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EMA/263892/2025
Committee for Advanced Therapies (CAT)
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Amtagvi

International non-proprietary name: lifileucel

Procedure No. EMEA/H/C/004741/0000

Note

Assessment report as adopted by the CAT/CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Term	Definition
ACT	adoptive cell transfer; or adoptive cell therapy
AE	adverse event
AJCC	American Joint Committee on Cancer
ATMP	Advanced Therapy Medicinal Product
BRAF	proto-oncogene B-Raf
CAT	Committee for Advanced Therapies
CCL2	C-C motif chemokine ligand 2
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
COVID-19	coronavirus disease 2019
CR	complete response
CSR	clinical study report
CTLA-4	cytotoxic T lymphocyte antigen-4
CXCL	C-X-C motif chemokine ligand
DCR	disease control rate
DMSO	dimethyl sulfoxide
DOR	duration of response
EAP	Expanded Access Protocol
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOA	end-of-assessment
ESMO	European Society of Medical Oncology
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
Gen	Generation
HNSCC	head and neck squamous cell carcinoma
ICF	informed consent form
ICI	immune checkpoint inhibitor
IFN-γ	interferon gamma
IL-2	interleukin-2
IRC	Independent Review Committee
iRECIST	modified RECIST criteria for immune-based therapeutics
IV	intravenous(ly)
LAG-3	lymphocyte activation gene-3
LDH	lactate dehydrogenase
MAA	Marketing Authorisation Application
max	maximum
MEK	mitogen-activated extracellular signal-regulated kinase
min	minimum
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NMA-LD	nonmyeloablative lymphodepletion
NN	non-complete response/non-progressive disease
NR	not reached
OKT3	muromonab CD3, murine monoclonal antibody to human CD3
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death protein-1
PDCO	Paediatric Committee
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
PR	partial response

Term	Definition
Q8H	every 8 hours
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease, standard deviation
SITC	Society for Immunotherapy of Cancer
SoD	sum of diameters
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TIL	tumour-infiltrating lymphocytes
TNF-α	tumour necrosis factor alpha
TPS	tumour proportion score
ULN	upper limit of the normal range
US	United States
uSCS	Updated summary of clinical safety
USPI	United States Prescribing Information

1. CAT recommendations

Based on the review of the data on quality, safety, efficacy, the application for Amtagvi (lifileucel) in 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* is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of outstanding issues. In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of outstanding issues.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality

- GMP certificates for the proposed manufacturing sites

Clinical

- Approvability is questioned due to a lower activity than is normally accepted for a CMA in solid tumours and a negative benefit/risk
- Uncertainty related on the efficacy at lower doses and the proposed dose range to be recommended in the SmPC

1.1. Questions to be posed to additional experts

Not applicable at the moment.

1.2. Inspection issues

1.2.1. GMP inspection(s)

A request for GMP inspection has been adopted for the following sites in order to verify the GMP compliance status:

• Iovance Biotherapeutics, LLC [Iovance Cell Therapy Center (iCTC)] 300 Rouse Boulevard, Philadelphia, Pennsylvania 19112 USA

• WuXi Advanced Therapies, Inc.4000 South 26th Street, and Wuxi 400 Rouse Boulevard, Philadelphia, Pennsylvania 19112 USA

The outcome of these inspections is required for the Committee to complete its examination of the application and will be needed by Day 181.

1.2.2. GCP inspection(s)

N/A

1.3. New active substance status

Based on the review of available data on the active substance, it is considered that the active substance lifileucel contained in Amtagvi is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

2. Executive summary

2.1. Problem statement

Claimed therapeutic indication

Amtagvi is 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.

2.1.1. Disease epidemiology

Melanoma is the sixth most commonly diagnosed form of cancer in Europe after breast, colorectal, lung, prostate, and bladder cancers (Sung 2021). A worldwide total of 325 000 new melanoma cases (174 000 males, 151 000 females) and 57 000 deaths (32 000 males, 25 000 females) was estimated for 2020 (GLOBOCAN 2020). The incidence is higher in the northern (cumulative risk 3.41% across both sexes) and western (3.18%) European regions compared to the southern (1.43%) and central/eastern (1.07%) European regions. The estimated number of deaths from melanoma was 26,360 in Europe, which represents approximately 46% of the 57,043 estimated deaths worldwide in 2020 (Steininger 2021).

2.1.2. Biologic features, aetiology and pathogenesis

Melanoma is an aggressive neoplasm of skin that arises from melanocytes. Several risk factors are associated with the development of melanoma such as UV light, the patient's phenotypic features (light skin, blue eyes, red or blond hair, number of nevi) and a genetic predisposition (increased risk in patients with dysplastic nevus syndrome, with familial melanoma or familial melanoma syndromes). Melanomas can be confined to the epidermis, where they may remain for several to many years (radial or horizontal phase of growth). A metastatic potential of melanoma is "acquired" with infiltration into dermis (UpToDate).

2.1.3. Clinical presentation, stage/prognosis

Majority of melanomas are detected early, when surgical resection can be curative and might be the only treatment modality needed. About 5% of patients have distant metastases at initial diagnosis (SEER Cancer Stat Facts: Melanoma of the Skin). While in situ and locally invasive melanomas are curable by surgery, metastatic disease is difficult to treat and remains a significant public health concern (Steininger 2021).

2.1.4. Management

First-line therapy for metastatic disease includes anti-PD-1 monotherapy (nivolumab or pembrolizumab) or the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) or relatlimab (anti-LAG-3) as well as therapies targeting driver mutations in the BRAF pathway for tumours with these mutations (Keilholz 2020; Dummer 2015; Tawbi 2022). Limited treatment options are available for patients who have progressed on ICI and target therapies if BRAF mutated. European Society of Medical Oncology (ESMO) treatment guidelines for metastatic melanoma caution that anti-PD-1 therapy rechallenge as monotherapy or in combination results in short lived responses or limited efficacy and do not offer any guidance on any treatment options (eg, chemotherapy) beyond targeted therapy and ICIs (Keilholz 2020). The ESMO guidelines recommend considering re-challenge with drugs that showed prior clinical activity after all alternative agents have been explored.

Table 1 **Response Rates of EMA-approved Melanoma Therapies in Previously ICI-treated Unresectable or Metastatic Melanoma Patients**

Therapy	Patient Population	Response Rates (Range)	Study Type	Comment
Cytotoxic Chemotherapy				
Dacarbazine	PD-1 exposed patients receiving dacarbazine (N=118)	10.2%	Retrospective	(Goldinger 2022)
Investigator choice agents	Second-line therapy in metastatic melanoma where chemotherapy was the control arm N=179 (Hamid) N=133 (Weber)	4% to 11%	Randomized prospective trials (KEYNOTE 002; CheckMate 037)	(Weber 2015; Hamid 2017)
PD-1 Blocking Antibody Monotherapy Retreatment after Progression				
PD-1 monotherapy after progression on a PD-1 blocking antibody	Compilation of PD-1 rechallenge case series (N=85); US single centre series (N=34)	15 to 16%	Retrospective series compilation	(Betof Warner 2020; Reschke 2020)
Ipilimumab Monotherapy / Ipilimumab + PD-1 Blocking Antibody Combination				
Ipilimumab monotherapy after pembrolizumab	Follow up of the KEYNOTE 006 trial (N=97)	4% to 14%	Prospectively enrolled	(Long 2017)
Ipilimumab + a PD-1 blocking antibody after progression on a PD-1 blocking antibody	N=70 (Olson) N=70 (Vanderwalde) N=37 (Zimmer) N=19 (Gaughan)	11% to 28%	Combination of prospective and retrospective studies	RECIST criteria not used; investigator-assessed responses; significant heterogeneity in inclusion criteria (Gaughan 2017; Zimmer 2017; Olson 2021; Vanderwalde 2022)
Ipilimumab after first line a PD-1 blocking antibody	N=116	8%	Real world evidence	(Cybulska-Stopa 2020)
Relatlimab + Nivolumab Combination				
Relatlimab/nivolumab combination after progression on a PD-1 blocking antibody	N=43; efficacy reported in 31 patients	16%	Prospective trial	(Ascierto 2017)

Abbreviations: EMA = European Medicines Agency; ICI = immune checkpoint inhibitor; PD-1 = programmed cell death protein-1; RECIST = Response Evaluation Criteria in Solid Tumors

Unmet medical need

A recently published European consensus-based interdisciplinary guideline for melanoma indicates that patients who do not respond to PD-1-based immunotherapy have very limited therapeutic options available and recommends clinical trials as the best option in this setting (Garbe 2022). This guideline also states that chemotherapy should be considered as the last-line treatment in patients with resistance to immunotherapies and, when applicable, targeted therapies, when participation in a clinical trial is not available due to the poor effectiveness. Subsequent therapies demonstrate a low activity and therefore there is an unmet medical need for this condition in patients who have progressed on or after standard therapies.

2.2. About the product

Lifileucel [autologous tumor infiltrating lymphocytes; Amtagvi] is a preparation of autologous, non-genetically modified tumor infiltrating lymphocytes (TIL). Tumour infiltrating lymphocytes (TIL) are cytotoxic and helper T cells that infiltrate tumours as a component of the immunological response to a patient's cancer. TIL migrate to tumour sites, in which they recognise and target a multitude of individualised, tumour specific neoantigens. Tumour neoantigens are mutated antigens, presented by human leukocyte antigen (HLA) on the surface of the tumour. TIL recognise the tumour-specific neoantigens via T-Cell receptor (TCR)-peptide human leukocyte antigen (pHLA) engagement. The TCR-pHLA interaction induces T cell activation and T cell-mediated tumour killing via secretion of cytokines and cytolytic enzymes, which form pores and disrupt the integrity of the tumour cell membrane and mediate tumour cell lysis.

2.3. The development programme/compliance with guidance/scientific advice

TIL therapy with lifileucel has been administered to adult patients with solid tumours in 5 Phase 2 and 1 Phase 3 Iovance sponsored studies:

- C-144-01 melanoma
- C-145-03 head and neck squamous cell carcinoma (HNSCC)
- C-145-04 cervical carcinoma
- IOV-COM-202 solid tumours
- IOV-LUN-202 non-small cell lung cancer
- **IOV-MEL-301 Phase 3 melanoma**

Currently, Studies C-144-01 (melanoma, the study that forms the basis of the clinical section of this MAA) and C-145-03 (HNSCC) are closed to the enrolment of new patients. An Expanded Access Protocol (EAP) was conducted in the US for the treatment of unresectable or metastatic melanoma. data from the EAP are not included in this submission.

Summary of received Scientific advices and pre-submission meeting

Procedure name and number	Summary
Scientific advice	The applicant sought advice on quality, nonclinical, and clinical aspects. Guidance was sought on the classification of starting materials, raw materials and excipients, release specifications, adequacy of functional and phenotypic assays in the assignment of identity and potency for Lifileucel, as well as the characterisation of impurities. As regard the non-clinical part, the applicant proposed to omit the preclinical pharmacology or toxicology studies for registration and rely instead on integrated review and summary of literature relevant to the mechanism of action and safety of TIL therapies: this was deemed overall acceptable while at the same time noting that in vitro PoC is expected for marketing authorisation. Key responses to clinical aspect: • the CHMP agreed that there is an unmet need in the sought indication, but expressed reservations regarding a CMA given in particular the limited size of the C-144-01 cohorts 2 and 4 (n=141 planned and 156 recruited), the absence of details regarding the differences of the cohorts at that time, as well as the multiple amendments which may impact the contextualisation of results, also considering the evolving melanoma landscape.
Pre-submission meeting	The discussion pertained to the following clinical and quality aspects:

	• Potential for submission of MAA for Conditional Marketing Authorisation, which was agreed by the Rapporteur team. This statement should not be considered as a pre-assessment of the data/application for approval.

2.4. General comments on compliance with GMP, GLP, GCP

GMP aspects

The EMA has reviewed the manufacturer information contained in the application form (Module 1) and available from the EEA National Competent Authorities and determined that all relevant sites have valid manufacturing authorisations or valid GMP certificates as appropriate, with the exception of: Iovance Biotherapeutics, LLC [Iovance Cell Therapy Center (iCTC)] 300 Rouse Boulevard, Philadelphia, Pennsylvania 19112 USA and WuXi Advanced Therapies, Inc. 4000 South 26th Street, Philadelphia, Pennsylvania 19112 USA for which an inspection will be recommended to the CAT/CHMP.

The sites where batch control testing is performed are the following, according to the flowchart (annex 5.8):

- Iovance Biotherapeutics, LLC [Iovance Cell Therapy Center (iCTC)], 300 Rouse Boulevard, Philadelphia, Pennsylvania 19112 USA
- WuXi Advanced Therapies, Inc. 400 Rouse Boulevard Philadelphia, Pennsylvania 19112 USA
- Eurofins Lancaster Laboratories, Inc. 2425 New Holland Pike, Lancaster, Pennsylvania 17601 USA

Furthermore, it is observed that the sites in charge of the batch control testing are located in the USA. It is noted that, as this is an ATMP, this product falls outside the MRA, hence the use of EEA batch testing site(s) is required (unless exemption is accepted during the evaluation phase). It is noted for trail purposes that the acceptability of the exemption provided by the applicant would be reviewed during the evaluation phase and granted if the case be.

GCP aspects

The applicant indicated that the pivotal study was performed in compliance with GCP, including the archiving of essential documents.

The applicant included the information regarding GCP compliance of the pivotal study(ies).

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. PRIME

Not applicable.

2.5.3. Accelerated assessment

The CHMP did not agree to the applicant’s request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on results from lifileucel in the

intended setting show slightly improved efficacy (in terms of ORR in patients that were treated) in a crude side-by-side comparison to existing therapies, and could potentially fulfil an unmet medical need in these patients. The safety profile is noted and needs careful and thorough assessment. Importantly, however, whether the magnitude of ORR in a selected patient group that went on to receive Amtagvi is large enough to warrant early access despite non-comprehensive data remains to be further evaluated. Thus, accelerated assessment is not presently considered sufficiently justified.

2.5.4. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data. In addition to providing results from 156 patients infused with Lifileucel in the study C-144-01, the applicant proposes collection of comprehensive data post-authorization from a Phase 3 Study IOV-MEL-301 (TILVANCE-301). Study IOV-MEL-301 (TILVANCE-301): The Phase 3 study evaluating lifileucel in combination with pembrolizumab for use in previously untreated unresectable or metastatic melanoma be utilized to confirm the clinical benefit. The proposed post approval confirmatory study for the conditional MAA, Study IOV-MEL-301 (TILVANCE-301), will serve to understand more fully describe the benefits of lifileucel in the treatment of advanced melanoma. The proposed Phase 3 confirmatory study is being conducted in an earlier line of treatment than the requested CMA and evaluating lifileucel in combination with pembrolizumab, therefore the CMA of lifileucel in a later line of treatment is unlikely to impact the conduct and completion of the Phase 3 study. Finally, there is precedence in the EU for conducting a study in an earlier line of treatment and in combination with the current standard of care to confirm the clinical benefit [selpercatinib, RETSEVMO®, Eli Lilly and Company].
  Estimated timing of the analyses:
  1) Interim Analysis #2 for progression-free survival (PFS) in 3Q2028;
  2) Final Analysis for overall survival (OS; key secondary endpoint) in 1Q2030;
  3) Final Study Report Date: 31 Mar 2031

- Unmet medical needs will be addressed. A recently published European consensus-based interdisciplinary guideline for melanoma by Garbe and colleagues indicates that patients who do not respond to PD-1-based immunotherapy have very limited therapeutic options available and recommends clinical trials as the best option in this setting (Garbe 2022). This guideline also states that chemotherapy should be considered as the last-line treatment in patients with resistance to immunotherapies and, when applicable, targeted therapies, when participation in a clinical trial is not available due to the poor effectiveness. European Society of Medical Oncology (ESMO) treatment guidelines for metastatic melanoma also caution that anti-PD-1 therapy rechallenge as monotherapy or in combination results in short lived responses or limited efficacy and do not offer any guidance on any treatment options (eg, chemotherapy) beyond targeted therapy and ICIs (Keilholz 2020). The ESMO guidelines recommend considering rechallenge with drugs that showed prior clinical activity after all alternative agents have been explored. Remaining available treatment options in the European Union (EU) are currently limited to dacarbazine (which is authorised in several EU member states but not all and is listed as a palliative or bridging therapy in the ESMO guidelines) and clinical trials or best supportive care. Data on response rates to EMA-approved agents that have been explored in the second line after progression on PD-1 blocking therapy are limited and derived from

control arms of prospective randomized studies, smaller retrospective case series or meta-analyses of such data, real world evidence, or limited numbers of prospectively treated patients with investigator-assessed responses. There are several caveats with the latter, including the response criteria used (Response Evaluation Criteria in Solid Tumors [RECIST] or the modified RECIST for immunebased therapeutics [iRECIST] criteria) and inclusion of only CTLA-4 naïve patients. Another caveat is the inclusion of a significant proportion of patients progressing after PD-1 exposure in the adjuvant setting alone (eg, Olson 2021; Vanderwalde 2022). Lifileucel is a one-time first-in-class treatment option with a novel mechanism of action that is distinct from immune checkpoint blockade. The toxicity profile and time course of adverse events (AEs) of the lifileucel regimen are also different from those of ICIs. Of note, the AEs following the preparative lymphodepleting regimen are consistent with AEs from a single administration of this chemotherapy regimen. Patients treated with chemotherapy, either as a monotherapy or in combination, would receive repeated chemotherapy cycles and would experience many of the same AEs as those observed in Study C-144-01 following lymphodepletion but would derive lower ORR and shorter DOR.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required, as there are limited treatment options for the indicated population. This is supported by the lifileucel attributes such as an important therapeutic differentiation due to the novel mechanism of action, personalized medicine approach that employs manufacturing from patient's own melanoma tumour tissue, and a one-time treatment with antitumor activity demonstrated in later lines of therapy where patients have failed multiple prior therapies and hence supports a conditional marketing authorisation.

2.5.5. New active substance status

The applicant requested the active substance lifileucel contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

2.5.6. Orphan designation

Not applicable.

