Term (PT)	Any Grade n (%)	Grade 3/4 n (%)
Blood and lymphatic system disorders		
Thrombocytopenia	129 (82.7)	120 (76.9)
Anaemia	97 (62.2)	78 (50.0)
Neutropenia	66 (42.3)	45 (28.8)
Febrile neutropenia	65 (41.7)	65 (41.7)
Leukopenia	54 (34.6)	42 (26.9)
Lymphopenia	49 (31.4)	38 (24.4)
Cardiac disorders		
Tachycardia	45 (28.8)	4 (2.6)
Gastrointestinal disorders		
Diarrhoea	48 (30.8)	2 (1.3)
Nausea	36 (23.1)	3 (1.9)
Vomiting	33 (21.2)	1 (0.6)
General disorders and administration site conditions		
Chills	117 (75.0)	8 (5.1)
Pyrexia	81 (51.9)	17 (10.9)
Fatigue	51 (32.7)	6 (3.8)
Oedema peripheral	32 (20.5)	2 (1.3)
Investigations		
Aspartate aminotransferase increased	33 (21.2)	4 (2.6)
Alanine aminotransferase increased	28 (17.9)	5 (3.2)
Weight increased	26 (16.7)	2 (1.3)
Blood alkaline phosphatase increased	23 (14.7)	4 (2.6)
Metabolism and nutrition disorders		
Hypophosphataemia	58 (37.2)	41 (26.3)
Hypokalaemia	43 (27.6)	6 (3.8)
Hypomagnesaemia	31 (19.9)	0
Decreased appetite	30 (19.2)	3 (1.9)
Hypocalcaemia	29 (18.6)	6 (3.8)
Hypoalbuminaemia	28 (17.9)	4 (2.6)
Respiratory, thoracic, and mediastinal disorders		
Hypoxia	35 (22.4)	19 (12.2)
Dyspnoea	31 (19.9)	7 (4.5)

Skin and subcutaneous tissue disorders		
Rash	40 (25.6)	6 (3.8)
Alopecia	38 (24.4)	0
Rash maculo-papular	24 (15.4)	10 (6.4)
Vascular disorders		
Hypotension	52 (33.3)	17 (10.9)

Adapted from Tables 22 and 24 in module 5.3.5.2 (STN125773/0).

Reviewer Comment: *All of these are known AEs associated with either a component of the NMA-LD and/or IL-2 components of the treatment regimen.*

Table 7 shows the number of patients with AEs assessed by the investigator as related to lifileucel ONLY. The Applicant assessed AEs in the cardiac and vascular categories could be related to infusion reactions from the TIL or related to IL-2 administration.

Table 7: TEAEs Related to LN-144 Only

Grouped Term Preferred Term	Any Grade n (%)	Grade 3 n (%)
Number of Patients Reporting at least one TEAE Related to LN-144 only within Grouped Terms by Maximum Grade	7 (4.5)	1 (0.6)
Cardiac arrhythmia terms [1]	4 (2.6)	1 (0.6)
Sinus tachycardia	2 (1.3)	1 (0.6)
Tachycardia	2 (1.3)	0
Vascular hypotensive disorders [2]	3 (1.9)	0
Hypotension	3 (1.9)	0
Immune-mediated/autoimmune disorders [3]	2 (1.3)	0
Vitiligo	2 (1.3)	0

Adapted from Table 2.7.4.2.1_R1 (STN125773/0)
[1] MedDRA 24.0 SMQ of Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias) and Preferred terms of Bradycardia and Tachycardia.
[2] MedDRA 24.0 HLT of Vascular hypotensive disorders.
[3] Narrow MedDRA 24.0 SMQ of Immune-mediated/autoimmune disorders.

Treatment Emergent Serious AEs (SAEs)

Treatment Emergent SAEs by Preferred Term are shown in Table 8. Seven SAEs were assessed by the investigator as related to both lifileucel and at least one other component(s) of the treatment regimen. Three SAEs were assessed as related to lifileucel ONLY. The two premature discontinuations of lifileucel infusions were due to anaphylactic reactions.

Table 8: Treatment Emergent SAEs by Preferred Term: Pooled Cohorts 2 and 4 (Safety Analysis Set)

	Pooled Cohorts 2 and 4 (N=156)			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Number of patients reporting at least one Treatment-Emergent SAE by Maximum Grade	54 (34.6)	24 (15.4)	24 (15.4)	4 (2.6)
Febrile neutropenia	8 (5.1)	8 (5.1)	0	0
Thrombocytopenia [1]	7 (4.5)	0	7 (4.5)	0
Acute kidney injury	4 (2.6)	1 (0.6)	0	0
Pneumonia	4 (2.6)	3 (1.9)	0	1 (0.6)
Acute respiratory failure	3 (1.9)	0	2 (1.3)	1 (0.6)
Hypotension	3 (1.9)	3 (1.9)	0	0
Hypoxia	3 (1.9)	2 (1.3)	1 (0.6)	0
Neutropenia [2]	3 (1.9)	0	3 (1.9)	0
Pulmonary oedema	3 (1.9)	2 (1.3)	1 (0.6)	0
Pyrexia [3]	3 (1.9)	2 (1.3)	0	0
Anaphylactic reaction [4]	2 (1.3)	1 (0.6)	1 (0.6)	0
Aspartate aminotransferase increased [3]	2 (1.3)	0	1 (0.6)	0
Capillary leak syndrome	2 (1.3)	1 (0.6)	0	0
Delirium	2 (1.3)	1 (0.6)	0	0
Dyspnoea	2 (1.3)	1 (0.6)	1 (0.6)	0
Encephalopathy	2 (1.3)	1 (0.6)	1 (0.6)	0
Pleural effusion	2 (1.3)	2 (1.3)	0	0
Sepsis[3]	2 (1.3)	0	2 (1.3)	0
Tumour pain	2 (1.3)	2 (1.3)	0	0
Acidosis	1 (0.6)	1 (0.6)	0	0
Acute myocardial infarction	1 (0.6)	0	1 (0.6)	0
Alanine aminotransferase increased [3]	1 (0.6)	1 (0.6)	0	0
Anaemia	1 (0.6)	1 (0.6)	0	0
Anxiety	1 (0.6)	1 (0.6)	0	0
Arrhythmia	1 (0.6)	0	0	1 (0.6)
Ascites	1 (0.6)	1 (0.6)	0	0
Atrial fibrillation	1 (0.6)	1 (0.6)	0	0
Brain oedema [3]	1 (0.6)	1 (0.6)	0	0
Cerebrovascular accident	1 (0.6)	0	1 (0.6)	0
Chills [3]	1 (0.6)	1 (0.6)	0	0
Colitis	1 (0.6)	0	0	0
Decreased appetite	1 (0.6)	1 (0.6)	0	0
Depressed level of consciousness	1 (0.6)	1 (0.6)	0	0