2.5.7. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products as there are no authorised orphan medicinal products for a condition related to the proposed indication.

2.5.8. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0440/2023 on the agreement of a paediatric investigation plan (PIP) and the granting of a partial waiver.

At the time of submission of the application, the PIP P/0440/2023 was not yet completed as some measures were deferred.

The PDCO agreed the PIP (EMEA-002776-PIP01-20) for autologous tumour-infiltrating lymphocytes (LN-144/LN-145) for the treatment of all conditions included in the category of malignant neoplasms

(except haematopoietic and lymphoid tissue neoplasms) in December 2020. The proposed broad condition covers the planned indication for the treatment of melanoma in adults.

A waiver was also granted for the paediatric population weighing less than 8 kg based on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible.

The targeted indication in the PIP is treatment of paediatric patients with a relapsed or refractory solid tumour for which no effective therapy is known.

Since the time of its initial agreement the PIP was modified twice. Both were minor modifications concerning the study timelines of one non-clinical study.

The current agreed PIP includes the following studies:

Study 1

In vitro study to assess the feasibility of producing tumour infiltrating lymphocytes (TIL) from paediatric tumour samples using the same process used to manufacture TIL products from tumour tissue from adults to characterise the phenotype of paediatric TIL (TP-19-028); already completed and checked for compliance (EMEA-C2-002776-PIP01-20-M02).

Study 2

Multi-centre, open-label, single-arm study to evaluate the safety and tolerability and anti-tumour activity of autologous tumour-infiltrating lymphocytes (LN-144/LN-145) in paediatric patients from 8 kg of body weight and less than 18 years of age (and adults) with a relapsed or refractory solid malignant tumour for which no effective therapy is available (IOV-PED-101); deferred and planned to be completed by July 2026.

Study 3

Multi-centre, open-label, single-arm study to evaluate the safety and tolerability and anti-tumour activity of autologous tumour-infiltrating lymphocytes (LN-144/LN-145) in paediatric patients from 8 kg of body weight and less than 18 years of age (and adults) with a solid malignant tumour selected based on the results of study IOV-PED-101 (IOV-PED-201); deferred and planned to be completed by 2031.

3. Scientific overview and discussion

3.1. Quality aspects

Introduction

Lifileucel finished product (FP) is supplied as a cell suspension for intravenous infusion formulated in cryopreservation medium suitable for infusion. One dose of lifileucel consists of 1.8×10^9 to 100×10^9 total viable cells in a total volume of 100-400 mL filled into 1 to 4 CE marked cryogenic bags.

3.1.1. Active substance

3.1.1.1. General information

Lifileucel is a live cell suspension comprised of tumor-infiltrating lymphocytes (TIL) cultured with OKT3 (anti-CD3 antibody), interleukin-2, and allogeneic irradiated peripheral blood mononuclear cells (iPBMC). The active substance (AS) is composed of viable TIL derived from a patient's own resected

tumor(s) and is primarily comprised of T cells of the CD4+ and CD8+ lineages, that are predominantly effector memory (Tem) and central memory (Tcm) subtypes.

3.1.1.2. Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Lifileucel is manufactured in a continuous process that begins with receipt of the resected tumor at the manufacturing facility and ends with the formulation and cryopreservation of the expanded cells. The manufacturing process is described and a process flow table and a diagram of the manufacturing process are provided. The main manufacturing steps are: Tumor Processing and TIL Migration; Stimulation and Initial Expansion; and Expansion, Formulation and Cryopreservation. Tables showing relevant control prameters for each step are provided.

Control of critical steps and intermediates

The applicant has implemented in-process controls (IPC) for controlling the manufacturing process. They were established using a risk-based approach. Responses to excursions outside of IPC limits are managed through Quality System and includes deviations, and corrective and preventive actions (CAPAs).

Process Validation and/or Evaluation

The process validation lifecycle approach consists of three stages: Process Design, Process Performance Qualification (PPQ) and Continued Process Verification (CPV).

Process Performance Qualification studies were completed at each of the two intended commercial manufacturing facilities. For PPQ validation, critical process parameters, in-process controls, and critical quality attributes, were monitored and evaluated to demonstrate process consistency and support the process control strategy.

The applicant indicates that a CPV program has been established to ensure that the commercial manufacturing process remains in a state of control during commercial production. The program includes periodic assessment of process variables including selected process parameters, in-process controls, and final product CQA results. However, no descriptions of the different elements of the CPV program have been provided. The applicant was asked to detail the CPV strategy in the dossier and to provide annual CPV updates for the first three years. In the response, the applicant has described the planned continuous process verification (CPV) program and commits to submitting annual CPV updates for the first 3 years post-approval. However, this information has not been included in the corresponding section of the dossier and should be included**.**

The Aseptic Process Validation (APV) at each of the two manufacturing sites and the results of the Shipping Validation are included in the dossier and are considered adequate.

Process Validation and/or Evaluation

Several PPQ batches were manufactured as part of PPQ and provided complete end-to-end process validation.

Critical process parameters (CPPs), in-process controls (IPCs), and final finished product release results were monitored and evaluated during the manufacture of these batches. The results of the CPPs, which were within the NOR and PAR, and of the IPCs are presented. Validation of the manufacturing process has been performed at the two sites proposed for manufacture of the commercial product. pre-REP TIL and vendor sourced tumors were used as starting material for the manufacture of PPQ batches. For Validation, Critical process parameters (CPPs), in-process controls

(IPCs), and final finished product release results were monitored and evaluated during the manufacture of PPQ batches. The results of the CPPs, which were within the NOR and PAR, and of the IPCs are presented. The data supports the consistency of the manufacturing process in the two manufacturing sites, although some CPP and IPC data are missing, and some acceptance criteria should be clarified. The applicant provides this information including the results for all IPCs that were listed in the "Control of critical steps and intermediates" section for all PPQ batches. The available data of these additional IPCs were provided in the response but the information have not been included in the corresponding section of the dossier and should be included.

For all batches, both those derived from cryopreserved pre-REP TIL and those derived from vendor-sourced tumor tissue, data from the analysis of PPQ Final Product Release are provided. Both set of batches meet the established specifications, which include those tests currently tested for release, and additional specifications related to the T cell populations contained in the product.

Process Validation and/or Evaluation

Several PPQ batches were manufactured as part of PPQ. Some batches were manufactured with cryopreserved pre-REP TIL as the starting material and some batches were manufactured utilizing vendor sourced and extended access program (EAP) tumors as the starting material to provide complete end-to-end process validation.

Critical process parameters (CPPs), in-process controls (IPCs), and final finished product release results were monitored and evaluated during the manufacture of these batches. As for the validation the data obtained supports the consistency of the manufacturing process but some information concerning CPP and IPC was missed. The applicant has provided this information in the response, but it should also be included in the dossier**.**

There are two manufacturing suites in use at one site. The applicant confirms that both suites were used to manufacture the PPQ batches. This is considered acceptable to justify that the PQQ batches are representative of both suites. Section 3.S.2.5 has been updated with this information.

Manufacturing process development

This process for manufacture of TIL was used as a basis for development of the Gen 1 manufacturing process, which was used to manufacture lifileucel to initiate clinical studies.

The Gen 1 manufacturing process was developed and transferred for manufacture of initial clinical supply (Cohort 1). Data from Cohort 1 are not included in this filing as the data are not registrational nor supportive.

The Gen 2 manufacturing process was developed and the finished product formulation includes a cryopreservation medium to enable product storage at < -150°C (vapor phase of liquid nitrogen, LN2).

The history of the manufacturing process development, process characterisation studies, process control strategy, process comparability and ancillary characterisation studies are described in the dossier.

The manufacturing process development and characterisation studies consisted in the following steps: Quality Target Product Profile (QTPP); Process Parameter Risk Assessment and Classification; Process Development and Characterization by Operational Stage; Post-Process Characterization Parameter Classification.

Quality Target Product Profile (QTPP): For the CQA assessment, a list of relevant product quality attributes that may have potential impact on product quality was assembled. The list consisted of product related attributes and process related attributes. In addition, phenotypic attributes were also assessed as potential CQAs for potency and identity.

Process Parameter Risk Assessment and Classification: Process parameters were classified depending on their impact to the designated product CQAs. Classification of the parameters were determined based on the impact observed in clinical manufacturing and PPQ, targeted studies performed during process charactersation, and generally accepted parameters for T cell culture.

Process Development and Characterisation by Operational Stage: The manufacturing process for lifileucel is a continuous process and there are no hold steps between tumor processing at the manufacturing site, cell expansion, finished product (FP) formulation, and cryopreservation. The finished product (FP) is produced in a 12-stage process, which include: 1) Tumor Resection; 2) Tumor Shipment, Receipt, and Storage; 3) Tumor Wash and Fragmentation; 4) TIL Migration-Pre-REP; 5) Stimulation and Expansion–REP (Part 1 of 2); 6) Expansion Scale-Out– REP (Part 2 of 2); 7) Concentration and Washing; 8) Formulation and Filling; 9) Visual Inspection and Labeling; 10) Cryopreservation and Storage; 11) Transportation to the Administration Site; 12) finished product Thaw and Administration.

Process characterisation was accomplished by 1) performing process risk and critical quality attributes impact assessments, 2) analysing manufacturing process data, 3) performing process characterization studies, and 4) evaluating the criticality of process parameters and ranges in order to define the process control strategy. Characterisation studies were performed.

The control strategy was developed based on historical knowledge gained through product development, process development, process characterisation and historical manufacturing experience through the course of clinical development. Furthermore, the process control strategy was assessed for robustness through the performance of process performance qualification (PPQ) studies.

Established targets and ranges are based on manufacturing experience and process characterisation studies.

The proven acceptable ranges (PARs) of CPPs are either statistically justified, based on process characterisation studies, or generally accepted scientific data.

During process development and characterisation, the effect of process parameters on product quality attributes was assessed and appropriate operational and in-process controls (IPC) were established.

Small-scale models were used as part of the lifileucel process development and characterization studies. A scale comparison assessment was performed to determine whether the small-scale model was comparable to the proposed commercial scale manufacturing process and is concluded that the down-scale model provides a linear comparability to the full-scale model for the Gen 2 process.

The information presented by the applicant regarding the development of the manufacturing process control strategy is considered adequate and, in general, the conclusions reached are supported with a point to be further investigated.

In addition, a summary of root cause analysis of OOS batches manufactured, as well as CAPA identified was missing. The applicant has now provided summaries of the root cause analyses, corrective actions and information on the actual hold times as requested. In brief, processing time was not deemed as the cause for the OOS results. The response is considered acceptable.

The applicant was also requested to justify the use of IL-2 in the final formulation. The response indicated that IL-2 is maintained in the final formulation for theoretical reasons, and even though no benefit of IL-2 was demonstrated in process development studies, the issue is not further pursued.

Manufacturing process development – comparability

Comparability between the different manufacturing sites has been performed and several studies are included in the dossier.

Comparability studies were performed in accordance with the International Council for Harmonisation (ICH) Q5E guidelines and European Medicines Agency (EMA) Q&A on Comparability considerations for ATMP (2019).

The comparability assessment included selected in-process parameters, the final finished product specifications, product characterisation attributes, and stability.

A combination of statistical and visual assessment methods was used to compare samples manufactured at any 2 facilities. The data presented showed comparability between manufacturing sites, although some differences are observed. Despite these differences falling within the acceptance criteria for comparability, the applicant was requested to further provide a justification. The applicant has presented the justification for the differences detected and the issue was considered resolved.

The applicant has provided additional justifications and clarifications for some issues that were unresolved but there are still some questions that need additional clarification.

Control of materials

Raw, starting materials are listed, media and buffer composition are provided too. Raw materials are described including several materials from animal or human origin employed in AS and FP manufacture. The information provided is comprehensive and complete.

Starting materials are autologous tumour tissue and allogenic iPBMC derived from blood donations collected at authorized centres in the EU. Both materials are collected in compliance with requirements of Directive 2006/17/EC. iPBMC cells are subsequently isolated, irradiated and transferred. In general, the information provided regarding the manufacture, control, storage and transport of the starting materials is adequate but some clarifications are issued.

Characterisation

Lifileucel is an autologous live cell suspension consisting of tumor-infiltrating lymphocytes (TILs) derived from patient´s resected tumor samples, which have been cultured and expanded with OKT3, IL-2 and irradiated allogeneic feeder cells.

The proposed MoA is through tumor neoantigen recognition via TCR-pHLA engagement, which activates a tumoricidal response resulting in production of cytokines, such as IFN-γ.
Characterisation of the product has been focused to determine A) cellular composition and phenotype and B) biological activity/mechanism of action (MoA).

A) <u>Cellular Composition</u>

FP lots from two cohorts (cohort 2 and cohort 4) from clinical study C-144-01 have been used to determine the cellular composition of lifileucel.

The phenotypic markers used to define the cellular composition of lifileucel FP lots were selected by a three-tiered comprehensive risk and criticality assessment of phenotypic attributes, based on 1) alterations in phenotypic expression over the course of the manufacturing process, 2) analyses of phenotypic attributes in over 140 historical C-144-01 FP lots and 3) scientific literature.

Based on the analyses performed, the attributes selected for characterisation of the cellular composition and phenotype for lifileucel are considered adequate.

B) <u>Biological activity</u>

The applicant has developed two assays to characterise the biological activity of lifileucel. Some additional data was requested concerning the proposed potency assays.

Impurities

Product- and process-related impurities have been identified and characterised for lifileucel.

- Product-related impurities include residual cell populations that may remain in the FP after the expansion. The % of these residual cell populations were tested and found to be low (<1% as median value for each cell type).

For residual tumor cells, a quantification and a risk assessment were performed. Quantification was performed. The applicant presented characterisation data demonstrating that are effectively eliminated early in the manufacturing process.
The risk assessment included the following data: 1) culturing conditions, which may survive but not proliferate, 2) reported studies demonstrating that circulating tumor cells can unlikely induce metastatic lesions, as they may die due to hemodynamic forces or nutrient starvation in the peripheral circulation and 3) frequent monitoring of patients for the formation of new lesions.
Based on the low levels and the autologous origin of the cells, it is not anticipated that residual product-related impurities would pose a risk to patient safety, which is endorsed.
Residual cells are quantified at FP release.

- Process-related impurities include reagents used during production. When possible, the theoretical residual amounts of the reagents were determined based on the capability of removal by the manufacturing process, representing the potential worst-case residual amounts per dose of FP.
Residual process-related impurities were measured in FP batches.
Based on the low levels of process-related impurities found in the FP lots tested and based on the theoretical calculation of removal by the washes carried out during product manufacturing, process-related impurities are not tested at FP released, which is acceptable.

3.1.1.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

Since manufacture of lifileucel is a continuous process, cross-reference is made to Finished Product.

3.1.1.4. Stability

Since manufacture of lifileucel is a continuous process, cross-reference is made to Finished Product.

3.1.2. Finished Medicinal Product

3.1.2.1. Description of the product and pharmaceutical development

Lifileucel finished product (FP) is supplied as a cell suspension for intravenous infusion formulated in cryopreservation medium suitable for infusion. One dose of lifileucel consists of 1.8×10^9 to 100×10^9 total viable cells in a total volume of 100-400 mL filled into 1 to 4 CE marked cryogenic bags. The FP requires no diluents nor vehicles for clinical administration.

The components of the finished product are described. The intended commercial formulation was developed to enable cryopreservation of the finished product. The suitability of the container closure system was evaluated as part of the FP stability studies, and extractables and simulated leachables studies were performed, concluding that the risks from leachable- related toxicities are negligible.

A compatibility assessment was conducted, and the lifileucel FP was found to be compatible with saline from three suppliers and blood filter set at the recommended infusion rate.

3.1.2.2. Manufacture of the product and process controls

The manufacturers are listed in Section 3.2.P.3.1. A valid proof of GMP compliance has been provided for all sites.

The applicant has requested an exemption from the requirements for re-testing lifileucel upon importation into the EU Member State, according to Directive 2001/83/EC. Based on the autologous nature of the product and the limited amount of material, the request on the exemption for re-testing is considered acceptable.

For the description of the manufacturing process and process controls, controls of critical steps and intermediates, and process validation, cross-reference is made to 3.2.S.2.

Control of excipients

Each excipient lot is subject to review of the supplier's CoA, inspection, sampling, testing, and dispositioned in accordance with written procedures. Testing includes identity, sterility and bacterial endotoxin tests, at minimum. Additional testing may be performed as specified in the internal excipient specification.
Release specifications are presented for all excipients and are appropriately justified.
CoA are provided for all excipients used to formulate lifileucel; all results are within specifications acceptance criteria.

IL-2 is added in the final formulation to support the survival and expansion of TILs after *in vivo* transfer. The recombinant IL-2 product has been authorised in several EU states for the treatment of metastatic renal cell carcinoma. The applicant is the current marketing authorisation holder of aldesleukin in EU member states. A summary of the general information, manufacturers, description of manufacturing process, control of materials, process validation, characterisation, impurity testing, stability conclusion, and viral safety assessment in alignment with the approved procedure for Proleukin is provided in the dossier.
Certificates/statements have been provided to confirm the safety of the raw materials and compliance with EMEA/410/01 rev.3.

The applicant states that no novel excipients have been used during manufacture of lifileucel.

3.1.2.3. Product specification, analytical procedures, batch analysis

Specification

Specifications for the FP include testing of identity by different phenotypic markers, purity and impurities, potency, general tests (appearance, container integrity) and safety (endotoxin, mycoplasma and sterility). Although the inclusion of these quality attributes is considered adequate, some tests should be revised.

The applicant was requested to discuss/justify and tighten some acceptance limits.

Information on the sampling scheme should be included in the specification table for some tests.

The applicant has further described the method used for potency testing of lifileucel. Additional data was requested.

Analytical procedures

Release testing is performed both at intended commercial facilities. All the release tests are conducted at both sites, with some exceptions. Analytical procedures are described in sufficient detail; equipment and reagents used for each method are detailed, and procedures for sample processing are defined. For analytical methods that were validated at one site and later transferred to the additional testing site, validation to support technical transfer was conducted.

Validation of analytical procedures

Validation of analytical procedures is considered to be overall in accordance with ICH Q2. However, some additional information was missing and was requested.