Depression	1 (0.6)	1 (0.6)	0	0
Device related infection	1 (0.6)	1 (0.6)	0	0
Embolism	1 (0.6)	0	0	0
Encephalitis	1 (0.6)	1 (0.6)	0	0
Fatigue	1 (0.6)	1 (0.6)	0	0
Haematochezia	1 (0.6)	1 (0.6)	0	0
Hypophosphataemia	1 (0.6)	0	1 (0.6)	0
Infection [4,5]	1 (0.6)	0	0	0
Infusion related reaction	1 (0.6)	0	1 (0.6)	0
Intra-abdominal haemorrhage [3]	1 (0.6)	0	0	1 (0.6)
Melaena	1 (0.6)	1 (0.6)	0	0
Neuropathy peripheral	1 (0.6)	1 (0.6)	0	0
Neutropenic sepsis	1 (0.6)	0	1 (0.6)	0
Oliguria	1 (0.6)	1 (0.6)	0	0
Pancytopenia	1 (0.6)	1 (0.6)	0	0
Pulmonary embolism	1 (0.6)	1 (0.6)	0	0
Rash	1 (0.6)	1 (0.6)	0	0
Respiratory failure	1 (0.6)	0	1 (0.6)	0
Shock	1 (0.6)	0	1 (0.6)	0
Spinal cord compression	1 (0.6)	1 (0.6)	0	0
Tumour haemorrhage	1 (0.6)	0	1 (0.6)	0
Upper gastrointestinal haemorrhage	1 (0.6)	0	1 (0.6)	0
Urinary tract infection	1 (0.6)	1 (0.6)	0	0
Uveitis [4]	1 (0.6)	0	0	0
Vasogenic cerebral oedema	1 (0.6)	0	1 (0.6)	0
Venous thrombosis	1 (0.6)	1 (0.6)	0	0

Adapted from Tables 14.3.2.1.2.2.1_R1, 14.3.2.3.2.1_R1, 14.3.2.10.3_R1 (STN125773/0)
[1] AE grouped terms of platelet count decreased and thrombocytopenia.
[2] AE grouped terms of neutrophil count decreased and neutropenia.
[3] Number of patients with SAEs related to lifileucel and other components of the treatment regimen.
[4] Number of patients with SAEs related to lifileucel ONLY.
[5] The Applicant disagreed with the investigator that lifileucel was related to this case.

Reviewer Comment: *Except for the clear association between lifileucel and the SAEs anaphylactic reaction and uveitis (based on timing and mechanism of action), any of the other SAEs could be attributed to the NMA-LD or IL-2 treatment regimen components.*

5.1.2.2 Post Treatment-Emergent AEs

Post-treatment emergent AEs occurring with an incidence greater than or equal to 5% are shown in Table 9. Except for insomnia, all the AEs listed are known adverse reactions to one or both NMA-LD agents (fludarabine, cyclophosphamide) and/or IL-2. Insomnia is listed in postmarketing experience for Proleukin (IL-2), and sleep disorder is listed as a rare adverse reaction for fludarabine.

Table 9: Post-treatment-emergent AEs with an Incidence of ≥ 5% in either Cohort 4 or Cohort 2 presented by SOC, PT, and Grade for Pooled Cohorts 2 and 4 (N=156)

System Organ Class (SOC) Preferred Term (PT)	**Any Grade n (%)**	**Grade 3/4 n (%)**	**Grade 5 n (%)**
Blood and lymphatic system disorders			
Anaemia	28 (17.9)	14 (9.0)	0
Thrombocytopenia [1]	20 (12.8)	8 (5.1)	0
Neutropenia [2]	11 (7.1)	5 (3.2)	0
Leukopenia [3]	10 (6.4)	4 (2.6)	0
Lymphopenia [4]	10 (6.4)	4 (2.6)	0
Gastrointestinal disorders			
Vomiting	9 (5.8)	1 (0.6)	0
Diarrhoea	6 (3.8)	0	0
Nausea	6 (3.8)	1 (0.6)	0
General disorders and administration site conditions			
Fatigue	12 (7.7)	2 (1.3)	0
Pyrexia	5 (3.2)	0	0
Infections and infestations			
Sepsis[5]	5 (3.2)	4 (2.6)	1 (0.6)
Nervous system disorders			
Headache	7 (4.5)	0	0
Psychiatric disorders			
Insomnia	4 (2.6)	0	0
Renal and urinary disorders			
Acute kidney injury	5 (3.2)	2 (1.3)	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	6 (3.8)	3 (1.9)	0
Cough	4 (2.6)	1 (0.6)	0

Adapted from Table 23 in module 5.3.5.2 (STN125773/0).
[1] AE grouped terms of platelet count decreased and thrombocytopenia.
[2] AE grouped terms of neutrophil count decreased and neutropenia.
[3] AE grouped terms of white blood cell count decreased and leukopenia.
[4] AE grouped terms of lymphocyte count decreased and lymphopenia.
[5] Cause of death was metastatic melanoma complicated by sepsis.

Grade 3 or Higher Post-treatment AEs (Pooled Cohorts 2 and 4)

In the median study follow up of 27.6 months, 23.7% of patients experienced at least one Grade 3 or 4 post-treatment-emergent AE and 6 (3.8%) patients experienced a post-treatment-emergent AE that resulted in death. The most common Grade 3 or 4 post-treatment-emergent AEs were anemia (9%) and the grouped term thrombocytopenia (5.1%) (Table 9).

Reviewer Comment: *Any of the post-treatment AEs in Table 9 could be attributed to the NMA-LD or IL-2 components of the treatment regimen or the underlying disease.*

5.1.2.3 Deaths Following Lifileucel Infusion

A total of 105 deaths occurred in the 156 patients treated with the lifileucel regimen as of the data cut point of 15 Sep 2021. Most deaths were attributed to disease progression. Five deaths had unknown causes. Deaths attributed to adverse events are shown in Table 10. Six deaths occurred within 30 days of lifileucel administration. Two deaths in this period were attributed to progressive disease and 4 deaths were due to adverse events including *pneumonia, cardiac dysrhythmia, intra-abdominal hemorrhage, and acute respiratory failure*. None were assessed by the investigator or Applicant as related to lifileucel.

There were nine additional deaths due to adverse events from the beginning of the post-treatment emergent period until the data cut point. The adverse events included *failure to thrive (due to advanced melanoma), cerebral haemorrhage, multi organ dysfunction syndrome, septic shock, bone marrow failure, sepsis, failure to thrive, pulmonary embolism, and haemorrhage intracranial. Of these, the investigator assessed bone marrow failure as "possibly" related to lifileucel and related to all other components of the treatment regimen.*

Table 10: Deaths Due to Adverse Events Following Lifileucel Administration (Pooled Cohorts 2 and 4)

Preferred Term of AE	Study Day of AE Onset	Duration (days)	Investigator Assessed as Related to:
Treatment-Emergent Period			
pneumonia	17	1	CY, FLU, IL-2
cardiac dysrhythmia	24	1	CY
intra-abdominal hemorrhage	14	1	CY, FLU, IL-2
acute respiratory failure	4	3	CY,FLU
Post Treatment-Emergent Period			
failure to thrive	47	1	Melanoma
cerebral haemorrhage	95	1	Not related to study drugs
multi organ dysfunction syndrome	115	1	Not related to study drugs
septic shock	185	1	CY
bone marrow failure	150	1	CY,FLU,IL-2; possible TIL
sepsis	35	4	"died due to advanced melanoma"
failure to thrive	197	13	Not related to study drugs
pulmonary embolism	528	1	Not related to study drugs
haemorrhage intracranial	57	2	Not related to study drugs

Adapted from Listing 16.2.7.11 in module 5.3.5.2 Appendix 16.2.7 (STN125773/0).

CY = cyclophosphamide; FLU = fludarabine.

In response to a query by the clinical review team about a death in the treatment emergent period attributed to progressive disease in the context of the AEs *hypoxia, neutropenia, anemia, thrombocytopenia, anuria, and renal tubular necrosis* (STN125773/0.15), the Applicant noted a contribution of cyclophosphamide-induced renal events to the patient's demise could not be ruled out. In response to an additional query from the clinical review team (STN 125773/0.16), the Applicant acknowledged a possible contribution of *encephalitis* and *sepsis/septic shock* could not be ruled out in two other patient deaths classified as due to progressive disease. Thus, AEs not due to the underlying disease may have contributed to at least 3 additional deaths.