Batch analysis

Batch analysis data is provided for FP lots used in Study C-144-01 (Cohort 2 and Cohort 4), as well as for PPQ batches and clinical batches manufactured; the results obtained for all the release tests listed in the specifications have been included.

Characterisation of impurities

The applicant has provided a risk assessment for the potential of nitrosamine presence in the lifileucel finished product, as Per EMA/369136/2020, the Procedure under Article 5(3) of Regulation EC (No) 729/2004, nitrosamine impurities in human medicinal products.

Justification of specification

The specification acceptance criteria are based on the statistical analysis of the FP batches from C-144-01 Cohort 2 and Cohort 4, PPQ batches, EAP batches manufactured after the C-144-01 study, and commercial batches manufactured through 31 December 2024. Overall, the rationale for establishing most of the acceptance criteria is considered appropriate, since compendial requirements and results obtained for clinical batches (minimum, maximum and average values) have been taken into consideration. Associations of CQAs with clinical endpoints were found, therefore justifying their inclusion in specifications panel, but these attributes are not considered as predictive of clinical response.

Container-closure system

Lifileucel FP is filled in CE marked (Class IIa) cryopreservation bags. Components in contact with the product are CE marked and fulfil the USP Class VI requirements.

3.1.2.4. Stability of the product

Several PPQ batches, representative of the intended commercial manufacturing process were placed in long-term stability studies. Testing frequency used in the long-term stability studies is not compliant with ICH Q5C *"Stability Testing of Biotechnological/Biological Products"*. In particular, two time-points have been skipped, and testing at an additional time point was greatly reduced and performed using a container-closure system not representative of the intended commercial container-closure system *(Cryobags)*. However, data concerning the equivalence of both container-closure systems used during the stability studies has been provided**.**

The analytical methods employed in the stability study have been shown to be stability indicating in a forced-degradation study at 37 +/- 2°C, and their acceptance criteria were the same used at batch release. Validation of analytical methods used during the stability studies was performed using qualified analytical methods.

The results from the long-term stability study showed no meaningful degradation when FP material was stored up at the proposed shelf-life at the recommended storage conditions. Despite this, slight degradation tendencies for potency are noted as time progressed even though the acceptance criteria were met for all batches at all time-points.

In addition, an in-use stability study of thawed finished product has also been performed. Based on this data, the proposed stability shelf-life is considered acceptable**.**

No post-approval stability studies are planned.

3.1.2.5. Post approval change management protocol(s)

N/A

3.1.2.6. Adventitious agents

Control of mycoplasma, bacteria and fungi

Environmental monitoring of manufacturing suites and personnel is performed in compliance with the European Union Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Non-biological raw materials and components are certified as sterile by their vendors. In addition, aseptic process manufacturing has been initially validated through three consecutive successful runs and will continue to be executed at least biannually at each manufacturing facility.

TSE compliance

Several materials derived from material from human/animal origin, aside of the starting autologous tumor material and allogenic iPBMC feeder cells, are employed during AS and FP manufacture. Compliance of these materials with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated.

In addition, other recombinant materials of biological origin not derived from human/animal material are also employed in the manufacturing process. These are proleukin and recombinant IL-2.

Virus safety

As the final finished product is composed of living cells that must remain functional for their intended therapeutic effect the final product may not be exposed to heat, chemicals, or sterilized by filtration. In consequence, viral safety is ensured through adequate control of starting and raw materials, demonstration of aseptic manufacturing, and release testing of the final FP.

An assessment of viral safety risk has been performed in accordance with EU guideline EMEA/CHMP/BWP/39648/2005. Testing for adventitious viral contaminants is performed for all materials of direct animal/human origin in compliance with applicable regulations. For human derived components, all collection facilities screen their patients in accordance with EU Directive 2006/17/EC Annex I or II, as applicable. This includes prospective testing for anti-HIV ½, HBVsAg, anti-HBVc, anti-HCV and anti-treponema pallidum. In addition, and based on the nature of the DP (T-lymphocytes), testing for HTTLV ½ virus is recommended when applicable. Testing for other specific human viral contaminants such as HAV, West-nile virus, and parvovirus B19 is also included for relevant materials. The maintenance of traceability from donation/donor to the finished product is confirmed for all human-derived components.

3.1.2.7. GMO

N/A

3.1.3. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Manufacture

Lifileucel is manufactured in a continuous process that begins with receipt of the resected tumor at the manufacturing facility and ends with the formulation and cryopreservation of the expanded cells. The applicant has implemented in-process controls (IPC) for controlling the manufacturing process but it was not clear the criteria for the decision to terminate the batch when an action limit is not met. The applicant has clarified this issue, however this information was not included in the dossier. The applicant is requested to include it in the corresponding section.

The process validation lifecycle approach and strategy has been described and explained. Validation of the manufacturing process has been performed at the two sites proposed for manufacture of the commercial product. The data supports the consistency of the manufacturing process in the two manufacturing sites, although some data was initially missing. The applicant has provided this information and is now requested to include this information in the dossier.

In addition, the applicant confirms that PPQ batches are representative of the two suites where the manufacturing is taking place.

Information on the manufacturing process development and characterisation studies was provided. The information presented by the applicant regarding the development of the manufacturing process control strategy is considered adequate and the conclusions reached are supported.

Comparability between the current manufacturing sites and between the sites involved in the manufacture of clinical batches was performed and several studies are included in the dossier. Comparability studies were performed in accordance with the International Council for Harmonisation (ICH) Q5E guidelines and European Medicines Agency (EMA) Q&A on Comparability considerations for ATMP (2019). The comparability assessment included selected in-process parameters, the final finished product specifications, product characterisation attributes, and stability. A combination of statistical and visual assessment methods was used to compare samples manufactured at any 2 facilities.

The data presented showed comparability between manufacturing sites, although some differences are observed. Despite these differences falling within the acceptance criteria for comparability, the applicant was requested to further provide a justification. The applicant has provided additional clarifications for some issues that were unresolved but there are still some questions that need additional explanation.

Control of materials

Raw materials are described including several materials from animal or human origin employed in AS and FP manufacture. The information provided is comprehensive and complete.

Starting materials are autologous tumour tissue and allogenic iPBMC derived from blood donations collected at authorized centres in the EU. Both materials are collected in compliance with requirements of Directive 2006/17/EC. iPBMC cells are subsequently isolated, irradiated and transferred. In general, the information provided regarding the manufacture, control, storage and transport of the starting materials is adequate but some clarifications are issued.

Characterisation and impurities

Lifileucel is an autologous live cell suspension consisting of tumor-infiltrating lymphocytes (TILs) derived from patient´s resected tumor samples, which have been cultured and expanded with OKT3, IL-2 and irradiated allogeneic feeder cells.

The proposed MoA is through tumor neoantigen recognition via TCR-pHLA engagement, which activates a tumoricidal response resulting in production of cytokines, such as IFN-γ.

Characterisation of the product has been focused to determine its cellular composition and phenotype and its biological activity. Product- and process-related impurities have been identified and characterised for lifileucel. The information provided is acceptable, but some questions are raised regarding the content of several cellular impurities in the finished product.

Finished product

Lifileucel FP is supplied as a cell suspension for intravenous infusion formulated in cryopreservation medium suitable for infusion. One dose of lifileucel consists of 1.8×10^9 to 100×10^9 total viable cells in a total volume of 100-400 mL filled into 1 to 4 CE marked cryogenic bags.

The composition of the FP is adequately described. The suitability of the container closure system was evaluated as part of the FP stability studies, and extractables and simulated leachables studies were performed; information is requested on the elements that were evaluated as part of these studies. Container closure integrity was also assessed, but this test is not included in the stability testing protocol. The compatibility assessment is considered overall appropriate, although clarification is requested on the FP material used for these studies.

The manufacturers are listed in Section P.3.1. A pre-approval GMP inspection to two sites was recommended by the EMA. A valid proof of GMP compliance has been provided for all sites.

The applicant has requested an exemption from the requirements for re-testing lifileucel upon importation into the EU Member State, according to Directive 2001/83/EC. Based on the autologous nature of the product and the limited amount of material, the request on the exemption for re-testing is considered acceptable.

Control of finished product

The quality attributes included in the specifications' panel are overall considered appropriate for the quality control of the FP, but some acceptance criteria should be revised.

Analytical procedures are overall described in sufficient detail, and validation of analytical procedures is considered to be overall in accordance with ICH Q2. A question has been raised regarding the validation of a method.

Overall, the specifications' acceptance criteria are considered appropriate, but some limits should be revised.

It is still unclear if the method used for potency testing of lifileucel is representative of its MoA and, therefore, the applicant is requested to provide additional data.

A risk assessment for the potential of nitrosamine presence in the lifileucel finished product, as per EMA/369136/2020 has been provided.

Container-closure system

Lifileucel FP is filled in CE marked cryopreservation bags. Components in contact with the finished product are confirmed to have a CE marking and be compliant with USP Class VI requirements.

Stability

A stability study not compliant with ICH Q5C was performed with several PPQ batches, 3 manufactured at the intended commercial sites, representative of the intended commercial manufacturing process. Despite this, data demonstrating the equivalence of container-closure system employed in stability studies with intended commercial one has been presented.

In addition, an in-use stability study of thawed finished product has also been performed. Overall, the data indicate that the material was stable. Based on the stability data, the proposed stability shelf-life and in-use stability when stored at the recommended storage conditions, are considered acceptable.

Adventitious Agents Safety Evaluation

The final finished product is composed of living cells that must remain functional for their intended therapeutic effect so the final product may not be exposed to heat, chemicals, or sterilized by filtration. In consequence, viral safety is ensured through adequate control of starting and raw materials, demonstration of aseptic manufacturing, and release testing of the final FP.

In this regard, several materials derived from material from human/animal origin, aside of the starting autologous tumor material and allogenic iPBMC feeder cells, are employed during AS and FP manufacture. Compliance of these materials with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated.

In addition, an assessment of viral safety risk has been performed in accordance with relevant EU guidelines. Moreover, testing for adventitious viral contaminants is performed for all materials of direct animal/human origin in compliance with applicable regulations. For human derived components, all collection facilities screen their patients in accordance with EU Directive 2006/17/EC Annex I or II, as applicable. Several questions are raised to ensure its compliance to regulatory requirements. Finally, the maintenance of traceability for human-derived materials is confirmed.

The dossier presented in support of the Marketing Authorisation Application for AMTAGVY (Lifileucel) is, in general, of good quality, but some quality issues remain to be solved.

Therefore, from a quality point of view, AMTAGVI cannot be approved until the applicant resolves the List of outstanding issues.

3.2. Non-clinical aspects

3.2.1. Introduction

The non-clinical package is based mainly on literature references together with one study performed with the aim to demonstrate that Lifileucel presents with the key characteristics of an active TIL preparation. In general, this approach could be acceptable tacking into account the low relevance of in vivo models for highly patient specific products as well as the availability of decades of published results studying TILs in general.

3.2.2. Pharmacology

3.2.2.1. Primary pharmacodynamic studies

The applicant presents mainly literature data supporting the use of TILs in cancer patients. As current knowledge indicate that the in vivo efficacy of TILs may be affected by different factors (e.g. insufficient activation, dysfunctional states and/or an immunosuppressive tumour microenvironment) an in vitro study was conducted to investigate whether the expanded TILs exhibit the phenotypic and functional characteristics supporting anti-tumour effect.

The applicant's study examines the effects of a new manufacturing process on TILs derived from multiple tumor types, analyzing changes in T cell populations and markers of exhaustion and activation over time. In general, although literature information may be supportive of the phenotype presented as efficient by the applicant, there is no consensus as to what a good and efficient TIL preparation is.

The proposed potency assay evaluates marker production in response to a strong activation system, but this method is both non-physiological in its intensity and non-specific.

According to the applicant, from a potency assay perspective, if an autologous assay like this is used for a release assay, it would likely result in the unnecessary elimination of a significant number of TIL lots.

The applicant has not performed in vivo pharmacology studies with lifileucel. An extensive literature is available concerning TILs and their potential to treat various cancers in animal models used together in combination with cyclophosphamide treatment and/or with IL-2. The proposed literature information mainly describes the discovery of TILs and general knowledge about their mode of action. These are thus mainly studies from fundamental research that, although supportive of the theory, do not support specifically Lifileucel in itself. These studies allowed to identify characteristics of TILs linked to their efficacy and for which lifileucel may be tested. The proposed regimen and treatment modalities for Lifileucel is based on data generated with similar products in clinical trials. This is considered appropriate.

In compliance with the PIP, study REP-0344 was submitted. The report was submitted in sequence 0001. As requested, the non-clinical overview and pharmacology summary have been updated with data from this study which reports the findings related to the cultivation and characterization of TIL products sourced from seven paediatric tumours. The feasibility of expanding TIL from paediatric tumours via the Gen 2 manufacturing process was confirmed.

Study REP-0344 summarizes the results of culturing and characterizing TIL products generated from seven paediatric tumours (squamous cell carcinoma, osteosarcoma, two Ewing sarcomas, rhabdomyosarcoma and neuroblastoma). A range of cellular attributes, including T-cell content, % cellular impurities, % memory cells, differentiation state, and activation/exhaustion phenotype, were analysed. The attribute levels varied but were relatively similar to those reported in REP-0132. The applicant concludes that the TILs cultured from paediatric tumours showed a 71% success rate based on Gen 2 acceptance criteria, thus demonstrating the feasibility of expanding TILs from paediatric tumours using the Gen 2 manufacturing process.

3.2.2.2. Secondary pharmacodynamic studies

No provided studies.

3.2.2.3. Safety pharmacology programme

No provided studies.

3.2.2.4. Pharmacodynamic drug interactions

No provided studies.

3.2.3. Pharmacokinetics

No in vivo biodistribution studies were performed which is considered acceptable based on a risk-based approach. TILs are expected to distribute throughout the entire body and home to tumor sites. The observation of efficacy in in vivo animal tumor models support that normal trafficking capacities are retained in the product after ex vivo expansion. Literature data also support the capacity of these cells to migrate to target sites. The applicant has performed some PK analysis in patients to demonstrate persistence in peripheral blood (Cf. Clinical AR).

3.2.4. Toxicology

No in vivo animal studies were performed. Based on the patient specific nature of the product, and the difficulties to generate a relevant in vivo model to study its potential toxicity in vivo, the toxicology section consists of a review of available literature. Non-clinical studies and clinical trials are briefly summarized, supporting a low toxicity of the TIL preparation itself with respect to the seriousness of the indication.

Toxicities linked to TILs themselves mainly consist of reactions to the infusion (dyspnea, chills, fever) and to autoimmune reaction against normal melanocytes, which in the clinic manifests as a relatively frequent treatment-based vitiligo. Hematologic toxicities due to preparative chemotherapy and Grade 3 and 4 toxicities associated with high-dose IL-2 infusions are also reported but are thus related to the full treatment procedure and not to the TIL preparation in itself (se also 3.3.7 Clinical safety section).

No repro-toxicity studies have been performed, which is considered acceptable due to the patient-specific nature of the product and difficulties to generate a relevant animal model. Precautions in line with the subsequent absence of knowledge are included in the SmPC.

3.2.4.1. Single dose toxicity

Not applicable.

3.2.4.2. Repeat dose toxicity

Not applicable.

3.2.4.3. Genotoxicity

Not applicable.

3.2.4.4. Carcinogenicity

No studies have been performed.

3.2.4.5. Reproductive and developmental toxicity

No studies have been performed. The risks to a pregnancy are unknown. The SmPC section 4.6 reflects this absence of knowledge.

3.2.4.6. Toxicokinetic data

No provided studies.

3.2.4.7. Tolerance

Not applicable.

3.2.4.8. Other toxicity studies

No studies were provided. Tumor cells are autologous cells expressing mainly antigens from the "self". The possibility to induce or favour an autoimmune response also targeted against normal cells exists. Autoimmunity against normal melanocytes has been reported both in animal melanoma models and in clinical trials in the form of treatment induced vitiligo. Vitiligo is included in the SmPC as a common adverse event.

3.2.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, lifileucel is not expected to pose a risk to the environment.

3.2.6. Discussion on non-clinical aspects

Introduction and scientific advice

The applicant has not conducted in vivo studies with lifileucel, citing the rationale that the treatment is patient-specific and does not operate across different species. Instead, a comprehensive review of published non-clinical research with relevance to TIL therapy was presented as endorsed by a CHMP advice (EMA/SA/000100171). In the same advice CHMP stated that in vitro IFN-gamma secretion studies may suffice, but the applicant was recommended to also consider performing in vitro cytotoxicity studies by co-culturing TILs with patient cancer cells. Additionally, a dose selection rationale for clinical development was also expected for the MAA procedure. Upper and lower limits of the dose range are based on published data and observations during clinical trials, and therefore discussed in the clinical part of the assessment.

Integrated review and summary

The non-clinical overview refers to key publications in the field of adoptive cell therapy (ACT) with autologous TILs from 1980 and up until today. The publications covered the following topics: scientific rational and proof-of-concept studies, early clinical trials defining the critical properties of TIL for ACT, non-clinical and clinical data supporting the current lifileucel treatment regimen, studies of TIL MoA, and clinical studies demonstrating efficacy and safety of TIL. Each publication was assessed by the applicant highlighting the relevance to lifileucel. The review is considered adequate.

Comparison of D0 T-cells and D22 TIL expanded using Iovance's Gen 2 Protocol (REP-0132)

Purpose and scope

Current knowledge suggests that the efficacy of TIL may be influenced by various factors, such as insufficient activation, dysfunctional states, and/or an immunosuppressive tumour microenvironment. Therefore, an in vitro study was conducted to demonstrate that the TIL possess the phenotypic and functional characteristics that support an anti-tumour effect. Cellular properties of TIL expanded for 22 days were compared to endogenous T cells isolated from the same tumour (D0 T cells). T cells were characterized phenotypically for markers associated with lineage, memory, differentiation, activation and exhaustion. The characterizations were carried out on paired TIL samples from 7 different tumour types, including melanoma, head and neck squamous cell carcinoma, bladder cancer, ovarian cancer, breast cancer, and cervical cancer.