Reviewer Comment: *Although well characterized AEs associated with the NMA-LD and IL-2 components of the treatment regimen may have contributed to multiple deaths, as a structurally unmodified autologous product, it does not appear that lifileucel contributed significantly to any deaths in study C-144-01.*

5.1.2.4 Grade 5 SAEs Across the Gen 2 TIL Monotherapy Studies

Reports of Grade 5 SAEs included 20.0% of patients in the NSCLC cohorts, 9.4% of patients in the melanoma cohorts, 7.5% of patients in the cervical cancer cohorts, and none of the patients in the HNSCC cohort. Grade 5 SAEs reported in more than 1 patient is shown in Table 11. Only 1 Grade 5 event was listed as only related to TIL. A summary of SAEs of interest from the Gen 2 TIL Monotherapy Studies is in Appendix B.

Table 11: Grade 5 SAEs Reported in More Than 1 Patient

SAE	Total	Melanoma Study: C-144-01	Cervical C-145-04	NSCLC IOV-LUN-202 IOV-COM-202	HNSCC C-145-03
Multiple organ dysfunction syndrome	5	1-NR	2-(1-IL-2, 1-CY)	2 (1-NR, 1-TIL)	0
Septic shock/ Sepsis	6	2-NR	3 (1-CY,FLU; 2-NR)	1-NR	0
Acute respiratory failure	3	1-NR	1- TIL,IL2	1-CY	0
Failure to thrive	2	2-NR	0	0	0
Respiratory failure	2	0	1-NR	1- CY,FLU,IL2	0

NR = assessed by the Applicant as not related to TIL (lifileucel) or any other component of the treatment regimen; CY = cyclophosphamide; FLU = fludarabine

5.1.2.5 Analysis of AEs of Interest in the Safety Analysis Set

Hypersensitivity reactions (including *infusion related reaction* and *anaphylactic reaction*), *uveitis*, and *vitiligo* were classified by the Applicant as identified risks for lifileucel.

Hypersensitivity Reactions

There were a total of 9 cases (5.8%) of *infusion related reaction*, 2 cases (1.3%) of *anaphylactic reaction*, and 1 case (0.6%) of *hypersensitivity* during the treatment-emergent period and none during the post-treatment-emergent period. Six of the nine cases of *infusion related reaction* were assessed as related to lifileucel and were Grade 1 (5) or Grade 2 (1). Three were assessed as related to IL-2. Both cases of *anaphylactic reaction* were serious, occurred on the day of lifileucel infusion, were assessed as related to lifileucel only, resulted in early termination of the lifileucel infusion, and resolved promptly with appropriate treatment. The one case of hypersensitivity was Grade 3 and attributed to IL-2. The study protocol was amended to provide premedication and additional supportive therapy to mitigate these risks. The Applicant considers *hypersensitivity reactions* (including *infusion related reactions* and *anaphylactic reaction*) as identified risks.

Uveitis

There were 6 cases (3.8%) of *uveitis* during the treatment-emergent period (1 serious) and 2 cases (1.3%) during the post-treatment-emergent period. Seven of the eight cases were classified as moderate to severe but only one case was classified as serious. The median duration was 122 days, but there was significant variation (min: 2; max 400). Table 12 provides summary information on each case. Five cases were noted as related to lifileucel and three of those were also related to other components of the treatment regimen. There is a known association between IL-2 and uveitis. The Applicant noted that all patients with uveitis had also previously been treated with Immune Checkpoint Inhibitors (ICI) and anterior uveitis is a common AE associated with ICI use. However, per protocol ICI therapy was discontinued at least 28 days prior to the start of NMA-LD. Thus, the Applicant considered uveitis an identified risk for lifileucel based on the temporal relationship between uveitis and administration of lifileucel, the biological plausibility based on the mechanism of action of lifileucel in patients with metastatic melanoma, and the delay in onset of uveitis from the last ICI therapy.

Table 12: Uveitis Cases during the Treatment-Emergent and Post Treatment-Emergent Periods (Pooled Cohorts 2 and 4)

Uveitis Cases	Investigator Assessed as:			
Treatment-Emergent	Related to Lifileucel?	Related to other treatment?	Serious?	Recovered?
1	Possible	CY, FLU, IL2	No	No
2	Possible	No	Yes	Yes
3	Definite	IL2	No	Yes
4	Definite	No	No	Yes
5	No	?	No	Yes
6	No	IL2	No	Yes
Post Treatment-Emergent				
7	Probable	IL2	No	L-Yes

				R-No
8	Not likely	No	No	No

Adapted from Listing 16.2.7.3 and Listing 16.2.7.4 (STN125773/0)
CY = Cyclophosphamide; FLU = Fludarabine; IL2 = IL-2

Vitiligo

There were 9 cases (5.8%) of vitiligo during the treatment-emergent period and 4 cases (2.6%) during the post-treatment-emergent period. In 8 of 13 cases (61.5%), vitiligo was reported as related to lifileucel. In 5 of those 8 cases, IL-2 or IL-2 and the NMA-LD agents were also reported as related. As with uveitis, there is a known association between both ICIs and IL-2 and vitiligo. For the same reasons outlined for uveitis, the Applicant considers vitiligo an identified risk for lifileucel.

Reviewer Comment: *The Applicant assessment that hypersensitivity reactions, uveitis, and vitiligo are identified risks appears appropriate. With lifileucel and IL-2 being administered in close succession, the delayed onset of symptoms, and a known association with IL-2, it would be difficult to distinguish that only one agent was the primary cause of uveitis or vitiligo except in cases where IL-2 was not administered. It is notable that 3 cases did not resolve with standard care during the study observation period, but there is significant heterogeneity in uveitic diseases and failure rates for individual immunosuppressives in treating non-infectious uveitis are high [17].*

Cytokine Release Syndrome (CRS)

Cytokine Release Syndrome was reported in 5 of 156 (3.2%) patients who received lifileucel (pooled cohorts 2 and 4). Two *CRS* cases were Grade 3 and none were fatal. The time to onset for 4 cases considered TEAEs ranged from 1 to 9 days after lifileucel infusion. Only 2 of the 4 cases were reported as related to lifileucel with the Grade 3 case related to both lifileucel and IL-2 and a Grade 2 case related to lifileucel only. Two cases resolved with no treatment: one on the same day and one within 7 days of onset. The other two cases resolved with IV steroids, one on the same day and one within 4 days of onset.

Appendix 16.2 of module 5.3.2.3.2 indicates the patient with CRS of 4 days duration was also diagnosed with *immune effector cell-associated neurotoxicity syndrome (ICANS)* on the same day as *CRS* [study day 2, during the IL-2 infusion period]. The *ICANS* event had a duration of 8 days. Appendix 16.2 indicates the patient received tocilizumab on study day 2 and 3. In addition, overlapping the last 2 days of the *ICANS* event was an AE of *encephalopathy* described as CRS Encephalopathy listed as related to IL-2. This was the only report of ICANS in the Safety Populations of all five Gen 2 TIL monotherapy studies.

The Applicant stated that no laboratory markers of systemic inflammation were reported in association with the 4 TEAEs of *CRS* but noted that 3 of the 4 TEAEs of CRS occurred concurrently with *capillary leak syndrome* (n=3), *respiratory failure* (n=1), or *pyrexia* (n=1). The Applicant further noted that these AEs could be associated with either *CRS* or capillary leak syndrome, which has a known association with IL-2.

Although biomarkers of inflammation are often elevated in CRS [18], biomarker levels are not part of the American Society for Transplantation and Cellular Therapy (ASTCT) diagnostic criteria for CRS [19].