Activation status

Seven TIL products were analysed for the expression of CD markers by flow cytometry and compared to their respective D0 T cells to investigate the activation phenotype of the TILs.

IFN-γ secretion

Lastly in study REP-0132, TIL products were evaluated for T cell functionality and potency.

Study REP-0344 – TILs generated from paediatric tumours

In compliance with the PIP, study REP-0344 (formerly TP-19-028 and NC-IOV-PED-001) was submitted. The report was submitted in sequence 0001 without updating the non-clinical overview or

pharmacological summary with relevant data and conclusions. The applicant is requested to update the overview and summary (OC).

Study REP-0344 summarizes the results of culturing and characterizing TIL products generated from seven paediatric tumours (squamous cell carcinoma, osteosarcoma, two Ewing sarcomas, rhabdomyosarcoma and neuroblastoma). A range of cellular attributes, including T-cell content, % cellular impurities, % memory cells, differentiation state, and activation/exhaustion phenotype, were analysed. The attribute levels varied but were relatively similar to those reported in REP-0132. The applicant concludes that the TILs cultured from paediatric tumours showed a 71% success rate based on Gen 2 acceptance criteria, thus demonstrating the feasibility of expanding TILs from paediatric tumours using the Gen 2 manufacturing process.

Pharmacokinetics

The applicant´s reasons for not performing traditional PK/ADME studies were supported by several arguments substantiated with references from published articles.

The lack of pharmacokinetic studies/distribution studies is considered acceptable.

Toxicology

No toxicology studies were performed for Amtagvi. This is acceptable given the lack of relevant animal models and due to the nature of the product. Additionally, it is in line with the previously mentioned SA, where CHMP supported replacing of toxicology studies with an integrated review and summary of published non-clinical research with relevance to TIL therapy.

ERA

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, Amtagvi is not expected to pose a risk to the environment. An ERA is not needed.

3.2.7. Conclusion on non-clinical aspects

Pharmacology

The submitted non-clinical pharmacology package is supported.

Pharmacokinetics

Classical ADME studies were not performed by the applicant. The arguments (please refer to the discussion part) were overall supported and the lack of PK/biodistribution studies is considered acceptable.

Toxicology

The omission of toxicology studies is supported due to the lack of relevant animal models, the nature of the product, and is in line with previously SA from the CHMP, supporting a replacement of toxicology studies with an integrated review and submission of relevant published non-clinical literature.

Overall, the non-clinical part of the dossier is acceptable.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

Table 1 Description of Clinical Efficacy and Safety Studies of Lifileucel Included in the SCE

Number of Study Centers/ Locations	Study Design/Control Type/Objective Study Population Enrollment	Regimen/ Study Duration	Analysis Populations[1] Sex/Median (range) Age (FAS)	Efficacy Endpoint/ Hypothesis Testing
C-144-01: A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor-Infiltrating Lymphocytes (LN-144) for Treatment of Patients with Metastatic Melanoma **EudraCT**: 2017-000760-15 **NCT**: 02360579 **Status**: Enrollment closed				

N=50 (for Pooled Cohorts 2 and 4, N=49) Europe (N=27; France, Germany, Hungary, Spain, Switzerland, United Kingdom)
 	
US (N=23)
	Phase 2, prospective, uncontrolled, multicenter, interventional, safety and efficacy study
	
	Adult patients with unresectable or metastatic melanoma (Stage IIIc or IV) who progressed following ≥ 1 line of prior systemic therapy, including immune checkpoint inhibitor (eg, anti-PD-1), and if BRAF mutation-positive, after BRAF inhibitor ±MEK inhibitor therapy
	
	First patient/first visit: 16 Nov 2015
	
	Cohort 1: lifileucel (non-cryopreserved)[2]
	Planned: 30
	Received TIL: 23
	Complete 31Aug 2017
	
	Cohort 2: lifileucel (cryopreserved/Gen 2)[3]
	Planned: 66
	Received TIL: 67
	Complete 17 Jan 2019
	
	Cohort 3 (Retreatment)[4] second administration of lifileucel (cryopreserved/Gen 2; patients from Cohorts 1, 2, or 4)
	Planned: 10
	Received TIL: 12
	Follow-up ongoing
	
	Cohort 4: lifileucel (cryopreserved/Gen 2)[3]
	Planned: 75
	Received TIL: 89
	Complete 19 Dec 2019
		For all cohorts: NMA-LD + TIL+ ≥ 1 dose of IL-2
		1) **NMA-LD:** Cyclophosphamide IV (60 mg/kg × 2 doses) over 2 days with mesna followed by fludarabine IV (25 mg/m^2 × 5 doses) over 5 days
		2) **TIL infusion (lifileucel):** 24 hours after completion of NMA-LD
		3) **IL-2:** IV (600,000 IU/kg) approximately every 8 - 12 hours (maximum of 6 doses) starting within 3-24 hours after the completion of the lifileucel infusion
		
		Duration
		Screening: ≤ 28 days from signed ICF
		Enrollment (Tumor Harvest)
		Baseline Period: Days -21 to -10
		Treatment Period: Days -7 to 28
		Assessment Period[5]: Day 42 to 5 years after Day 0 or disease progression/ new anticancer therapy
		Follow-up Period: end of Assessment Period to 5 years after Day 0
			Enrolled (Tumor Harvest) Set:
			Pooled Cohorts 2 and 4
			N=189
			
			Safety Analysis Set (received lifileucel):
			Pooled Cohorts 2 and 4
			N=156
			
			Full Analysis Set - primary efficacy (received lifileucel that met product specification):
			Pooled Cohorts 2 and 4
			N=153
			Sex: 83 M/70 F
			Median Age (min, max): 56.0 years (20, 79)
				Primary Endpoint and Hypothesis Testing
				• Efficacy: ORR as assessed by IRC per RECIST v1.1
				• H_{01}: ORR ≤ 10%
				vs
				H_{a1}: ORR > 10%
				
				Secondary Endpoints
				• Safety
				• Efficacy:
				  • DOR, DCR, and PFS as assessed by IRC per RECIST v1.1
				  • ORR, DOR, DCR and PFS as assessed by investigator per RECIST v1.1
				  • OS

Abbreviations: BRAF = proto-oncogene B-Raf; F = female; DCR = disease control rate; DOR = duration of response; FAS = Full Analysis Set (administered lifileucel that met manufacturing product specifications); Gen = Generation; ICF = informed consent form; IL-2 = interleukin-2; IRC = Independent Review Committee; IV = intravenous;

M = male; max = maximum; MEK = mitogen-activated extracellular signal-regulated kinase; min = minimum; NMA-LD = nonmyeloablative lymphodepletion; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein-1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; US = United States; TIL = tumor-infiltrating lymphocytes

[1] Data from Cohort 1 are not summarized in this SCE because the non-cryopreserved product is no longer in clinical use and is not considered comparable to the cryopreserved product. Retreatment cohort (ie, Cohort 3; N = 12) data are also not summarized in the SCE; due to the small number of patients, interpretation of possible retreatment associated findings is limited.

[2] The non-cryopreserved product is no longer in clinical use.

[3] Cohorts 2 and 4 met the same primary eligibility criteria, had the same assessments, received the same lifileucel regimen, and received the same cryopreserved lifileucel that was produced using the same TIL manufacturing process, specification, and product formulation.

[4] Patients who were previously treated in Cohort 1, Cohort 2, or Cohort 4 had progressive disease and opted to be rescreened and retreated with the lifileucel regimen using cryopreserved lifileucel product.

[5] Day 42, then every 6 weeks until Month 6, and every 3 months for up to 5 years from Day 0 or until disease progression or the start of a new anti-cancer therapy.

3.3.1. Clinical pharmacology

The data supporting clinical pharmacology of lifileucel are based on one clinical study (C-144- 01) that included limited pharmacokinetics (i.e., persistence), pharmacodynamics, and dose-response assessments. The clinical pharmacology assessment focuses on Cohort 2 and 4 which are based on the same manufacturing process for generating cryopreserved lifileucel product.

In the context of a conditional MAA, further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and the Summary of Product Characteristics (SmPC) will be updated as necessary.

3.3.1.1. Pharmacokinetics

Bioanalytical methods

The proportion of unique TCR clonotypes from the AMTAGVI lots contributing to the peripheral blood TCR repertoire among infused patients was analyzed using a semi-quantitative polymerase chain reaction followed by next generation RNA sequencing. TCR repertoire analyses of Cohort 2 and Cohort 4 patients are presented in details in reports REP-0128 and REP-0272. A validation report is available for the iR-HTBIvc assay describing the validation criteria.

The non-suitability of the methods used to yield traditional PK parameters and described by the applicant is acknowledged. Different methods seem to be commonly employed to track the TCR clonotypes even

if official regulatory guidance for these technologies are lacking. Strategies using immune repertoire deep sequencing coupled with bioinformatic analyses are well described in the literature.

The validation of the method used had satisfactory performance regarding specificity, precision and robustness. Limit of detection (LoD), limit of quantification (LoQ), and linearity were also established.

ADME

Because of the cellular nature of lifileucel, conventional pharmacokinetic (PK) studies of absorption, distribution, metabolism, and excretion were not conducted. The product is administered as an intravenous infusion. Cohort 2 and Cohort 4 patients received IV lifileucel that is produced using the same cryopreserved TIL manufacturing process (Generation [Gen] 2) and product formulation.

Prior to lifileucel infusion, tumor-derived clonotypes can be detected in peripheral blood at a mean proportion of 16% which was increased to 83% at Day 4 post-infusion of lifileucel. The clonotypes declined to 51% at Day 14 and persisted in the range of 37% to 41% up to month 12 post-infusion of lifileucel. The kinetic profile of lifileucel in PBMC samples appear to constitute initial decline between Day 4 and 14, and persistence between Day 42 and Month 12. Due to experimental setup and data collection there are uncertainties in the determination of time to maximal expansion which is further accentuated by high inter-individual variability. Even if conventional ADME studies are usually not relevant for human cell-based medicinal products, in general, studies should be carried out to demonstrate tissue distribution. The need for biodistribution studies is dependent on the administration route as well as the structural or physiological containment of the cells. In the case of the TIL product, the distribution potential of the lymphocytes is judged limited and known to localize the tumour site specifically. The TIL product reaches its intended target specifically and is not expected to be distributed throughout the body and not expected to accumulate in unintended locations. (see also NC section and section 3.3.2. discussion on clinical pharmacology).

Substantial fractions of the TCR clonotypes were shown to persist in the blood of all infused patients, for all the assessed timepoints up to 1 year following lifileucel infusion. Clonotypes from lifileucel drug product lots were detected in 100% (120/120) of patients at Day 42, 100% (34/34) of patients at Month 6, and in 100% (22/22) of patients who had PBMC samples available at Month 12. Day 4 represents the maximum time to expansion post-infusion of lifileucel (82%). The proportion of TCR clonotypes declined to 51% at Day 14 (n=96) and remained between 37% and 41% from Day 42 (n=120) to month 12 (n=22) following the lifileucel infusion. It is worth noting that this measurement is a result of TIL persistence and the dynamic changes of endogenous lymphocytes during lymphodepletion and recovery, limiting the ability of the assay to assess quantitative changes of TIL persistence.

Persistence-response issues are discussed in section 3.3.2.

POP PK analysis

No POPPK analysis has been conducted.

Target population

Lifileucel is an autologous, patient-specific and non-modified product. The pharmacokinetics have mainly been documented in the target population and not in healthy volunteers.

Special populations

Dedicated studies in renal and hepatic impaired patient have not been carried out while renal and hepatic impairment are not expected to affect TIL expansion and persistence.

The impact of intrinsic factors on lifileucel persistence was retrospectively explored using persistence data at Day 42 and no association was observed between Day 42 persistence and age (≥65 versus <65

years old). The clinical relevance of the higher lifileucel persistence observed in males versus females is not known. Given the limited number of black and Asian populations in study C-144-01, it is difficult to draw any conclusions on the race/ethnic factor. The weight range in the clinical study was rather wide (44.9-141.9 kg) and the administration of the dose is not body-weight based.

Safety and efficacy of Amtagvi have not been established in paediatric patients.

Drug-drug interactions

Due to the nature of the product, no formal studies pertinent to pharmacokinetics using human biomaterials have been conducted with lifileucel. No PK drug interaction studies in humans have been performed with lifileucel as there is no mechanistic basis for a PK drug interaction. Cytokine levels have been followed during the clinical study and the results do not raise any concerns from the DDI-perspective.

3.3.1.2. Pharmacodynamics

Mechanism of action

Lifileucel mainly consists of autologous tumour-derived T cells and may contain some other immune cell types. Tumour infiltrating lymphocytes (TIL) are CD8+ and CD4+ T cells that infiltrate tumours as a component of the host immunological response. Following ex vivo expansion and re-infusion, TILs migrate to tumour sites, in which they recognise and target a multitude of individualised, tumour specific neoantigens via T-Cell receptor (TCR)-peptide human leukocyte antigen (pHLA) engagement. The TCR-pHLA interaction induces T cell activation and T cell-mediated tumour killing via secretion of cytokines and cytolytic enzymes, which form pores and disrupt the integrity of the tumour cell membrane and mediate tumour cell lysis.

The lifileucel regimen includes nonmyeloablative lymphodepletion (NMA-LD) prior to TILs infusion, previously shown to contribute to persistence of infused cells and duration of response to TIL therapy. After tumour resection, patients receive NMA-LD (cyclophosphamide on Days -7 to -6 and fludarabine on Days -5 to -1) followed by a single lifileucel infusion (Day 0) and ≤6 doses of IL-2 (Days 0-4).

Primary and Secondary pharmacology

Circulating levels of IL-15 and cytokines associated with Th1 and Th2 T-cell responses and immune activation were assessed in an exploratory analysis. Longitudinal changes of IL-15, IL-6, IL-7, IL-9, IL-10, IL-12 (p40), CCL2, CXCL10, IFN-γ, and TNF-α were measured at each timepoint. Peripheral blood samples were collected at baseline (pre-NMA-LD) and on Days 1, 4, 14, 42, and 84 post lifileucel infusion.

Both IL-15 and CXCL10 levels peaked around Day 1 to Day 4 following the lifileucel infusion, decreased over time, and returned to baseline levels within 1 to 3 months. This was consistent with the proposed mechanism of lymphodepletion for IL-15 and suggested that CXCL10, which has a role in the recruitment of immune cells to site of inflammation and tumours (Tokunaga 2018), may have the potential to serve as a PD marker for TIL activity. The mean IFN- γ level was below baseline on Day 1 to Day 4 following the lifileucel infusion and returned to baseline levels on and after Day 14. Other cytokines and chemokines listed above did not show any noticeable changes.

Overall, evaluation of the immune response data based on the patient's clinical response status showed that all cytokines and chemokines tested had overlapping distribution of values between the response and non-response groups.

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

Study C-144-01 includes 4 cohorts, where pharmacokinetic data from Cohort 2 and Cohort 4 are pooled together in this submission. Different manufacturing sites have been used, however, comparability between the manufacturing sites based on quality aspects have been discussed and it is concluded that it is acceptable to pool the pharmacokinetic data from cohort 2 and 4.

Bioanalytical methods

The proportion of unique TCR clonotypes from the AMTAGVI lots was analyzed using a semi-quantitative polymerase chain reaction followed by next generation RNA sequencing.

This bioanalytical method is out of scope of the EMA and ICH M10 guidelines on bioanalytical method validation. However, the analytical method is well described in literature, and the validation had satisfactory performance regarding specificity, precision and robustness. Limit of detection (LoD), limit of quantification (LoQ), and linearity was also established.

ADME

Lifileucel consists of non-genetically modified autologous T-cells hence there is no product-specific marker enabling in vivo tracking of individual clones derived from the drug product. The data supporting clinical pharmacology of lifileucel is based on one single arm clinical study (C-144-01) and on published literature mainly referring to TILs (not specifically lifileucel). The study includes 4 cohorts, where data from Cohort 2 and Cohort 4 are pooled together in this submission. In the Guideline for Human cell-based medicinal products (EMEA/CHMP/410869/2006) it is stated that "conventional ADME studies are usually not relevant" and "…monitoring of viability, proliferation/differentiation, body distribution/migration" are highlighted as important aspects to study. In this Application, persistence of unique T-cell receptor (TCR) clonotypes from lifileucel lots in the peripheral blood of patients were tracked over the time-course of the study (12 months).

Prior to lifileucel infusion, tumor-derived clonotypes can be detected in peripheral blood at a mean proportion of 16% which was increased to 83% at Day 4 post-infusion of lifileucel. Due to experimental setup and data collection there are uncertainties in the determination of time to maximal expansion which is further accentuated by high inter-individual variability. After day 14 the proportion declines and reaches a plateau at day 42 remaining at 37-42% throughout the study. Importantly, this measurement is relative to the total T-cell population in the blood and a result of TIL persistence and the dynamic changes of endogenous lymphocytes during lymphodepletion and recovery, limiting the ability of the assay to assess quantitative changes of TIL persistence. Additionally, the number of samples decreased notably 6 months after lifileucel infusion. Further limiting aspects of the methodology are that identical endogenous clones may theoretically arise, and RNA expression levels may differ between T-cells, therefore the method does not reflect concentrations but is a semi-quantitative measure of TIL persistence. Still, the provided data are considered sufficient to address the issue of persistence of the lifileucel drug product.

The migration/biodistribution of lifileucel has not been studied. The applicant claims that TILs localise to the tumour based on literature data of studies using radiolabeled TILs in melanoma patients. Tumour localisation would likely be required for anti-tumour effect, but results are not that clear between studies. Other organs implied for TIL migration are initially lungs followed by liver and spleen. In difference to normal lymphocytes TILs appear not to distribute to lymph nodes. The description of the biodistribution based on literature data is considered acceptable. Absence of NC biodistribution study is judged acceptable according to ICH S12 (see NC section).

No dose-exposure (persistence) correlation was observed.

A comparison of the persistence profiles (% TCR repertoire over time) between responding and non-responding patients has been provided and has shown a sufficiently similar % TCR repertoire in function of time between the two groups.