Listing 16.2.7.8 describes the fifth case of *CRS* (patient (b) (6)) as occurring during the NMA-LD period. The Applicant clarified in response to an IR (STN 125773/0.32, SN0033) that even though Listing 16.2.7.8 and the narrative for this case indicated *CRS* onset at Grade 1 was on Study Day 0, the symptoms were present prior to lifileucel infusion, and thus it was not considered a TEAE. *CRS* progressed to Grade 3 on study day 2 after 5 doses of IL-2, was classified an SAE, and assessed as "possibly" related to IL-2. IL-2 was discontinued after 5 doses due to the SAEs *capillary leak syndrome, dyspnea, and pulmonary edema* and AEs *respiratory failure and atrial fibrillation*.

Reviewer Comment: *The incidence of CRS was very low compared to Chimeric antigen receptor (CAR) T-cell therapy. Cytokine release syndrome is most frequently seen in CAR-T therapy but can be observed with any adoptive cell therapy (ACT) [20]. The Summary of Clinical Safety appeared to convey some diagnostic uncertainty regarding the CRS diagnoses in noting that no laboratory markers of systemic inflammation were reported, and concurrent capillary leak syndrome was reported in 3 cases.*

<u>Haemophagocytic Lymphohistiocytosis (HLH)</u>
There were 3 reports of *haemophagocytic lymphohistiocytosis (HLH)* in the Safety Populations of the five Gen 2 TIL monotherapy studies. Only one of these occurred in pooled Cohorts 2 and 4 of Study C-144-01 with onset on study day 47. It was Grade 1, was not considered a TEAE or related to lifileucel, and was unresolved at the time of death. A response to a clinical IR (125773/0.18) indicated the diagnosis was unsubstantiated as only 1 of 8 HLH diagnostic criteria (5 required for diagnosis) were present in the patient. (The narrative for an additional patient in Study C-144-01 indicated a diagnosis of *HLH* was considered multiple times but was not confirmed or treated. In response to the same IR, the Applicant indicated the patient only met 3 of 8 HLH diagnostic criteria.) The other two reports were from the two studies on non-small cell lung cancer and were Grade 3 and Grade 5. The Grade 3 *HLH* event was reported as related to all components of the treatment regimen and the fatal Grade 5 *HLH* event was reported as related to cyclophosphamide and fludarabine.

<u>Cytopenias (Thrombocytopenia, Neutropenia, Leukopenia, Lymphopenia)</u>
Cytopenias were experienced by 86.5% (135/156) of patients in the treatment-emergent period of which 30 (19.2%) were considered related to lifileucel and 5.8% (9/156) were considered SAEs. None of the SAEs were considered related to lifileucel and no cases were considered related to lifileucel only. Post-treatment-emergent cytopenias were experienced by 35 patients (22.4%). Cytopenic events are well characterized effects of the NMA-LD regimen. In addition, one trial referenced in labeling for IL-2 demonstrated *thrombocytopenia, anemia, and leukopenia* in over 10% of patients treated.

<u>Cardiac Arrhythmias</u>

Treatment-emergent cardiac arrhythmias occurred in 47.4% (74/156) of the patients in pooled cohorts 2 and 4 of which only 1.3% (2/156) were SAEs. *Tachycardia* (28.8% of patients) and *sinus tachycardia* (14.7% of patients) were the most reported arrhythmias. Of the two SAEs, one was an unspecified fatal dysrhythmia (*arrhythmia*) likely associated with cyclophosphamide-related cardiomyopathy and the other was *atrial fibrillation* assessed by the Applicant as related to IL-2. Cyclophosphamide and IL-2 have labeled cardiotoxic effects commonly associated with arrhythmias.

Vascular Hypotensive Disorders

Capillary leak syndrome and *hypotension* are included in a black box warning for Proleukin (aldesleukin [IL-2]). Vascular hypotensive disorders were reported in 41.0% (64/156) of patients in the treatment-emergent period of which 3.2% (5/156) were SAEs. None of the SAEs were fatal and all were reported as related to IL-2. Vascular hypotensive events reported as related to lifileucel occurred in 10.3% of patients of which only 3 were assessed as related only to lifileucel. These 3 events occurred with concurrent events (i.e., chills, pyrexia, nausea, sinus tachycardia/tachycardia, and tachypnea) the Applicant noted may suggest an infusion related reaction to either lifileucel or IL-2. Only 3 patients (1.9%) experienced post-treatment-emergent vascular hypotensive disorders.

Noninfectious Encephalopathy/Delirium

Labeling for Proleukin (aldesleukin [IL-2]) indicates that mental status changes including irritability, confusion, or depression may occur as a result of direct Proleukin-induced CNS toxicity. Common AEs noted in the label from a study of Proleukin included confusion in 34% and somnolence in 22% with 1 to 2% experiencing Grade 4 confusion, stupor, coma, and psychosis. Postmarketing events of cerebral lesions, encephalopathy, extrapyramidal syndrome, and demyelinating neuropathy have all been observed. Fludarabine has been associated with neurotoxicity primarily at high doses. However, recent reports have raised concern that reduced intensity conditioning with standard doses of fludarabine may be associated with delayed onset severe or more benign and reversible neurologic complications [21-23]. However, at least one author noted that late-onset neurotoxicity associated with fludarabine has not been reported in adoptive cell therapy (ACT) studies [24].

Adverse events in the grouped term noninfectious encephalopathy/delirium (MedDRA SMQ) were reported in 32.1% (50/156) of patients. SAEs under the same grouped term were reported in 3.2% (5/156) of patients, none of which were fatal or assessed by the Applicant as related to lifileucel. The median time to onset of any noninfectious encephalopathy/delirium event was 5.0 days (min 2, max: 130 days). Five days was also the median time to onset (min 2, max 22) for more severe events (equal or greater than Grade 3), consistent with timing for anticipated effects of IL-2 administration. Only 8.3% (13) of patients had noninfectious encephalopathy/delirium events that were reported as related to lifileucel and none were reported as only related to lifileucel. Ten patients (6.4%) experienced post-treatment-emergent noninfectious encephalopathy/delirium AEs.

Immune-mediated/Autoimmune Disorders

Adverse events in the grouped term immune-mediated/autoimmune disorders (MedDRA SMQ) were reported in 6.4% (10/156) of patients in the treatment-emergent period. None were classified as Grade 3 or 4 or reported as an SAE. *Vitiligo* (n = 9) and *cutaneous vasculitis* (n = 1) were the only 2 TEAEs reported under this grouped term. In 5 (3.2%) of these patients the AEs were reported as related to lifileucel, and 2 of these were reported as related only to lifileucel. *Vitiligo* was the only immune-mediated/autoimmune disorders event reported as related only to lifileucel. The cutaneous vasculitis event was Grade 1 and reported as related to all components of the lifileucel regimen. Five patients (3.2%) experienced an immune-mediated/autoimmune disorder AE in the post-treatment-emergent period. There were 4 reports of *vitiligo* and 1 report of *haemophagocytic lymphohistiocytosis,* all less than Grade 3 severity.

Reviewer comment: *The only AEs clearly related to lifileucel are hypersensitivity, uveitis, and vitiligo. All other AEs are known to be related to or associated with the NMA-LD and/or IL-2 components of the treatment regimen or the underlying disease being treated. Since lifileucel is administered in close proximity to other components of the treatment regimen, it is difficult to determine if lifileucel may contribute to development of or worsening of AEs with a known association to other components of the treatment regimen.*

5.1.2.6 Pregnancy

No data are available regarding the use of lifileucel in pregnancy or lactation and no preclinical reproductive studies have been conducted. Lifileucel is not recommended during pregnancy. Labeling for other components of the lifileucel treatment regimen (NMA-LD and IL-2) advise against use in pregnancy.