A comparison of the lifileucel persistence (% TCR repertoire over time) by number of IL-2 doses has been provided. No relationship between the persistence profiles (% TCR repertoire over time) and number of IL-2 doses is observed based on comparison of the percentage of the TCR repertoire from TIL clonotypes in the IL2 dose groups (1-2, vs, 3-4, vs 5-6).

The impact of intrinsic and extrinsic factors on persistence is discussed below in "special populations".

Special populations

Information regarding PK in special populations are not included in the EMA dossier.

The lack of data for RI and HI is acceptable, considering the nature of the product and the limits the conditioning treatment as well as the IL-2 co-treatment sets for the use of lifileucel

The lack of renal and hepatic impaired studies, and the fact that hepatic and renal impairment are not expected to affect TIL expansion and persistence, has been reflected in section 5.2 of the SmPC. It has also been added that Study C-144-01 required patients to have adequate organ function, which excluded patients with evidence of clinically relevant renal or hepatic impairment

It has been added in section 5.2 that there are limited data on lifileucel in black and Asian populations but there is no rationale to expect any difference between these subgroups and the overall population.

Upon request of FDA, the impact of intrinsic factors on lifileucel persistence was retrospectively explored using persistence data at Day 42. Since no association was observed between Day 42 persistence and age (≥65 versus <65 years old), it is adequately mentioned in section 4.2 of the SmPC that no dose-adjustment is required in patients ≥ 65 years of age.

The weight range in the clinical study was rather wide (44.9-141.9 kg). The administration of the dose is not body-weight based. Though not investigated it is considered unlikely that weight would have relevant impact on lifileucel exposure.
The SmPC mentions adequately in section 4.2 that the safety and efficacy of Amtagvi have not been established in paediatric patients. A PIP should be completed by January 2031.

A comparison of the persistence profiles (% TCR repertoire over time) between responding and non-responding patients was provided and showed a sufficiently similar % TCR repertoire in function of time between the two groups.

Drug-drug interactions

Due to the nature of the product, no formal studies pertinent to pharmacokinetics using human biomaterials have been conducted with lifileucel. No PK drug interaction studies in humans have been performed with lifileucel as there is no mechanistic basis for a PK drug interaction. Cytokine levels have been followed during the clinical study and the results do not raise any concerns from the DDI-perspective.

Pharmacodynamics

Due to the autologous nature of the product, the collective data showed high patient-to-patient variability, thus traditional PD parameters could not be calculated. No correlation between various types of cytokines and chemokines and the antitumor response was observed in longitudinal samples from cohort 2 and 4 of study C144-01.

There is a weak correlation between the number of cell infused and the tumor response in cohort 2 and 4 in study C144-01.

Persistence-response analysis including ORR and DOR for cohort 2 and 4 of study C144-01 were provided. Based on an analysis evaluating percentage of total TCR repertoire with TIL clonotypes on Day 42 vs ORR or DOR, no association between the TIL persistence and efficacy was observed.

3.3.3. Conclusions on clinical pharmacology

Pharmacokinetics

Overall, the role of the PK in this application is limited. Given the cellular nature of lifileucel, conventional pharmacokinetic (PK) studies of absorption, distribution, metabolism, and excretion were not conducted. Clonal T-cell populations were monitored through serial sampling of peripheral blood from patients treated with the lifileucel regimen, establishing a profile of in vivo expansion and persistence for the clonotypes. This is judged adequate in view of the autologous, non-genetically modified and patient-specific characteristics of the product.

No major issues have been identified and the other concerns are solved. The applicant has provided sufficient descriptive data for persistence of the lifileucel T-cell receptor (TCR) clonotypes in patients.

Pharmacodynamics

No correlation between various types of cytokines and chemokines and the antitumor response was observed.

Based on an analysis evaluating percentage of total TCR repertoire with TIL clonotypes on Day 42 vs ORR or DOR, no association between the TIL persistence and efficacy was observed.

3.3.4. Clinical efficacy

3.3.4.1. Dose-response studies

Traditional pharmacokinetic methods are not suitable for the evaluation of TIL therapy; thus, concentration-response assessments were not performed. For details see section in the Clinical Pharmacology.

Justification for the use of NMA-LD:

Preparation of the patient with the NMA LD regimen immediately prior to the infusion of lifileucel is hypothesized to eliminate suppressive influences (eg, regulatory T cells and cytokine sinks) to provide an optimal milieu supporting the expansion, trafficking, engraftment, and antitumour cytotoxicity of the transferred TIL (Klebanoff 2005). The NMA LD doses and schedules were developed and tested in clinical studies and were found to be safe and have the intended activity in this patient population (Dudley 2005; Itzhaki 2011; Rosenberg 2011; Pilon-Thomas 2012; Radvanyi 2012).

Justification for the proposed dose range of Lifleucel:

Each dose of lifileucel in Study C-144-01 was to contain between 1×10^9 to 150×10^9 viable cells that met the prespecified release criteria. The proposed dose of lifileucel to be used commercially falls within this range, between 1.8×10^9 to 100×10^9 viable cells that meet the proposed release criteria. The upper limit of the protocol-specified dose range of the lifileucel product was selected based on the known published upper limit of cells infused in prior clinical studies of TIL for the treatment of melanoma (Dudley 2005; Radvanyi 2012). The lower limit of the protocol-specified dose range was selected based on observations after dosing of the initial patients in Study C-144-01. At that time, a clinically meaningful response (ie, best overall response by Investigator of partial response [PR]) had

been observed in 1 patient who had received lifileucel with a total cell count of 1.2×10^9 viable cells. However, there is concerns regarding the recommended dose range.

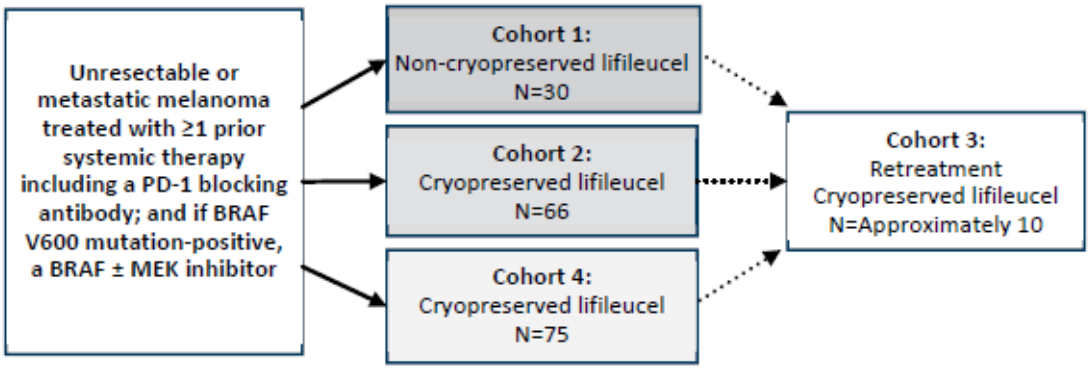
Justification for the use of IL-2:

The IL-2 dose and abbreviated schedule used in the lifileucel regimen were selected based upon review of the data from clinical studies of ACT with TIL in patients with metastatic melanoma (Dudley 2002b; Itzhaki 2011; Rosenberg 2011; Radvanyi 2012; Goff 2016). These data suggest that a higher dose intensity or cumulative exposure was not associated with improved clinical benefit. Notably, Goff et al reported on a population of 99 patients with melanoma treated with TIL and observed the numerically highest ORR in the subgroup of patients who received 3 to 5 doses of IL-2 (Goff 2016). Furthermore, there were data showing that higher doses may be associated with increased toxicity (Rosenberg 2011). Given these findings, in order to optimize the risk/benefit of IL-2 exposure, with the goal of minimizing toxicity yet providing an exposure that improves the clinical benefit of ACT with lifileucel, the lifileucel regimen includes up to a maximum of 6 doses of IL-2 (at a dose of 600,000 IU/kg [the approved dose level for aldesleukin] every 8 to 12 hours).

3.3.4.2. Main study

Study C-144-01 is a Phase 2, global, multicentre, multicohort, single-arm clinical trial evaluating the efficacy and safety of TIL in adult patients with advanced melanoma (American Joint Committee on Cancer [AJCC] version 7.0 staging system Stage IIIC or Stage IV). The TIL regimen was investigated as a one-time treatment and included an NMA LD preparative regimen followed by a single infusion of TIL and post-infusion administration of IL-2. The study was not designed as a dose-response study because the entire patient-specific lot is administered.

Figure 1 Schematic of Planned Study Cohorts



Abbreviations: BRAF = proto-oncogene B-Raf; MEK = mitogen-activated extracellular signal regulated kinase.
Note: Provides planned number of patients to receive lifileucel infusion.

Figure 2 Study Flow Chart

Abbreviations: EOA = end of assessment; ICF = informed consent form; IL-2 = interleukin-2; NMA-LD = nonmyeloablative lymphodepletion; OS = overall survival.
Note: Cohort 3 patients (ie, patients who were previously treated in Cohort 1, 2, or 4, had progressed, and opted to be retreated with the lifileucel regimen) may have had a second tumor resection, if needed, especially when new lesions were available and feasible for resection.

3.3.1. Study C-144-01

Methods

Study participants

Main inclusion criteria according to the latest protocol version:

Patients must meet ***all*** of the following inclusion criteria to be eligible for participation in the study:

a) Patients with unresectable or metastatic melanoma (Stage IIIc or Stage IV; per the AJCC version 7)
b) Patients must have progressed following ≥ 1 prior systemic therapy including a PD-1 blocking antibody; and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination with MEK inhibitor
c) Prior to study Enrollment, documentation of radiological disease progression after the most recent therapy
d) At least one measurable target lesion, as defined by RECIST v1.1
    - Lesions in previously irradiated areas (or other local therapy) should not be selected as target lesions, unless treatment was ≥ 3 months prior to Screening, and there has been demonstrated disease progression in that particular lesion
    - If a lesion is partially resected to generate TIL, and remains visible on the baseline scan after surgery, then the partially resected lesion can be used for RECIST v1.1 response assessment, but only as a non-target lesion
e) At least one resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection to generate TIL; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization is ≤ 3 days)
f) Patients must be ≥ 18 years of age at the time of consent. Enrollment of patients > 70 years of age may be allowed after consultation with the Medical Monitor
g) Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2) and an estimated life expectancy of ≥ 3 months
h) In the opinion of the Investigator, patients must be able to complete all study required procedures
i) Patients must have the following hematologic parameters:
    - Absolute neutrophil count (ANC) ≥ 1000/mm3
    - Hemoglobin (Hb) ≥ 9.0 g/dL
    - Platelet ≥ 100,000/mm3

Note: Transfusions or growth factors are not allowed 28 days prior to signing the informed consent form (ICF) and continuing through the Screening Period.

j) Patients must have adequate organ function:
   - Serum alanine transaminase (ALT)/serum glutamic-pyruvic transaminase (SGPT) and aspartate transaminase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) ≤ 3 times the upper limit of normal (ULN); patients with liver metastasis ≤ 5 times ULN
   - Estimated creatinine clearance (eCrCl) ≥ 40 mL/min using the Cockcroft-Gault formula
   - Total bilirubin ≤ 2 mg/dL. Patients with Gilbert's syndrome must have a total bilirubin ≤ 3 mg/dL.

k) Patients must have recovered from all prior therapy-related AEs to ≤ Grade 1 (per Common Terminology Criteria for Adverse Events [CTCAE] v4.03), except for alopecia or vitiligo, prior to Enrollment (tumor resection)
   - Patients with documented ≥ Grade 2 diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitor(s) must have been asymptomatic for at least 6 months and/or had a normal colonoscopy post-immune checkpoint inhibitor treatment, by visual assessment, prior to tumor resection
   - Patients with immunotherapy-related endocrinopathies stable for at least 6 weeks (eg, hypothyroidism), and controlled with hormonal replacement (non-corticosteroids), are allowed.

l) Patients must have a washout period of ≥ 28 days from prior anticancer therapy(ies) to the start of the planned NMA-LD preconditioning regimen:
   - Targeted therapy: MEK/BRAF or other targeted agents
   - Chemotherapy
   - Immunotherapy: anti-CTLA-4/anti-PD-1, other mAb, or vaccine
   - Palliative radiation therapy is permitted so long as it does not involve lesions being selected for TIL, or as target or non-target lesions. Washout is not required if all related toxicities have resolved to ≤ Grade 1 as per CTCAE v4.03.

m) Patients of childbearing potential or their partners of childbearing potential must be willing to take the appropriate precaution to avoid pregnancy or fathering a child for the duration of the study and practice an approved, highly effective method of birth control during treatment and for 12 months after receiving the last protocol-related therapy.

n) Patients (or legally authorized representative) must have the ability to understand the requirements of the study, have provided written informed consent

Main exclusion criteria:

1. Patients who have been shown to be BRAF mutation positive (V600), but have not received prior systemic therapy with a BRAF inhibitor alone or a BRAF inhibitor in combination with a MEK inhibitor.
2. Patients who have received an organ allograft or prior cell transfer therapy
3. Patients with melanoma of uveal/ocular origin
4. Patients who have a history of hypersensitivity to any component or excipient of LN-144 or other study drugs:
   • NMA-LD preconditioning regimen (cyclophosphamide, mesna, and fludarabine)
   • Antibiotics (ABX) of the aminoglycoside group (ie, streptomycin, gentamicin); except those who are skin-test negative for gentamicin hypersensitivity
   • Any component of the LN-144 infusion product formulation including DMSO, HSA, IL-2, and dextran-40
5. Patients with symptomatic and/or untreated brain metastases (of any size and any number)
   • Patients with definitively treated brain metastases may be considered for enrollment, and must be stable for ≥ 14 days prior to beginning the NMA-LD preconditioning regimen

6. Patients who are on chronic systemic steroid therapy for any reason
7. Patients who have active medical illness(es) that would pose increased risk for study participation, including: active systemic infections requiring systemic ABX,coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system
8. Patients who have ≥ Grade 2 hemorrhage within 14 days prior to Enrollment (tumor resection)
9. Patients who are seropositive for any of the following:
   • Human immunodeficiency virus (HIV)-1 or HIV-2 antibodies
   • Hepatitis B antigen (HBsAg), hepatitis B core antibody (anti-HBc), or hepatitis C antibody (HCV Ab); patients with acute or chronic hepatitis infections may be enrolled if the viral load by polymerase chain reaction (PCR) is undetectable with/without active treatment.
   • Syphilis (rapid plasma reagin [RPR] test or venereal disease research laboratory [VDRL] test)
   • Cytomegalovirus (CMV) IgM antibody titer or PCR assay and Epstein-Barr virus (EBV) IgM or PCR assay indicating active infection
   • Positive herpes simplex virus (HSV)-1 and HSV-2 IgM serology or PCR assay
   o Patients who are HSV immunoglobulin M (IgM) or PCR assay positive will need to receive appropriate treatment and become IgM or PCR assay negative prior to starting the NMA-LD preconditioning regimen
10. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency disease [SCID] and acquired immunodeficiency syndrome [AIDS])
11. Patients who have a left ventricular ejection fraction (LVEF) < 45% or New York Heart Association (NYHA) functional classification Class > 1
    • Patients ≥ 60 years of age and who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias must have a cardiac stress test. Patients with any irreversible wall movement abnormalities are excluded
12. Patients who have a documented forced expiratory volume in 1 second (FEV1) of ≤ 60%
13. Patients who have had another primary malignancy within the previous 3 years (with the exception of carcinoma in situ of the breast, cervix, or bladder; localized prostate cancer; and non-melanoma skin cancer that has been adequately treated)
14. Patients who have received a live or attenuated vaccine within 28 days of beginning the NMA-LD preconditioning regimen
15. Patients who are pregnant or breastfeeding
16. Patients whose cancer requires immediate attention or who would otherwise suffer a disadvantage by participating in this trial
17. Patients protected by the following constraints:
    • Hospitalized persons without consent or persons deprived of liberty because of a judiciary or administrative decision
    • Adult persons with a legal protection measure or persons who cannot express their consent
    • Patients in emergency situations who cannot consent to participate in the trial

Treatments

The Treatment Period is from Day -7 (start of NMA-LD preconditioning regimen) and continue to Day 28. Treatment completion is defined as having received LN-144 infusion.

For participating sites for Cohort 4, hospitalization was not required for NMA-LD by protocol; however, sites could admit and treat patients for NMA-LD administration in an inpatient setting per their local institutional standards. For participating sites for Cohort 2, the protocol did not require hospitalization for NMA-LD for all patients enrolled to the cohort, only for patients enrolled and treated under protocol versions 6 and 7, which required hospitalization for mesna administration.

Patients are hospitalized prior to the planned Lifileucel infusion for overnight hydration. Patients remain hospitalized until completion of the IL-2 administration, or as per institutional standards.

Treatment regimen:

For all cohorts:

1. NMA-LD: Cyclophosphamide IV (60 mg/kg × 2 doses) over 2 days with mesna (15 mg/kg over the first 2 hours followed by mesna 3 mg/kg/hour over the remaining 22 hours). Followed by fludarabine IV (25 mg/m2 × 5 doses) over 5 days
2. Lifileucel infusion: After completion of NMA-LD
3. IL-2 IV (600,000 IU/kg) approximately every 8-12 hours (maximum of 6 doses) with the first dose within 3-24 hours after the completion of the lifileucel infusion

Lifileucel is a preparation of TIL derived from an individual patient's tumor for patient-directed immunotherapy. Lifileucel is provided as **a single dose for infusion** containing 1×10^9 to 150×10^9 viable cells suspended in a cryopreservation medium. Patients were to receive the full dose of product that was manufactured. Lot numbers are patient-specific.
Treatment Duration: 11 to 12 Days
NMA-LD Day -7 to Day -1
Lifileucel Day 0
IL-2 Day 0 up to Day 4

Dose adjustments/discontinuation:
NMA-LD

Fludarabine dose will be adjusted according to eCrCl as follows:

- eCrCl 50–79 mL/min: reduce dose to 20 mg/m2
- eCrCl 40–49 mL/min: reduce dose to 15 mg/m2
- Dose hold or discontinuation of fludarabine will only be allowed in the case of toxicity described in the package insert.