5.2 Gen 2 TIL Monotherapy Studies 90-Day Safety Update

Adverse Events

The following was noted in the 90-day Safety Update. All patients in all tumor cohorts (i.e., melanoma, cervical cancer, NSCLC (non-small cell lung cancer), and HNSCC (head/neck squamous cell cancer) experienced at least 1 AE after the start of NMA-LD up to the start of new anti-cancer therapy or the data cutoff date (except for 1 patient in the NSCLC study). The incidence of Grade 4 and 5 AEs was similar across the Gen 2 TIL monotherapy studies. Reported AEs were generally hematological toxicities associated with NMA-LD and nonhematological toxicities (chills, nausea, pyrexia, diarrhea, fatigue, vomiting, hypotension, tachycardia, decreased appetite, electrolyte disturbances, and peripheral edema) associated with both NMA-LD and IL-2.

The incidence of hypokalaemia in the NSCLC cohorts was the only AE that increased by more than 10% compared to the BLA data (47.5% vs 57.6%). The incidence of Grade 3 anaemia (52.5% vs 64.4%) and Grade 4 neutropenia (57.5% vs 67.8%), both

in the NSCLC cohorts, were the only Grade 3, 4, or 5 events that increased by more than 10% as compared to the BLA data.

In patients receiving ***above*** compared to ***at or below*** the median TIL dose, a disproportionately higher rate of specific AEs was noted in each of the Gen 2 TIL monotherapy studies. However, the Applicant noted no clinically significant changes in the differences noted in the 90-day safety update data. For the melanoma cohorts AEs were unchanged, continuing to show the following dose related differences: *decreased appetite* (28.2% vs 12.8%), *vitiligo* (14.1% vs 2.6%), *arthralgia* (14.1% vs 2.6%), and events in the hypopigmentation disorders high level term (HLT) (17.9% vs 2.6%), which includes *vitiligo* and *skin hypopigmentation*. In the cervical cancer cohorts, the incidence of *nausea* (36.0% vs 19.2%) continued to be higher in the above median dose group. The incidence of arthralgia (12.0% vs1.9%) and other events in the joint related signs and symptoms HLT were also noted to be elevated in the above median dose group, but the Applicant indicated they could not conclude a disproportionate difference existed based on the small sample size.

For the NSCLC cohorts, the Applicant noted slight but clinically insignificant changes in previously noted differences in rates of reported adverse events as noted in Table 13.

Table 13: Disproportionately Reported Adverse Events Comparing Above Median to At or Below Median Dose of TIL in the Non-Small Cell Lung Cancer Cohort

Adverse Event	Original BLA Text	Safety Update Text
Febrile neutropenia	47.1% vs 13.6%; any grade and Grade 3	50.0% vs 11.5%; any grade and Grade 3
Hypokalaemia	47.1% vs 9.1%	42.9% vs 19.2%)
*Grade 3 Vascular hypotensive disorders HLT**	41.2% vs 4.5%	39.3% vs 3.8%

Adapted from Table 7 Adverse Events by Median TIL Dose, 90-DAY SAFETY UPDATE REPORT, BLA 125773/SN0014.
*Includes events of hypotension, capillary leak syndrome, and orthostatic hypotension

In the HNSCC cohorts, the rates were unchanged with only *pyrexia* (80.0% vs 28.6%) exhibiting a notable difference based on TIL dose.

The Applicant concluded there was no consistent correlation between the administration of TIL above the median dose and the types of AEs experienced across tumor types.

A disproportionately higher rate of AEs in patients receiving ***at or below*** compared to ***above*** the median TIL dose was only reported in the melanoma and cervical cancer cohorts. In the melanoma cohorts, the comparison was unchanged and only noted with *asthenia* (20.5% vs 7.7% (the Applicant noted this may be due to reporter terminology preference, as there was no meaningful difference in the incidence of events within the Asthenic conditions HLT (48.7% vs 47.4%)).

In the cervical cancer cohort, comparing at or below vs above median TIL doses, there were slight but clinically insignificant changes in previously noted differences in rates of reported AEs as noted in table 14.

Table 14: Disproportionately Reported Adverse Events Comparing At or Below Median Dose to Above Median Dose of TIL in the Cervical Cancer Cohort

Adverse Event	Original BLA Text	Safety Update Text
Asthenia	18.0% vs 0%	17.3% vs 0%
Hypertension	18.0% vs 2%	17.3% vs 2.0%
Blood bilirubin increased	12.0% vs 0%	11.5% vs 0%
Rashes, eruptions and exanthems NEC HLT	32.0% vs 13.7%	34.6% vs 10.0%
Renal failure and impairment HLT		
-Any grade	26.0% vs 9.8%	25.0% vs 10.0%
-Grade 4	10.0% vs 0%	9.6% vs 0% Grade 4
Confusion and disorientation HLT	12.0% vs 0%	11.5% vs 0%

Adapted from Table 7 Adverse Events by Median TIL Dose, 90-DAY SAFETY UPDATE REPORT, BLA 125773/SN0014.

The Applicant concluded there was no consistency in the types of AEs experienced in patients receiving above the median versus at/below the median TIL dose and there was insufficient evidence to suggest the TIL dose impacts the safety profile.

The System Organ Class (SOC) code with the highest incidence of SAEs remained the Blood and lymphatic system disorders SOC for the melanoma, cervical cancer, and HNSCC cohorts and Respiratory, thoracic and mediastinal disorders SOC for the NSCLC cohorts.

Reviewer comment: *The AEs reported in the 90-day Safety Update were consistent with those reported previously. Even though disproportionately higher rates of some AEs were identified in association with either above median or at or below median TIL dose, there does not appear to be a consistent pattern across tumor types and in some cases the results are counterintuitive. This may be a result of confounding due to differences in underlying comorbidities between the patients in the two groups or other factors.*

Deaths

Between the original BLA and the 90-day Safety Update Report, there were 9 additional deaths reported across the Gen 2 TIL monotherapy cohorts. In the cervical cancer cohort, there was 1 death from “progressive disease”. In the lung cancer cohorts, there were 8 additional deaths including 5 from the “disease under study”, 1 from “acute respiratory failure” (assessed by the investigator as related to cyclophosphamide), 1

from “cyclophosphamide-associated cardiomyopathy”, and 1 from unknown causes. There were no additional deaths reported from the HNSCC cohort.

Reviewer comment: *Most deaths were from the underlying disease or related to an NMA-LD agent, consistent with previous reports.*

6 Pharmacovigilance Plan

6.1 Summary of Pharmacovigilance Plan (PVP)

The Applicant submitted a PVP to STN 125773/0.3 on 17 April 2022 in response to an Information Request (IR) sent on 31 March 2023. A subsequent IR was sent to the Applicant on 28 July 2023 requesting the following:

1. A protocol synopsis for a general safety surveillance postmarketing study that will further characterize the safety profile of lifileucel.

2. Additional information and clarification of cytokine release syndrome (CRS) case reports.

3. Revisions to the PVP including:
   a) Adding “long-term safety” as Missing Information
   b) Adding uveitis as an Important Identified Risk
   c) Adding cytokine release syndrome (CRS) as an Important Potential Risk
   d) Updating the table of Important Risks and Missing Information to include the additions above and proposed mitigation measures.
   e) Addition of references to study (IOV-MEL-301) to assess the efficacy and safety of lifileucel (LN-144) and the proposed general safety surveillance postmarketing study in item 1 to the PVP Action Plan for Safety Issues.
   f) Addition of a missing reference to USPI Section 5.1. in Risk Minimization Measures for Hypersensitivity Reactions in Table 3-3 of the PVP

In response to the IR, the Applicant submitted the protocol synopsis of a postmarketing safety surveillance study (IOV-MEL-401), clarified the CRS case reports, and provided a revised PVP on 25 August 2023 to STN125773/0.32 (SN0033). The updated summary of safety concerns and proposed actions is shown in Table 15.