Lifileucel will be administered IV and infused by gravity beginning at a rate of 1 mL/min for the first 5 minutes. If no adverse reaction is observed, the infusion rate can then
increase to between 5 and 10 mL/minute for the completion of the infusion. During periods of infusion interruption, any remaining cryobags of LN-144 should be kept in the cryoshipper. Any thawed LN-144 should be infused within 3 hours of being thawed.

IL-2
The standard approach to the administration of IL-2 is to continue dosing until Grade 3 or 4 events occur, but this study calls for 1–6 doses based on tolerance.

- IL-2 dosing is allowed for up to 4 days post-LN-144 infusion to allow for proper management of any IL-2 toxicities
- If toxicities can be easily reversed within 24 hours by supportive measures, then the additional doses of IL-2 (up to the protocol-defined maximum of six doses) may be given
- IL-2 dosing may be held or stopped at the discretion of the Investigator
- Skipping IL-2 doses is allowed if patient experiences a Grade 3 or Grade 4 toxicity (Appendix 4 and Appendix 5). If > 2 doses of IL-2 are skipped, then IL-2 administration will be discontinued

Some patients may undergo tumor resection but will not receive infusion of LN-144. Such patients will perform an EOA visit and transition directly into the OS Follow-up Period of the study.

Patients may discontinue any component of the study regimen. Criteria for discontinuation from treatment:

- Withdrawal of consent to treatment (every effort should be made to continue OS Follow-up, when applicable).
- Grade ≥ 3 drug-related immune AEs that involve vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-144 infusion.
- Grade ≥ 3 allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator.
- Meeting criteria for permanent discontinuation of IL-2 treatment (must have received at least one dose of IL-2; Appendix 5).
- Determination by the Investigator that continued treatment is not in the best interest of the patient.
- Administration of prohibited concomitant medications/start of new anti-cancer therapy.
- Death.

Prohibited treatment

• Systemic therapies intended to treat melanoma or any medications that may have an antitumor effect.
• Use of systemic corticosteroids are not allowed starting 21 days prior to beginning the NMA-LD preconditioning regimen, through treatment, and up to 60 days post-LN-144 infusion. Prophylactic use of systemic corticosteroids is not allowed under any circumstances. Such medications should only be used to treat immediate life-threatening conditions.
• Palliative radiation therapy that involves lesions selected as target or non-target.
• Investigational drugs (other than LN-144).
• Live or attenuated vaccine within 28 days prior to beginning the NMA-LD preconditioning regimen or within 3 months after the last dose of IL-2 (Day 84) until ANC is ≥ 1000/mm3.

Cyclophosphamide and fludarabine toxicities

Expected toxicities with cyclophosphamide and fludarabine administration, as well as supportive care and management of toxicities are listed in the package inserts. Treatment will be given as per institutional standards. In general, the use of the NMA-LD preconditioning regimen (cyclophosphamide and fludarabine) prior to LN-144 administration can lead to myelosuppression.

Lifileucel toxicity prevention and management

During infusion of LN-144, appropriate emergency medications (eg, epinephrine and diphenhydramine) should be available at bedside, and institutional emergency guidelines should be followed as needed.

The following medications will be administered to the patient prior to LN-144 infusion as follows or as per institutional standards:
• Within 24 hours, hydration
• Within 30–60 minutes, premedicate the patient with acetaminophen (650 mg) or equivalent, and diphenhydramine (25–50 mg IV), or another H1-histamine antagonist

• Prophylactic use of systemic corticosteroids is not allowed under any circumstances; such medications should only be used to treat immediate life-threatening conditions

Additional supportive therapy may include:
• Continued acetaminophen (650 mg q4h) or equivalent
• Indomethacin (50–75 mg q6h)
• Ranitidine (150 mg q12h)
• Meperidine (25–50 mg)
• Other medications as per institutional standards

Assessments	Screening, Enrollment, & Baseline Period			Treatment Period (All visit dates are calculated from LN-144 infusion [Day 0])													Assessment Period (All visit dates are calculated from LN-144 infusion [Day 0])			Overall Survival Follow-up Period [a]
	Screening (≤ 28 days from ICF signature)	Enrollment/Tumor Resection	Baseline (Day -21 to Day -10)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (± 3 days)	End of Treatment Visit Day 28 (± 3 days)	Every 6 Weeks (Week 6 [+ 7 days], Week 12 [± 3 days], and Week 18 [± 3 days])	Every 3 Months (± 1 Week) (Starting at Month 6)	EOA Visit [b]	Every 3 Months (± 3 Weeks)
PROPHYLACTIC MEDICATIONS																				
Ondansetron				X	X															
Filgrastim [bb]												X	X	X	X	X	X	X		
Fluconazole [cc]												X	X	X	X	X	X	X		
TMP-SMX DS, or appropriate ABX [dd]																X	X	X		
Broad spectrum ABX				X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Valacyclovir/acyclovir [w]	X [w]	X [w]	X [w]													X	X	X		

w In patients who are seropositive for HSV IgM or PCR assay at Screening, herpetic treatment will be initiated and must be completed prior to starting NMA-LD to ensure patient is seronegative for HSV (IgM). Patients who are not HSV IgM positive at Screening will begin herpetic prophylaxis on Day 14 (or as the Investigator deems
bb Filgrastim or biosimilar may be administered beginning on Day 1 and continued each day until ANC > 1000/mm3 × three consecutive days, discontinue if ANC rises to > 10,000/mm3, or follow institutional standards.
cc Fluconazole should be administered beginning on Day 1 and continue each day until ANC > 1000/mm3. If ANC count remains < 1000/mm3 at 6 months postchemotherapy, prophylaxis will continue until the CD4 count is > 200/mm3 for at least 6 months, or as per institutional standards.
dd TMP-SMX DS should be administered once daily, beginning on Day 14 and continue until the ALC reaches > 1000/mm3 for three consecutive days; if at 6 months ALC < 1000/mm3, continue until CD4 count is > 200/mm3 for at least 6 months.
appropriate) and continue until ALC > 1000/mm3.

IL-2 Toxicity

The most commonly seen Grade 4 events are pulmonary and renal impairment, and mental status changes. These toxicities may sometimes require intubation for protection of the patient's airway. It is important to note that although patients require significant supportive measures during this period, almost all toxicities are reversible, and most patients have experienced no long-term sequelae following this treatment regimen. However, fatal complications are possible. Subcutaneous administration of IL-2 is not permitted.

Study assessments

All visits following the Lifileucel infusion are calculated from the Lifileucel infusion (Day 0).
Tumor assessments are planned for: Screening and Baseline (Day -21 to Day -10).
Tumor response assessments are planned for: Week 6 (Day 42), then every 6 weeks until Month 6 (Week 24), and every 3 months (12 weeks) for up to 5 years from Day 0 or until the EOA visit has been completed.
Tumor response assessments will be performed by clinical examination (skin lesions) and by conventional or spiral CT scans of the chest, abdomen, pelvis, and MRI of the brain.
Photographic documentation and caliper measurement will be performed for superficial dermal and subcutaneous lesions that cannot be assessed by radiographic scan.
Tumor response will be determined using RECIST v1.1 with a modification to require confirmation of PD per irRECIST performed at least 28 days from the last date of progression, as applicable, as

assessed by the Investigator. All locally-obtained images will be forwarded to a central imaging facility for the IRC assessment of tumor responses.
After the EOA Visit, the OS Follow-up Period begins and continues for up to 5 years from Enrollment or until discontinuation from the study, with telephone contact every 3 months to obtain survival status and subsequent anti-cancer therapy information.

Assessments	Screening, Enrollment, & Baseline Period			Treatment Period (All visit dates are calculated from LN-144 infusion [Day 0])														Assessment Period (All visit dates are calculated from LN-144 infusion [Day 0])			Overall Survival Follow-up Period [a]
	Screening (≤ 28 days from ICF signature)	Enrollment/Tumor Resection	Baseline (Day -21 to Day -10)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (± 3 days)	End of Treatment Visit Day 28 (± 3 days)	Every 6 Weeks (Week 6 [+ 7 days], Week 12 [± 3 days], and Week 18 [± 3 days])	Every 3 Months (± 1 Week) (Starting at Month 6)	EOA Visit [b]	Every 3 Months (± 3 Weeks)
PROPHYLACTIC MEDICATIONS																					
Ondansetron				X	X																
Filgrastim [bb]												X	X	X	X	X	X	X	X		
Fluconazole [cc]												X	X	X	X	X	X	X	X		
TMP-SMX DS, or appropriate ABX [dd]																X	X	X	X		
Broad spectrum ABX				X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Valacyclovir/acyclovir [w]	X [w]	X [w]	X [w]													X	X	X	X		

Biomarkers:
Biomarkers, or immune monitoring, include peripheral blood mononuclear cells (PBMCs), serum, plasma and tumor specimens that will be collected to test for cellular and soluble factors, via immunological assays and molecular assays related to exome sequencing, TCR sequencing, mRNA analysis, and immunohistochemistry staining.

Objectives

Primary Objective
Evaluate the efficacy of LN-144 in patients with unresectable or metastatic melanoma using the ORR, as assessed by the IRC per RECIST v1.1.
Secondary objectives
- Evaluate the efficacy endpoints of duration of response (DOR), disease control rate (DCR), and PFS, as assessed by the IRC per RECIST v1.1

- Further evaluate efficacy of LN-144 in patients with unresectable or metastatic melanoma by assessing ORR, DOR, DCR, and PFS, as assessed by the Investigator per RECIST v1.1

- Evaluate OS

- Characterize the safety profile of LN-144 in patients with unresectable or metastatic melanoma

Outcomes/endpoints
Primary endpoint
The primary efficacy endpoint is ORR as assessed by the IRC using RECIST v1.1, which will be analyzed in FAS. It is derived as the number of patients who have the best overall response (BOR) of complete response (CR) or partial response (PR) as assessed by IRC divided by the number of patients in the FAS x 100%. In order for the BOR to be categorized as CR or PR, a confirmatory evaluation is required 4 weeks or more apart after the first CR or PR. To determine BOR, all tumor response assessments up to the first PD per RECIST v1.1 should be considered. Any further tumor response assessments after the first PD or after the start of a new anti-cancer therapy are not considered.

Patients without any baseline or any post-baseline measurements are considered non-evaluable (NE). ORR is expressed as a binomial proportion and will be summarized as a point estimate and its two-sided 95% confidence interval based on the Clopper Pearson exact method.

Secondary endpoints

DOR, DCR, and PFS will be analyzed per RECIST v1.1 as assessed by IRC and by investigator, respectively.

DOR is defined as the time (in months) from the time point at which the initial measurement criteria per RECIST v1.1 are met for a CR or PR, whichever response is observed first, until the first date that PD is objectively documented, or the patient expires. Patients not experiencing PD or who have not died prior to the time of data cut will have their event times censored at the last adequate tumor assessment. For patients who received new anticancer therapies, DOR will be censored at the date of last tumor response assessment prior to the start of new anticancer therapies. Patients with PD or death immediately after two or more consecutive missing tumor assessment visits, the DOR will be censored at the last adequate tumor assessment prior to the missing tumor assessments. The median DOR and its 95% CI will be obtained using the KM method for patients achieving a response (CR or PR).

DCR is defined as the proportion of patients who have the BOR of CR or PR, stable disease (SD), or non-CR/non-PD, where non-CR/non-PD is only for patients without target lesions. DCR is expressed as a binomial proportion and will be summarized using a point estimate and its two-sided 95% CIs based on the Clopper-Pearson exact method.

PFS is defined as the time (in months) from the date of lifileucel infusion to PD or death due to any cause, whichever occurs earlier for Safety Analysis Set, and from the date of TH to PD or death due to any cause for TH set. Patients not experiencing PD or not having died at the time of the data cut will have their event times censored at the last adequate tumor assessment. For patients who received new anti-cancer therapy, the PFS will be censored at the date of last tumor response assessment prior to the start of new anticancer therapies. Patients with PD or death immediately after two or more consecutive missing tumor assessment visits, the PFS will be censored at the last adequate tumor assessment prior to the missing tumor assessments. The median PFS with its 95% CIs and PFS at appropriate time points (e.g. Months 6, 9, 12, and 18) will be obtained using the KM method.

OS is defined as the time (in months) from the date of LN-144 infusion to death due to any cause. Patients not having died at the time of data cut will have their event times censored on the last date of their known survival status. The date of last known alive will be derived as the latest among dosing records, safety and any other assessment dates indicating that a patient is alive. The median OS with its 95% CI and OS at appropriate time points (e.g. Months 6, 9, 12, and 18) will be obtained using the KM method.

ORR as assessed by Investigator per RECIST v1.1 will be analyzed for FAS patients in the same fashion as assessed by IRC per RECIST v1.1. ORR is expressed as a binomial proportion and will be summarized using a point estimate and its two-sided 95% CIs based on the Clopper-Pearson exact method.

Sample size

Cohort 1: Infused 23 patients using the non-cryopreserved autologous TIL product manufacturing process. Enrollment into this cohort was stopped to focus on the Gen-2 cryopreserved autologous TIL product.

Cohort 2: Approximately 60 patients are planned to be infused in Cohort 2. Sixty patients will allow estimation of ORR using the maximum half width of the two-sided 95% Clopper-Pearson Confidence Interval (CI) of less than 13.2% when ORR is expected to range from 20–50%.

Cohort 3: This cohort is expected to infuse approximately 10 patients from Cohorts 1, 2, or 4 who have elected to undergo a second LN-144 treatment.

Cohort 4: Approximately 75 patients are planned to be infused and receive cryopreserved LN-144. A sample size of 75 patients in the FAS will provide more than 90% power to demonstrate statistical significance to H0: ORR ≤ 10% at a two-sided overall significance level of 0.05 using the exact test assuming the true response rate for LN-144 therapy in this study population is 25%.

Randomisation and blinding (masking)

This study is an open-label, single arm study; as such, treatment was not blinded.

To maintain the integrity of the study-conduct and ensure the validity of the IRC data as well as the efficacy data as assessed by the Investigator in this single-arm registrational study, data restriction and confidentiality procedures were initiated for Cohort 4 up to the database lock. In addition, an Independent Data Monitoring Committee (IDMC), established via protocol v9.0, provided oversight of the study to ensure it was conducted with the highest quality, scientific, and ethical standards. It also ensured the quality and consistency of data collection and analyses across international sites (ie, Europe and the US).

Analysis sets

The TH Set (also termed Enrolled Set) is defined as all tumor-resected patients for production of LN-144, regardless of whether they have received LN-144 or not.

The Safety Analysis Set is defined as patients who have received any LN-144 infusion.

The FAS is defined as patients who have received LN-144 that meets the final manufacturing product Specifications.

Statistical methods

Analysis of the Primary Efficacy Endpoint

The ORR as assessed by the IRC is expressed as binomial proportions and will be summarized for the best overall response using a point estimate and its two-sided confidence limits based on the Clopper Pearson exact method, at an overall alpha level of 0.05.

Analysis of the Secondary Efficacy Endpoints

The DCR is expressed as binomial proportions and will be summarized using both a point estimate and its two-sided 95% confidence limits based on the Clopper-Pearson exact method.

The PFS, OS, and DOR are time-to-event variables subjected to right censoring. Kaplan- Meier probabilities and related summary statistics will be provided for the entire time-to event curve as well as for the following landmark event-free rates: 6 months, 12 months, 18 months, and 24 months from

the date on which patients received LN-144 infusion (Day 0), depending on the maturity of the study data at the time of analysis.

Planned subgroup analyses

Subgroup analysis of ORR and DCR by IRC will be performed in the following critical demographic and baseline disease characteristics for the Safety Analysis Set and TH set. Other subgroup analyses may be performed if deemed necessary.

- Age category (< 65 years and ≥ 65 years)
- Gender (male, female)
- Number of prior lines of therapy (1 to 3 vs ≥ 4)
- Prior anti-CTLA4 therapy use (yes, no)
- BRAF mutation status (BRAF V600E or V600K mutated, others including BRAF wild type, other mutation or unknown)
- Geographic region (United States, Europe)
- ECOG performance status at baseline (0, ≥1)
- Tumor PD-L1 expression (TPS ≥5%, TPS <5%; TPS ≥1%, TPS <1%)
- LDH value at baseline (≤ ULN, > ULN; ≤ ULN, 1-2xULN, >2xULN)
- Primary refractory to anti-PD-1/anti-PD-L1 (yes, no)
- Contract Manufacturing Organization (WuXi, Lonza, and Moffitt)
- Baseline target lesion SOD (<70, ≥70 mm; < median vs ≥ median)
- Number of baseline target and non-target lesions (≤ 3, >3)
- Patients with baseline liver lesion
- Patients with baseline brain and/or liver lesion
- Time from stop of anti-PD-1/PD-L1 to TIL infusion (≤ median vs > median)
- Cumulative time on prior anti-PD-1/PD-L1 (≤ median vs > median)
- Mucosal melanoma (yes, no)

Error probabilities, adjustment for multiplicity and interim analyses

At the time of primary analysis, the hypothesis testing of the primary efficacy endpoint, ORR as assessed by the IRC per RECIST v1.1, will be performed in Cohort 4 for the FAS as following:

Hypothesis for Cohort 4: H01: ORR≤ 10% vs. Ha1: ORR>10%

The null hypothesis H01 will be tested at significance level of 5% (two-sided). The hypothesis will be rejected if the lower bound of the two-sided 95% Clopper-Pearson CI for the primary efficacy endpoint in Cohort 4 FAS is greater than 10%. The study is considered to have met its primary objective if the null hypothesis H01 is rejected.

If the null hypothesis for Cohort 4 (H01) is rejected, a second hypothesis testing of the primary efficacy endpoint will be performed based on the combined Cohorts 2 and 4 data. The same enrollment criteria, the same cryopreserved TIL manufacturing process, and the same treatment regimen between Cohort 2 and Cohort 4 support pooling of the data.

Hypothesis for combined Cohorts 2 and 4: H02: ORR≤ 10% vs. Ha2: ORR>10%

Similarly, H02 will be tested at significance level of 5% (two-sided). The hypothesis will be rejected if the lower bound of the two-sided 95% Clopper-Pearson CI for the primary efficacy endpoint in combined Cohorts 2 and 4 FAS is greater than 10%.