Table 15: Summary of Safety Concerns and Planned Pharmacovigilance Activities

Safety Concern	**Actions Proposed***
Important Identified Risks	
Uveitis	• USPI Section 6.1 – listed as an adverse drug reaction • Non-interventional postmarketing safety surveillance study of lifileucel in patients with metastatic melanoma in the real-world setting

	• A Phase 3, multicenter, randomized, open-label, parallel group, treatment study to assess the efficacy and safety of the lifileucel regimen in combination with pembrolizumab compared with pembrolizumab monotherapy in participants with untreated, unresectable or metastatic melanoma
Important Potential Risks	
Cytokine release syndrome	• Non-interventional postmarketing safety surveillance study of lifileucel in patients with metastatic melanoma in the real-world setting • A Phase 3, multicenter, randomized, open-label, parallel group, treatment study to assess the efficacy and safety of the lifileucel regimen in combination with pembrolizumab compared with pembrolizumab monotherapy in participants with untreated, unresectable or metastatic melanoma
Missing Information	
1. Safety in pediatric, adolescent, and young adult population < 18 years of age	• Phase 1 interventional study in pediatric, adolescent, and young adult participants with solid tumors
2. Long-term safety	• Non-interventional postmarketing safety surveillance study of lifileucel in patients with metastatic melanoma in the real-world setting • A Phase 3, multicenter, randomized, open-label, parallel group, treatment study to assess the efficacy and safety of the lifileucel regimen in combination with pembrolizumab compared with pembrolizumab monotherapy in participants with untreated, unresectable or metastatic melanoma

Adapted from Applicant's Pharmacovigilance Plan, SN0033, Table 3-5 (STN125773/0.32). *In addition to routine pharmacovigilance activities.

An additional IR was sent to the Applicant indicating they would be required to conduct enhanced pharmacovigilance for 3 years after product licensure to better characterize specific adverse events and other potentially related events following lifileucel administration as follows:
a. Submit expedited (15-day) reports for all adverse events (AEs) regardless of seriousness or expectedness (label status) for the following:
i. Uveitis
ii. Cytokine Release Syndrome
iii. Immune effector cell-associated neurotoxicity syndrome (ICANS)
iv. Hemophagocytic Lymphohistiocytosis (HLH)

They were also asked to provide aggregate safety assessment (based on interval and cumulative postmarketing safety data) in periodic safety reports for the above AEs in individuals who receive lifileucel.

The Applicant's proposal for postmarketing safety Study IOV-MEL-401 for 5-year follow-up of patients who receive lifileucel in the post-licensure setting was acknowledged and the Applicant was instructed to provide updates on this postmarketing safety study in your periodic safety reports.

The Applicant replied to STN 125773.0.44/SN0045 on 31 October 2023 acknowledging and agreeing to all the above items.

7 DPV Assessment of Applicant's Pharmacovigilance Plan

7.1 Important Identified Risks: Uveitis

The Applicant agreed to add uveitis as an important identified risk to further characterize this AE following administration of lifileucel. Uveitis can have a significant impact on quality of life if not effectively controlled and may result in loss of vision [17, 25]. At least 3 cases of uveitis in study C-144-01 were classified as unresolved. Uveitis was only reported in the melanoma cohorts. This addition to the PVP is also supported by the Applicant's inclusion of uveitis as an adverse event of special interest in their proposed Phase 3 efficacy and safety study (IOV-MEL-301) comparing lifileucel and pembrolizumab with pembrolizumab monotherapy.

Except for hypersensitivity reactions, the Applicant considered other serious adverse events to be consistent with the known safety profiles of the NMA-LD regimen and IL-2 with no indication that lifileucel contributes to an increase in frequency or severity of adverse events associated with the NMA-LD or IL-2 therapy.

7.2 Important Potential Risk: Cytokine Release Syndrome

Five cases of cytokine release syndrome (CRS) were reported in study C-144-01 of which only one was assessed as serious by the investigator and related to IL-2. . Only 2 non-serious cases were reported as related to lifileucel, one of which was reported as related only to lifileucel. The reporting rate is very low compared to CAR-T products; however, CRS may be seen with any adoptive cell therapy (ACT) [20]. The Applicant indicated that no biomarkers of inflammation were reported for these cases. In addition, the Applicant noted that there is significant overlap between the signs and symptoms of capillary leak syndrome and CRS, an entity associated with IL-2, adding to diagnostic uncertainty. In addition, residual IL-2 may remain in the lifileucel infusion from the manufacturing process. After initially indicating there were no important potential risks, the Applicant agreed to include CRS as an important potential risk for lifileucel. Since the data presented do not clearly implicate lifileucel as related to the reported CRS cases or definitively support the diagnostic accuracy of these cases, further characterization of the association with lifileucel is needed.

7.3 Missing Information: 1. Safety in pediatric, adolescent, and young adult population < 18 years of age. 2. Long-term safety

The Applicant indicated the effects of lifileucel in this population is not known.

The specified pediatric age groups included in the proposed Phase I trial to assess lifileucel in this cohort is an appropriate next step. Use in pregnancy and lactation is missing information for lifileucel. However, since lifileucel is not intended to be used alone, the known teratogenicity and/or fetotoxicity associated with the NMA-LD agents and IL-2 should preclude use in pregnancy or when breast feeding.

To further characterize the safety profile of lifileucel, the Applicant agreed to add long-term safety as missing information and provided a protocol synopsis for a general safety surveillance postmarketing study.

The Applicant provided a detailed list of the major risks associated with the non-myeloablative lymphodepletion regimen and IL-2 along with specific risk minimization measures. Routine pharmacovigilance is proposed for these with the rationale that the risks are known, adequately characterized, will be followed up via signal detection and adverse reaction reporting, and risk minimization messages in the product information will be adhered to by prescribers.

The updated version of the PVP is satisfactory and routine pharmacovigilance in conjunction with enhanced pharmacovigilance for specific AEs and other proposed actions will be adequate to monitor the safety profile.

8 Authorized Treatment Centers

IOVANCE intends to designate Authorized Treatment Centers (ATC) through a qualification process to ensure an institution is capable of tumor procurement, the receipt and storage of lifileucel drug product, and the infusion of lifileucel products (STN 125773/0, SN0003; module 3.2.A.1). The qualification process includes an Evaluation and Gap Analysis (EGA) and role specific training for personnel followed by an independent review by IOVANCE's Quality unit to confirm IOVANCE procedures were followed during the EGA and required training was completed. Monitoring post-qualification will be conducted by IOVANCE ATC Operations and IOVANCE Quality will do for-cause audits/investigations of critical deviations.

In response to an IR (STN 125773/0.33), IOVANCE clarified that an ATC could be a hybrid of inpatient and outpatient settings depending on capabilities, but IOVANCE would maintain process controls over the model chosen. In addition, the lifileucel proposed USPI recommends IL-2 be administered in an inpatient setting under supervision of a qualified physician experienced in the use of anticancer agents. Administration of lifileucel and IL-2 would be at the same ATC but may be in different settings (inpatient/outpatient) consistent with the qualification of the ATC.

Reviewer comment: The Applicant designation for "ATC" is focused on site-based procedures for appropriate product manufacturing/handling and delivery to patients. Of note, designation of ATC is determined by Applicant and not a requirement by FDA. Based on our assessment of the available data, OBPV has determined that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary to ensure the benefits outweigh the risks of the product.

9 DPV Conclusions

Specific risks identified for lifileucel include hypersensitivity reactions, uveitis, and vitiligo. Anaphylactic reactions are the most significant of these, but were infrequent (2/156), are managed with standard treatment guidelines and as a category are well characterized. Vitiligo is non-serious and managed with standard treatment guidelines. Noninfectious uveitis may be chronic or recurrent and associated with significant morbidity. Including this as an important identified risk may provide additional information on patient risk factors and the most effective management approaches in this population. The Applicant's inclusion of uveitis as an adverse event of special interest in the Phase 3 efficacy and safety study (IOV-MEL-301) also supports this. Review of the Applicant's safety data did not reveal significant safety concerns beyond those known to be associated with the NMA-LD agents and IL-2. Thus, the Applicant's plan to use routine and enhanced pharmacovigilance for post-approval safety monitoring for lifileucel in conjunction with the Phase 3 adult, Phase 1 pediatric, and voluntary non-interventional postmarketing safety surveillance studies is satisfactory.

The teratogenic and fetotoxic effects associated with the NMA-LD and IL-2 components of the lifileucel regimen preclude use in pregnancy or while breast feeding. Available safety data do not indicate a need for safety-related postmarketing requirement (PMR) studies or a Risk Evaluation and Mitigation Strategy (REMS).

There are no safety-related postmarketing commitment (PMC) studies. As mentioned above, a phase 3 efficacy and safety study comparing lifileucel and pembrolizumab with pembrolizumab monotherapy, a phase 1 pediatric and young adult study, and a voluntary non-interventional postmarketing safety surveillance study are planned to further characterize safety.

10 DPV Recommendations

Should this submission be approved, the revised PVP (STN 125773/0.32, SN0033, received August 25, 2023) is adequate and OBPV/DPV recommends the following for postmarketing safety monitoring of lifileucel:

- Routine pharmacovigilance (PV) activities: adverse event reporting in accordance with 21 CFR 600.80
- Enhanced PV in accordance with 21 CFR 600.80, for a period of 3 years post-licensure:

    - Applicant will submit expedited (15-day) reports, regardless of label status or seriousness, for events involving uveitis, cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS), hemophagocytic lymphohistiocytosis (HLH)
    - Applicant will provide aggregate safety assessment (based on interval and cumulative post marketing safety data) in periodic safety reports for the above adverse events
- Voluntary study for postmarketing safety surveillance: The Applicant will conduct a postmarketing surveillance study to monitor clinically important identified and potential risks, serious adverse events, and the long-term safety profile of lifileucel in adult participants with metastatic melanoma. The study plans to enroll 300 patients, and each patient will be followed for 5 years. The Applicant will provide updates on this postmarketing safety study in periodic safety reports.

The Applicant is planning to distribute the product at Applicant designated “authorized treatment centers” and voluntarily provide training materials to these centers for product manufacturing/handling and delivery to patients.

The available data do not indicate a safety signal which would require a REMS or PMR study under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, and there are no agreed upon PMCs for safety studies. Refer to the final version of the U.S. Prescribing Information (USPI) submitted by the Applicant for the final agreed-upon language for labeling.

References

1. *Cancer Stat Facts: Melanoma of the Skin*. Cancer Stat Facts 2023 [cited 2023; Available from: https://seer.cancer.gov/statfacts/html/melan.html.
2. Arance, A., et al., *Phase II LEAP-004 Study of Lenvatinib Plus Pembrolizumab for Melanoma With Confirmed Progression on a Programmed Cell Death Protein-1 or Programmed Death Ligand 1 Inhibitor Given as Monotherapy or in Combination.* J Clin Oncol, 2023. **41**(1): p. 75-85.
3. Ascierto, P.A., et al., *Nivolumab and Relatlimab in Patients With Advanced Melanoma That Had Progressed on Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy: Results From the Phase I/IIa RELATIVITY-020 Trial.* J Clin Oncol, 2023. **41**(15): p. 2724-2735.
4. Kuroda, H., et al., *Tumor-infiltrating B cells and T cells correlate with postoperative prognosis in triple-negative carcinoma of the breast.* BMC Cancer, 2021. **21**(1): p. 286.
5. Hendry, S., et al., *Assessing Tumor-infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method From the International Immunooncology Biomarkers Working Group: Part 1: Assessing the Host Immune Response, TILs in Invasive Breast Carcinoma and Ductal Carcinoma In Situ, Metastatic Tumor Deposits and Areas for Further Research.* Adv Anat Pathol, 2017. **24**(5): p. 235-251.
6. Hendry, S., et al., *Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immuno-Oncology Biomarkers Working Group: Part 2: TILs in Melanoma, Gastrointestinal Tract Carcinomas, Non-Small Cell Lung Carcinoma and Mesothelioma, Endometrial and Ovarian Carcinomas, Squamous Cell Carcinoma of the Head and Neck, Genitourinary Carcinomas, and Primary Brain Tumors.* Adv Anat Pathol, 2017. **24**(6): p. 311-335.
7. Rosenberg, S.A. and N.P. Restifo, *Adoptive cell transfer as personalized immunotherapy for human cancer.* Science, 2015. **348**(6230): p. 62-8.
8. Kristensen, N.P., et al., *Neoantigen-reactive CD8+ T cells affect clinical outcome of adoptive cell therapy with tumor-infiltrating lymphocytes in melanoma.* J Clin Invest, 2022. **132**(2).
9. Efremova, M., et al., *Neoantigens Generated by Individual Mutations and Their Role in Cancer Immunity and Immunotherapy.* Front Immunol, 2017. **8**: p. 1679.
10. Maibach, F., et al., *Tumor-Infiltrating Lymphocytes and Their Prognostic Value in Cutaneous Melanoma.* Front Immunol, 2020. **11**: p. 2105.
11. Chavez-Galan, L., et al., *Cell death mechanisms induced by cytotoxic lymphocytes.* Cell Mol Immunol, 2009. **6**(1): p. 15-25.
12. Goff, S.L., et al., *Randomized, Prospective Evaluation Comparing Intensity of Lymphodepletion Before Adoptive Transfer of Tumor-Infiltrating Lymphocytes for Patients With Metastatic Melanoma.* J Clin Oncol, 2016. **34**(20): p. 2389-97.
13. Kardalas, E., et al., *Hypokalemia: a clinical update.* Endocr Connect, 2018. **7**(4): p. R135-R146.
14. Adhikari, S., et al., *Hypophosphatemia in cancer patients.* Clin Kidney J, 2021. **14**(11): p. 2304-2315.