The null hypothesis for combined Cohorts 2 and 4 (H02) will only be tested after the null hypothesis for Cohort 4 (H01) is rejected. This fixed sequence testing procedure is used to ensure strong control of the family-wise error rate at a two-sided significance level of 5%. The statistical hypothesis for the primary efficacy endpoint will be tested only once at the primary statistical analysis. The primary efficacy endpoint might be summarized descriptively based on a different data cut after the primary statistical analysis but not for statistical hypothesis testing.

Changes from protocol-specified analyses
- FAS definition is further clarified as "patients who have received LN-144 that meets the final manufacturing product specifications"
Justification: to ensure that efficacy analyses will be performed on patients who received LN- 144 that meets product specifications to align with FDA's Response to Sponsor's Question 4 in the memorandum dated June 24, 2019.

- Safety Analysis Set is added for safety analyses, defined as "patients who have received any LN-144 infusion".
Justification: to ensure that safety analyses will be performed on all patients who received any LN-144 infusion irrespective of meeting final product specifications.

- An additional hypothesis testing will be performed on combined Cohorts 2 and 4 data after the null hypothesis of primary endpoint based on Cohort 4 is rejected.
Justification: Given the same enrollment criteria, the same cryopreserved TIL manufacturing process, and the same treatment regimen between Cohort 2 and Cohort 4, data from combined two cohorts with larger sample size provide additional evidence to evaluate the primary efficacy endpoint in unresectable or metastatic melanoma patient population in addition to data from Cohort 4. The family-wise error rate at a two-sided significance level of 5% is controlled since null hypothesis for combined Cohorts 2 and 4 will only be tested after null hypothesis for Cohort 4 is rejected.

Results

Participant flow

Figure 3 Patient Populations from Screening to Full Analysis Set

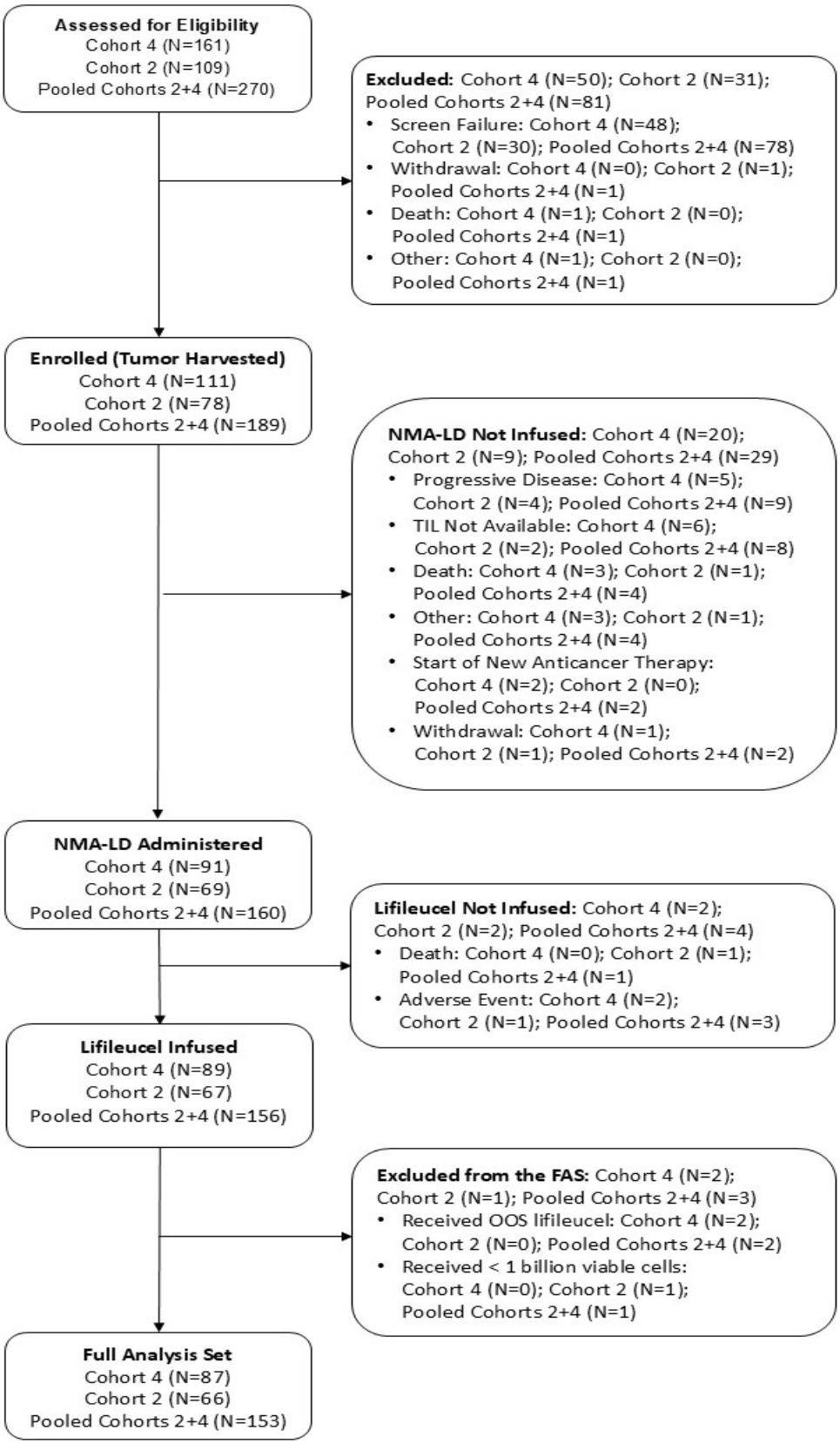

Assessed for Eligibility
Cohort 4 (N=161)
Cohort 2 (N=109)
Pooled Cohorts 2+4 (N=270)
Excluded: Cohort 4 (N=50); Cohort 2 (N=31); Pooled Cohorts 2+4 (N=81)
• Screen Failure: Cohort 4 (N=48); Cohort 2 (N=30); Pooled Cohorts 2+4 (N=78)
• Withdrawal: Cohort 4 (N=0); Cohort 2 (N=1); Pooled Cohorts 2+4 (N=1)
• Death: Cohort 4 (N=1); Cohort 2 (N=0); Pooled Cohorts 2+4 (N=1)
• Other: Cohort 4 (N=1); Cohort 2 (N=0); Pooled Cohorts 2+4 (N=1)
Enrolled (Tumor Harvested)
Cohort 4 (N=111)
Cohort 2 (N=78)
Pooled Cohorts 2+4 (N=189)
NMA-LD Not Infused: Cohort 4 (N=20); Cohort 2 (N=9); Pooled Cohorts 2+4 (N=29)
• Progressive Disease: Cohort 4 (N=5); Cohort 2 (N=4); Pooled Cohorts 2+4 (N=9)
• TIL Not Available: Cohort 4 (N=6); Cohort 2 (N=2); Pooled Cohorts 2+4 (N=8)
• Death: Cohort 4 (N=3); Cohort 2 (N=1); Pooled Cohorts 2+4 (N=4)
• Other: Cohort 4 (N=3); Cohort 2 (N=1); Pooled Cohorts 2+4 (N=4)
• Start of New Anticancer Therapy: Cohort 4 (N=2); Cohort 2 (N=0); Pooled Cohorts 2+4 (N=2)
• Withdrawal: Cohort 4 (N=1); Cohort 2 (N=1); Pooled Cohorts 2+4 (N=2)
NMA-LD Administered
Cohort 4 (N=91)
Cohort 2 (N=69)
Pooled Cohorts 2+4 (N=160)
Lifileucel Not Infused: Cohort 4 (N=2); Cohort 2 (N=2); Pooled Cohorts 2+4 (N=4)
• Death: Cohort 4 (N=0); Cohort 2 (N=1); Pooled Cohorts 2+4 (N=1)
• Adverse Event: Cohort 4 (N=2); Cohort 2 (N=1); Pooled Cohorts 2+4 (N=3)
Lifileucel Infused
Cohort 4 (N=89)
Cohort 2 (N=67)
Pooled Cohorts 2+4 (N=156)
Excluded from the FAS: Cohort 4 (N=2); Cohort 2 (N=1); Pooled Cohorts 2+4 (N=3)
• Received OOS lifileucel: Cohort 4 (N=2); Cohort 2 (N=0); Pooled Cohorts 2+4 (N=2)
• Received < 1 billion viable cells: Cohort 4 (N=0); Cohort 2 (N=1); Pooled Cohorts 2+4 (N=1)
Full Analysis Set
Cohort 4 (N=87)
Cohort 2 (N=66)
Pooled Cohorts 2+4 (N=153)

Table 1 Patient Disposition (Tumor Harvested Set)

	Cohort 4 (N=111) n (%)	Cohort 2 (N=78) n (%)	Pooled Cohorts 2 and 4 (N=189) n (%)
Tumor Harvested Set (Enrolled Set)	111 (100)	78 (100)	189 (100)
Safety Analysis Set	89 (80.2)	67 (85.9)	156 (82.5)
Full Analysis Set	87 (78.4)	66 (84.6)	153 (81.0)
Patients who received lifileucel of < 1 billion viable cells	0	1 (1.3)	1 (0.5)
Patients who received lifileucel out of specifications	2 (1.8)	0	2 (1.1)
Patients who did not receive lifileucel	22 (19.8)	11 (14.1)	33 (17.5)
Patients Who Received 2 Courses of Lifileucel Treatment	7 (6.3)	4 (5.1)	11 (58)
Patients in Tumor Harvested Set Who Did Not Receive lifileucel [1]	22 (19.8)	11 (14.1)	33 (17.5)
Primary Reason for Not Receiving lifileucel			
Adverse Event	2 (1.8)	1 (1.3)	3 (1.6)
Death	3 (2.7)	2 (2.6)	5 (2.6)
Partial Withdrawal of Consent	1 (0.9)	0	1 (0.5)
TIL Not Available	6 (5.4)	2 (2.6)	8 (4.2)
Withdrawal by Patient	0	1 (1.3)	1 (0.5)
Progressive Disease	5 (4.5)	4 (5.1)	9 (4.8)
Start of a New Anti-cancer Therapy	2 (1.8)	0	2 (1.1)
COVID-19	0	0	0
Other	3 (2.7)	1 (1.3)	4 (2.1)
Patients in Full Analysis Set Who Discontinued Assessment Period [2]	79 (90.8)	61 (92.4)	140 (91.5)
Primary Reason for End of Assessment			
Completed	0	6 (9.1)	6 (3.9)
Adverse Event	2 (2.3)	0	2 (1.3)
Death	3 (3.4)	7 (10.6)	10 (6.5)
Lost to Follow-up	1 (1.1)	0	1 (0.7)
Physician Decision	0	1 (1.5)	1 (0.7)
Partial Withdrawal of Consent	2 (2.3)	0	2 (1.3)
Withdrawal by Patient	0	2 (3.0)	2 (1.3)
Progressive Disease	65 (74.7)	42 (63.6)	107 (69.9)
Start of a New Anti-cancer Therapy	5 (5.7)	3 (4.5)	8 (5.2)
COVID-19	0	0	0
Other	1 (1.1)	0	1 (0.7)
Patients in Full Analysis Set Who Discontinued from Study [2]	71 (81.6)	59 (89.4)	130 (85.0)
Primary Reason for End of Study			
Completed	0	7 (10.6)	7 (4.6)
Death	67 (77.0)	48 (72.7)	115 (75.2)
Lost to Follow-up	1 (1.1)	4 (6.1)	5 (3.3)
Withdrawal by Patient	3 (3.4)	0	3 (2.0)
COVID-19	0	0	0

Abbreviations: COVID-19 = coronavirus disease of 2019; TIL = tumor-infiltrating lymphocytes
Notes: The Tumor Harvested Set (Enrolled Set) is defined as all tumor-resected patients for production of lifileucel regardless whether they received lifileucel or not.
The Safety Analysis Set is defined as patients who received any lifileucel infusion.
The Full Analysis Set is defined as patients who received lifileucel that met the manufacturing product specifications.
[1] Percentages are calculated using Tumor Harvested Set.
[2] Percentages are calculated using Full Analysis Set.
Source: C-144-01, Program: t14-1-2-2-1-disp-c2c4-th Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Three lifileucel-infused patients in the Safety Analysis Set were excluded from the FAS because they were infused with lifileucel that did not meet the manufacturing product specification (2 patients in Cohort 4) or received a dose of lifileucel that was less than the minimum dose specified per product release criteria (1 patient in Cohort 2).

In total 22 patients in cohort 4 TH dataset did not receive Lifleucel due to different reasons (table 1). No detailed anylysis was provided for patients listed under categories “TIL not available” (6 patients) and “other” (3 patients). The applicant should provide the specific reasons why patients did not receive lifileucel (new OC).

Recruitment

TH dataset:

	Cohort 4	**Cohort 2**
First patient enrolled	26 Feb 2019	11 Apr 2017
Last patient enrolled	19 Dec 2019	17 Jan 2019
First patient's lifileucel infusion	26 Mar 2019	17 May 2017
Last patient's lifileucel infusion	15 Jan 2020	11 Mar 2019

Data cut-off date for primary analysis: 15 Sep 2021

Latest data cut-off date: 30 Jun 2023

Study status: closed

At the DCO (30 Jun 2023) for Cohort 2 and 4 had a median follow-up of 45.6 months for responses (previously 21.5 months in the primary analysis) and a median of 48.1 months of follow-up for survival (previously 27.6 months in the primary analysis).

The applicant proposes pooling of data from cohort 2 and 4 based on similarity of included population, recipient of the cryopreserved TIL, treatment regimen and observed ORR results which are similar in both cohorts and are over 10%. However, in view of the methodological concerns regarding study integrity in cohort 2, pooling of data from the cohorts is not agreed upon. In addition, due to the numerous protocol amendments in cohort 2, cohort 4 is considered to be the pivotal part of Study C-144-01 where potentially a reasonable level of pre-definition has been in place before inclusion of patients. This is discussed further in section 3.3.5 *Discussion on clinical efficacy.*

Conduct of the study

The original protocol (Version 1) was dated 30 Dec 2014. The final version (ie, Version 9) was dated 22 Oct 2019.

Table 4 Protocol Amendments

Version No.	Date	Key Change(s)	Rationale
1	19 Dec 2014	Initial IND/Initial Protocol Version	N/A
2	NA	Not submitted to IND/No patients treated	N/A
3	16 Jul 2015	Inclusion/Exclusion Criteria	
		Included patients > 18 years of age	Based on unmet need
		Safety Procedures	
		DSMB added	Enhance safety monitoring
		Updated text of "The final cell product" and added information on product administration	Provided clarity, and additional details on product description and administration for consistency
		Correct IL-2 administration route and management of IL-2 toxicity	Corrected IL-2 administration to occur by IV infusion and not IV bolus, toxicity managed by Institution standard
4	18 Jul 2016	Inclusion/Exclusion Criteria	
		Clarified criteria for patients > 65 years of age	Safety precaution
		Excluded patients with melanoma of uveal/ocular origin	These tumors are genetically distinct from cutaneous melanomas; thus, they should be studied separately
		No lower limit of number of TIL infused	No data existed justifying a lower limit
		Secondary Efficacy Endpoints	
		Added CR rate, PFS, DOR, and OS	Include additional measures of efficacy
5	04 Feb 2017	Study Design	
		Added 2 cohorts to evaluate treatment with cryopreserved lifileucel product (Cohorts 2 and 3)	Include the investigation of a cryopreserved lifileucel product and allow the option of retreatment for eligible patients
		Total patients changed from 20 to 40 (20 Cohort 1 + 20 Cohort 2; Cohort 3 = retreatment cohort)	
6	13 May 2017	Study Design	
		Increased total planned pts, from 40 to 60 (30 Cohort 1 [closed] + 30 Cohort 2)	Accommodate study objective changes and statistical analyses
		Study Objectives	
		Primary objective changed from "characterize safety profile" to "evaluate efficacy using the objective response rate (ORR)". Safety profile characterization changed to secondary objective.	Align with regulatory guidance
		Inclusion Criteria	
		Patients must have unresectable metastatic melanoma (Stage IIIc or Stage IV) and must have progressed following ≥ 1 line of prior systemic therapy, including immune checkpoint inhibitor (eg, anti-PD-1), and if BRAF mutation-positive, after BRAF inhibitor systemic therapy	Align patient population with regulatory guidance and study objectives
		Added patients must have an "estimated life expectancy of > 3 months"	Same as above
		Specified that patients > 70 years of age must have Medical Monitor's consent to be enrolled	Safety precaution
7	23 Mar 2018	Study Design	
		Total patients (ie, Cohort 1 [closed] + Cohort 2) increased from 60 to 85 (minimum of 60 in Cohort 2)	Accommodate study objective changes and statistical analyses
		Study Objectives	Align with regulatory guidance
		Primary objective pertaining to efficacy evaluation using ORR was clarified by adding "as assessed by the Investigator per…"	
		Secondary objective pertaining to assessment of response rates and PFS by the IRC was clarified, with addition of "…per RECIST v1.1"	
		Study Drug Administration	
		Required premedication prior to the infusion of lifileucel for prophylaxis	Provide additional safety precautions and guidance due to 2 SAEs of hypersensitivity reactions.
8	20 Dec 2018	Study Design	
		Added Cohort 4, ~ 75 patients	Align with regulatory guidance to support product registration
		Primary endpoint of ORR per RECIST v1.1 was to be assessed by the IRC, not Investigator.	
		Statistical and analysis plans updated to include the following analysis populations: Tumor Harvested Set (TH Set; Enrolled Set) and Full Analysis Set (FAS)	Define analysis populations
		Study Procedures	
		IRC to be implemented to review Cohort 4 efficacy data	Align with regulatory guidance to support product registration

		Updated lifileucel Toxicity Prevention and Management to provide clearer, more comprehensive AE management guidance.	Provide safety guidance
9	22 Oct 2019	Study Design Established IDMC	Align with regulatory guidance to support product registration; ensure highest quality, scientific, and ethical standards; and consistency of study conduct and data collection/analysis across international study sites
		Updated the role of the DSMB	Clarification of the DSMB responsibility for Cohort 3 (Protocol Version 8.0, Addendum 1)
		Study Drug Administration Replaced prior guidance allowing stopping fludarabine dosing after 2 doses, based solely upon ALC levels being below a specified threshold (ie, 100/mm^3). Clarified that the full 5-dose fludarabine course is to be given with dose hold or discontinuation allowed only in the case of toxicity described in its prescribing information or per institutional standards.	Ensure thorough lymphodepletion and that dosing practices are consistent.
		Clarified range of cell numbers per lifileucel dose: 1×10^9 to 150×10^9 cells. Clarified patients would receive the full dose of product manufactured and released.	See Dose Selection (Section 9.4.4)
		High-resolution CT with PO/IV contrast or contrast-enhanced MRI is the preferred imaging modality for assessing radiographic tumor response.	PET is not an allowable modality for RECIST assessment. PET alone is not sufficient for tumor assessment.
		All references to an interim analysis of data for Cohort 4 were deleted.	Per discussion with FDA, no interim analysis is planned.