15. Wolf, J.E., Jr., *Safety and tolerability in the MORE trial.* Cutis, 2006. **78**(1 Suppl): p. 19-25.
16. Dutcher, J.P., et al., *High dose interleukin-2 (Aldesleukin) - expert consensus on best management practices-2014.* J Immunother Cancer, 2014. **2**(1): p. 26.
17. Knickelbein, J.E., et al., *Comparative efficacy of steroid-sparing therapies for non-infectious uveitis.* Expert Rev Ophthalmol, 2017. **12**(4): p. 313-319.
18. Murthy, H., et al., *Cytokine Release Syndrome: Current Perspectives.* Immunotargets Ther, 2019. **8**: p. 43-52.
19. Lee, D.W., et al., *ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells.* Biol Blood Marrow Transplant, 2019. **25**(4): p. 625-638.
20. Wolf, B., et al., *Safety and Tolerability of Adoptive Cell Therapy in Cancer.* Drug Saf, 2019. **42**(2): p. 315-334.
21. Annaloro, C., et al., *Severe fludarabine neurotoxicity after reduced intensity conditioning regimen to allogeneic hematopoietic stem cell transplantation: a case report.* Clin Case Rep, 2015. **3**(7): p. 650-5.
22. Beitinjaneh, A., et al., *Toxic leukoencephalopathy following fludarabine-associated hematopoietic cell transplantation.* Biol Blood Marrow Transplant, 2011. **17**(3): p. 300-8.
23. Lee, M.S., et al., *Clinical and imaging features of fludarabine neurotoxicity.* J Neuroophthalmol, 2010. **30**(1): p. 37-41.
24. Lowe, K.L., et al., *Fludarabine and neurotoxicity in engineered T-cell therapy.* Gene Ther, 2018. **25**(3): p. 176-191.
25. Kaleemunnisha, S., S. Sudharshan, and J. Biswas, *Quality of life in non-infectious uveitis patients on immunosuppressive therapy.* Middle East Afr J Ophthalmol, 2014. **21**(3): p. 225-31.

APPENDIX A: Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
26 Jun 2023	Applicant	STN125773/0	Module 1.11.3 Response to Clinical IR#1: revised Module 5.3.5.2 14 Tables and Figures and 14 Patient Narratives
10 Jul 2023	Applicant	STN125773/0	Module 1.11.3 Response to Clinical IR#2
19 Jul 2023	Applicant	STN125773/0	Module 1.11.3 Response to Clinical IR#3
27 Jul 2023	Applicant	STN125773/0	Module 1.11.3 Response to Clinical IR#4
15 Aug 2023	Applicant	STN125773/0	Module 1.11.3 Response to Clinical IR#6
28 Aug 2023	Applicant	STN125773/0	Module 1.11.3 Response to Clinical IR#8
25 Aug 2023	Applicant	STN125773/0.32	Module 1.11.3 Response to DPV IR#2
31 Oct 2023	Applicant	STN125773/0.44	Module 1.11.3 Response to DPV IR#3
29 Sep 2022	Applicant	STN125773/0	Module 1.14.1.3 Draft labeling text
17 Apr 2023	Applicant	STN125773/0.3	Module 1.16.1, Draft US Pharmacovigilance Plan (Response to IR#1)
25 Aug 2023	Applicant	STN125773/0.32	Module 1.16.1, Revised US Pharmacovigilance Plan (Response to IR#2)
29 Sep 2022	Applicant	STN125773/0.3	Module 2.5 Clinical overview
29 Sep 2022	Applicant	STN125773/0.1	Module 2.7.4 Summary of clinical safety
27 Mar 2023	Applicant	STN125773/0.2	Module 3.2.A.1 Facilities and Equipment – Authorized Treatment Centers
29 Sep 2022	Applicant	STN125773/0	Module 5.2, Tabular listing of all clinical studies
29 Sep 2022	Applicant	STN125773/0.1	Module 5.3.5.2 C-144-01 2 Synopsis, Report Body, 14 Tables and Figures, 14 Patient Narratives, 16.2 Patient Data Listings
29 Sep 2022	Applicant	STN125773/0.1	Module 5.3.5.3 Integrated Summary of Safety (ISS) Lifileucel (LN-144) and ISS Tables, Figures and Listings
21 Jun 2023	Applicant	STN125773/0.1	Module 5.3.5.3 90-Day Safety Update Report and Tables and Listings

APPENDIX B: Summary of SAEs of Interest Across Gen 2 TIL Monotherapy Studies

Table B1: Summary of Serious Adverse Events of Interest - Gen 2 TIL monotherapy - Safety Population

	Melanoma C-144-01 Cohorts 2+4 (N=160)			Cervical Cancer C-145-04 Cohorts 1+2+4 (N=107)			NSCLC IOV-LUN-202 Cohorts 1+2+ IOV-COM-202 Cohort 3B (N=59)				HNSCC C-145-03 Cohort 2 (N=18)	
Grade	Any n (%)	3 n (%)	4 n (%)	Any n (%)	3 n (%)	4 n (%)	Any n (%)	3 n (%)	4 n (%)	5 n (%)	Any n (%)	3 n (%)
Category *-Adverse Event*												
Noninfectious encephalopathy/ delirium [1]	9(5.6)	4(2.5)	1(0.6)	5(4.7)	4(3.7)	1(0.9)	6(10.2)	2(3.4)	2(3.4)	1(1.7)	1(5.6)	1(5.6)
-Aphasia	2(1.3)	0	0	0	0	0	0	0	0	0	0	0
-Delirium	2(1.3)	1(0.6)	0	0	0	0	2(3.4)	1(1.7)	1(1.7)	0	0	0
-Encephalopathy	2(1.3)	1(0.6)	1(0.6)	1(0.9)	0	1(0.9)	1(1.7)	0	1(1.7)	0	0	0
-Confusional state	1(0.6)	0	0	0	0	0	1(1.7)	0	0	0	0	0
-Depressed level of consciousness	1(0.6)	1(0.6)	0	1(0.9)	1(0.9)	0	0	0	0	0	0	0
-Dysarthria	1(0.6)	0	0	0	0	0	0	0	0	0	0	0
-Mental status changes	1(0.6)	1(0.6)	0	0	0	0	1(1.7)	1(1.7)	0	0	0	0
-Muscular weakness	1(0.6)	0	0	1(0.9)	1(0.9)	0	0	0	0	0	0	0
-Delusion	0	0	0	1(0.9)	1(0.9)	0	0	0	0	0	0	0
-Dysphagia	0	0	0	0	0	0	0	0	0	0	1(5.6)	1(5.6)
-Leuko-encephalopathy	0	0	0	0	0	0	1(1.7)	0	0	1(1.7)	0	0
-Metabolic encephalopathy	0	0	0	1(0.9)	1(0.9)	0	0	0	0	0	0	0
-Seizure	0	0	0	1(0.9)	1(0.9)	0	0	0	0	0	0	0
-Somnolence	0	0	0	0	0	0	1(1.7)	0	1(1.7)	0	0	0

Hypersensitivity reactions [2]	3(1.9)	1(0.6)	2(1.3)	4(3.7)	2(1.9)	1(0.9)	0	0	0	0	0	0
-Anaphylactic reaction	2(1.3)	1(0.6)	1(0.6)	1(0.9)	0	1(0.9)	0	0	0	0	0	0
-Infusion related reaction	1(0.6)	0	1(0.6)	3(2.8)	2(1.9)	0	0	0	0	0	0	0
Cytokine release syndrome	1(0.6)	1(0.6)	0	1(0.9)	0	0	0	0	0	0	0	0
Uveitis	1(0.6)	0	0	0	0	0	0	0	0	0	0	0
Immune-mediated/ autoimmune disorders [3]	0	0	0	0	0	0	2(3.4)	1(1.7)	0	1(1.7)	0	0
-Haemophagocytic lymphohistiocytosis	0	0	0	0	0	0	2(3.4)	1(1.7)	0	1(1.7)	0	0

Adapted from Table 8, module 5.3.5.3 90-day Safety Update Tables and Listings (STN 125773/0). Only columns with one or more reports within a grade are included in the table. NSCLC = non-small cell lung cancer; HNSCC = head and neck squamous cell cancer.

[1] SMQ (narrow and broad) of Noninfectious encephalopathy/delirium.

[2] Include PTs of infusion related reaction, anaphylactic reaction, and hypersensitivity.

[3] SMQ (narrow) of Immune-mediated/autoimmune disorders.