Abbreviations: AE = adverse event; ALC = absolute lymphocyte count; BRAF = proto-oncogene B-Raf; CR = complete response; CT = computerized tomography; DOR = duration of response; DSMB = Data and Safety Monitoring Board; FAS = Full Analysis Set; FDA = Food and Drug Administration; IDMC = Independent Data Monitoring Committee; IL-2 = interleukin-2; IND = Investigational New Drug; IRC = Independent Review Committee; IV = intravenous; MRI = magnetic resonance imaging; N/A = not applicable; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein 1; PET = positron emission tomography; PFS = progression-free survival; PO = per os; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TH = Tumor Harvested; TIL = tumor-infiltrating lymphocytes.

The number of patients in the Tumour Harvested analysis set (N=189) that were enrolled under each protocol version are presented in the table below.

Version No.	Date	Cohort 2	Cohort 4
1	19 Dec 2014	0	0
2	NA	0	0
3	16 Jul 2015	0	0
4	18 Jul 2016	3	0
5	04 Feb 2017	17	0
6	13 May 2017	38	0
6.1	18 SEP 2017	2	0
7	23 Mar 2018	18	0
8	20 Dec 2018	0	111
9	22 Oct 2019	0	0
Total		78	111

Table 1 Important Protocol Deviations (Cohorts 2 and 4 Tumour Harvested Set)

Category	Cohort 4 (N=111) n (%)	Cohort 2 (N=78) n (%)	Pooled Cohorts 2 and 4 (N=189) n (%)
Number of patients with at least one important protocol deviation	2 (1.8)	3 (3.8)	5 (2.6)
Eligibility Criteria	0	1 (1.3)	1 (0.5)
Investigational Product	1 (0.9)	0	1 (0.5)
Informed Consent	1 (0.9)	2 (2.6)	3 (1.6)

The applicant stated that the study was conducted in accordance with the provisions of the Declaration of Helsinki (Oct 2008) and all revisions thereof, and in accordance with FDA regulations (21 Code of Federal Regulations [CFR] Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

Baseline data

Tumor Harvested Dataset

Clinical Study Report Addendum — Protocol: C-144-01

Table 14.1.5.5.1 Demographics
Cohorts 2 and 4 Tumor Harvested Set

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Gender, n (%)			
Female	51 (45.9)	37 (47.4)	88 (46.6)
Male	60 (54.1)	41 (52.6)	101 (53.4)
Age, (years)			
n	111	78	189
Mean (SD)	54.0 (12.65)	54.0 (11.45)	54.0 (12.14)
Median	55.0	55.0	55.0
Min, Max	25, 74	20, 79	20, 79
Age, n (%)			
<40	18 (16.2)	9 (11.5)	27 (14.3)
>=40 - <65	66 (59.5)	53 (67.9)	119 (63.0)
>=65	27 (24.3)	16 (20.5)	43 (22.8)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	1 (0.9)	2 (2.6)	3 (1.6)
Black or African American	2 (1.8)	2 (2.6)	4 (2.1)
White	107 (96.4)	73 (93.6)	180 (95.2)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (0.9)	1 (1.3)	2 (1.1)
Ethnicity, n (%)			
Hispanic or Latino	3 (2.7)	5 (6.4)	8 (4.2)
Not Hispanic or Latino	107 (96.4)	63 (80.8)	170 (89.9)
Unknown	1 (0.9)	10 (12.8)	11 (5.8)
Weight (kg)			
n	111	78	189
Mean (SD)	78.84 (19.062)	82.39 (19.932)	80.30 (19.453)
Median	77.10	80.55	78.70
Min, Max	44.9, 133.7	46.3, 143.6	44.9, 143.6
BMI (kg/m^2)			
n	111	78	189
Mean (SD)	26.37 (5.166)	27.72 (6.082)	26.93 (5.587)
Median	25.26	26.88	26.05
Min, Max	16.2, 41.8	17.5, 46.8	16.2, 46.8
Region, n (%)			
US	66 (59.5)	66 (84.6)	132 (69.8)
Europe	45 (40.5)	12 (15.4)	57 (30.2)
Country, n (%)			
United States	66 (59.5)	66 (84.6)	132 (69.8)
France	1 (0.9)	2 (2.6)	3 (1.6)
Germany	26 (23.4)	0	26 (13.8)
Hungary	0	2 (2.6)	2 (1.1)
Spain	12 (10.8)	3 (3.8)	15 (7.9)
Switzerland	1 (0.9)	1 (1.3)	2 (1.1)
United Kingdom	5 (4.5)	4 (5.1)	9 (4.8)

BMI = Body Mass Index. SD = Standard Deviation.

Source: C-144-01, Program: t14-1-5-5-1-demo-c2c4-th.sas, Data: ADSL (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Table 2 Baseline Disease Characteristics – Cohorts 2 and 4 Tumour Harvested Set

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Screening ECOG Score, n (%)			
0	78 (70.3)	50 (64.1)	128 (67.7)
1	33 (29.7)	28 (35.9)	61 (32.3)
>=2	0	0	0
Prior therapy treatment setting, n (%)			

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Adjuvant/Neoadjuvant only	5 (4.5)	4 (5.1)	9 (4.8)
Metastatic only	67 (60.4)	50 (64.1)	117 (61.9)
Both Adjuvant/Neoadjuvant and Metastatic	39 (35.1)	24 (30.8)	63 (33.3)
Number of Adjudicated Prior Therapies			
n	111	78	189
Mean (SD)	3.2 (1.65)	3.3 (1.71)	3.3 (1.67)
Median	3.0	3.0	3.0
Min, Max	1, 8	1, 9	1, 9
Prior Therapy Category, n (%)			
Anti-CTLA4	92 (82.9)	61 (78.2)	153 (81.0)
Anti-PD-1/PD-L1	111 (100)	78 (100)	189 (100)
Anti-PD-1/CTLA4 Combo	63 (56.8)	40 (51.3)	103 (54.5)
BRAF/MEK Inhibitor [1]	33 (29.7)	20 (25.6)	53 (28.0)
IL-2	7 (6.3)	8 (10.3)	15 (7.9)
Patients with > 1 prior line containing anti-PD-1/L1, n (%)	67 (60.4)	39 (50.0)	106 (56.1)
Resistance to prior anti-PD-1/L1 defined by SITC definition, n (%)			
All resistant	105 (94.6)	75 (96.2)	180 (95.2)
Primary resistance to prior anti-PD-1/L1 [2]	72 (64.9)	61 (78.2)	133 (70.4)
Secondary resistance to prior anti-PD-1/L1 [3]	33 (29.7)	14 (17.9)	47 (24.9)
Late Progressor	2 (1.8)	2 (2.6)	4 (2.1)
Not Evaluable	4 (3.6)	1 (1.3)	5 (2.6)
Cumulative Duration on Prior Anti-PD-1/L1 (Months)			
n	111	78	189
Mean (SD)	12.513 (12.1801)	8.184 (8.6629)	10.726 (11.0503)
Median	9.791	4.895	6.932
Min, Max	0.20, 75.83	1.35, 51.12	0.20, 75.83
Stage at Study Entry, n (%)			
IIIC	3 (2.7)	10 (12.8)	13 (6.9)
IV	108 (97.3)	68 (87.2)	176 (93.1)
Disease metastasis at Study Entry, n (%)			
M0	0	NA	NA
M1a	13 (11.7)	NA	NA
M1b	14 (12.6)	NA	NA
M1c	69 (62.2)	NA	NA
M1d	12 (10.8)	NA	NA
Resected Tumour Site, n (%)			
Lymph Node	27 (24.3)	23 (29.5)	50 (26.5)
Skin/Subcutaneous	31 (27.9)	12 (15.4)	43 (22.8)
Other	13 (11.7)	29 (37.2)	42 (22.2)
Lung	14 (12.6)	1 (1.3)	15 (7.9)
Liver	8 (7.2)	6 (7.7)	14 (7.4)
Peritoneal/Retroperitoneal	6 (5.4)	2 (2.6)	8 (4.2)
Other Visceral	4 (3.6)	3 (3.8)	7 (3.7)
Breast	4 (3.6)	2 (2.6)	6 (3.2)
Musculoskeletal	4 (3.6)	0	4 (2.1)
Missing	1 (0.9)	0	1 (0.5)
Patients with Mucosal Melanoma, n (%)	9 (8.1)	4 (5.1)	13 (6.9)

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
% PD-L1 Tumour Proportion Score (TPS) per Central Laboratory, n (%)			
PD-L1 High/Positive (TPS >=1%)	39 (35.1)	37 (47.4)	76 (40.2)
PD-L1 Negative (TPS <1%)	21 (18.9)	12 (15.4)	33 (17.5)
PD-L1 Positive (TPS >=5%)	20 (18.0)	23 (29.5)	43 (22.8)
PD-L1 Negative (TPS <5%)	40 (36.0)	26 (33.3)	66 (34.9)
Missing	51 (45.9)	29 (37.2)	80 (42.3)
BRAF Status, n(%)			
Mutated (V600E or V600K)	33 (29.7)	22 (28.2)	55 (29.1)
Wild Type	73 (65.8)	51 (65.4)	124 (65.6)
Other	5 (4.5)	1 (1.3)	6 (3.2)
Unknown	0	4 (5.1)	4 (2.1)
Baseline Lactate Dehydrogenase (U/L), n (%)			
<=ULN	37 (33.3)	43 (55.1)	80 (42.3)
1-2 x ULN	46 (41.4)	24 (30.8)	70 (37.0)
>2 x ULN	28 (25.2)	11 (14.1)	39 (20.6)
Target Lesion Sum of Diameter Assessed by Investigator (mm)			
n	103	71	174
Mean (SD)	103.44 (70.955)	110.11 (74.230)	106.16 (72.172)
Median	84.00	102.00	86.00
Min, Max	10.0, 325.0	11.0, 343.0	10.0, 343.0
Number of Baseline Target and Non-target Lesions Assessed by Investigator			
n	103	71	174
Mean (SD)	6.2 (2.94)	5.5 (2.75)	5.9 (2.87)
Median	6.0	5.0	5.5
Min, Max	1, 15	1, 14	1, 15
Number of Baseline Target and Non-target Lesions Assessed by Investigator, n (%)			
<=3	18 (16.2)	17 (21.8)	35 (18.5)
>3	85 (76.6)	54 (69.2)	139 (73.5)
Missing	8 (7.2)	7 (9.0)	15 (7.9)

[1] Includes patients who are BRAF V600E or V600K mutated and received BRAF Inhibitor +/- MEK Inhibitor.
[2] Includes primary resistance to prior anti-PD-1/PD-L1 in metastatic setting and primary resistance/early relapse to prior anti-PD-1/PD-L1 in adjuvant setting (Kluger 2020).
[3] Includes secondary resistance to prior anti-PD-1/PD-L1 in metastatic setting and late relapse in adjuvant setting (Kluger 2020).

Table 3 Summary of Baseline Brain and Other Visceral Lesion - Cohorts 2 and 4 Tumour Harvested Set

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Patients with Baseline Brain Lesion by investigator, n (%)	17 (15.3)	8 (10.3)	25 (13.2)
Patients with Baseline brain lesion only (no any other visceral lesions) by investigator, n (%)	1 (0.9)	3 (3.8)	4 (2.1)
Patients with Baseline Brain and Other Visceral Lesion (including liver) by investigator, n (%)	16 (14.4)	5 (6.4)	21 (11.1)
Patients with Baseline Brain and Liver Lesion by investigator, n (%)	11 (9.9)	3 (3.8)	14 (7.4)
Patients with Baseline Brain and Other Visceral Lesion (excluding liver) by investigator, n (%)	5 (4.5)	2 (2.6)	7 (3.7)
Patients with Baseline Liver Lesion by investigator, n (%)	42 (37.8)	26 (33.3)	68 (36.0)

Table 4 Prior Anticancer Therapies (Cohorts 2 and 4 Tumour Harvested Set)

	Cohort 4 (N=111)	**Cohort 2 (N=78)**	**Pooled Cohorts 2 and 4 (N=189)**
Prior therapy treatment setting, n (%)			
Adjuvant/Neoadjuvant only	5 (4.5)	4 (5.1)	9 (4.8)
Metastatic only	67 (60.4)	50 (64.1)	117 (61.9)
Both Adjuvant/Neoadjuvant and Metastatic	39 (35.1)	24 (30.8)	63 (33.3)
Number of Prior Treatment Lines (per Adjudication)			
Mean (SD)	3.2 (1.65)	3.3 (1.71)	3.3 (1.67)
Median	3.0	3.0	3.0
Min, Max	1, 8	1, 9	1, 9

Table 5 Summary of Prior Radiotherapy (Cohorts 2 and 4 Tumour Harvested Set)

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Number of Patients with Prior Radiotherapy, n (%)	63 (56.8)	42 (53.8)	105 (55.6)
Prior Radiotherapy Adjudicated Radiation Site, n (%)			
Abdomen	16 (14.4)	7 (9.0)	23 (12.2)
Extremity	3 (2.7)	4 (5.1)	7 (3.7)
Head and Neck	37 (33.3)	24 (30.8)	61 (32.3)
Lumbar	2 (1.8)	0	2 (1.1)
Other	2 (1.8)	7 (9.0)	9 (4.8)
Pelvis	13 (11.7)	9 (11.5)	22 (11.6)
Thorax	19 (17.1)	12 (15.4)	31 (16.4)

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Total Cumulative Dose, cGY [1]			
n [2]	49	31	80
Mean (SD)	8574.3 (23712.41)	25552.4 (39912.87)	15153.3 (31872.72)
Median	215.0	4800.0	1098.0
Min, Max	8, 129600	18, 144000	8, 144000
Time from the last stop date of prior radiotherapy to Tumour Harvest (months)			
n	63	42	105
Mean (SD)	11.406 (15.7200)	12.043 (16.4199)	11.660 (15.9282)
Median	6.768	5.142	6.144
Min [3], Max	-0.69, 66.63	0.46, 81.74	-0.69, 81.74

Notes: Radiotherapy modality details were not collected in database.
[1] Total cumulative dose is calculated by the number of doses multiplied by radiation (cGY) per dose.
[2] Refers to the number of patients with non-missing number of doses and radiation per dose.
[3] The last day of prior radiotherapy was after TH for 1 patient.

Safety analysis set (supportive)

Table 14.1.5.2.2 Demographics
Cohorts 2 and 4 Safety Analysis Set

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Gender, n (%)			
Female	44 (49.4)	28 (41.8)	72 (46.2)
Male	45 (50.6)	39 (58.2)	84 (53.8)
Age, (years)			
n	89	67	156
Mean (SD)	55.4 (11.93)	54.3 (11.40)	54.9 (11.68)
Median	58.0	55.0	56.0
Min, Max	25, 74	20, 79	20, 79
Age, n (%)			
<40	9 (10.1)	7 (10.4)	16 (10.3)
>=40 - <65	57 (64.0)	46 (68.7)	103 (66.0)
>=65	23 (25.8)	14 (20.9)	37 (23.7)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	1 (1.1)	2 (3.0)	3 (1.9)
Black or African American	2 (2.2)	1 (1.5)	3 (1.9)
White	85 (95.5)	64 (95.5)	149 (95.5)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1 (1.1)	0	1 (0.6)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.4)	5 (7.5)	8 (5.1)
Not Hispanic or Latino	85 (95.5)	55 (82.1)	140 (89.7)
Unknown	1 (1.1)	7 (10.4)	8 (5.1)

Weight (kg)			
n	89	67	156
Mean (SD)	78.35 (18.699)	82.86 (19.130)	80.29 (18.957)
Median	77.10	80.90	78.90
Min, Max	44.9, 133.7	49.7, 141.9	44.9, 141.9
BMI (kg/m^2)			
n	89	67	156
Mean (SD)	26.57 (5.188)	27.61 (5.814)	27.02 (5.472)
Median	25.79	26.38	26.10
Min, Max	16.2, 41.8	18.2, 45.6	16.2, 45.6
Region, n (%)			
US	55 (61.8)	56 (83.6)	111 (71.2)
Europe	34 (38.2)	11 (16.4)	45 (28.8)
Country, n (%)			
United States	55 (61.8)	56 (83.6)	111 (71.2)
France	1 (1.1)	2 (3.0)	3 (1.9)
Germany	19 (21.3)	0	19 (12.2)
Hungary	0	2 (3.0)	2 (1.3)
Spain	10 (11.2)	3 (4.5)	13 (8.3)
Switzerland	0	1 (1.5)	1 (0.6)
United Kingdom	4 (4.5)	3 (4.5)	7 (4.5)

BMI = Body Mass Index. SD = Standard Deviation.

Source: C-144-01, Program: t14-1-5-2-2-demo-c2c4-saf.sas, Data: ADSL (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Table 6 Baseline Disease Characteristics - Cohorts 2 and 4 Safety Analysis Set

	Cohort 4 (N=89)	**Cohort 2 (N=67)**	**Pooled Cohorts 2 and 4 (N=156)**
Screening ECOG Score, n (%)			
0	64 (71.9)	43 (64.2)	107 (68.6)
1	25 (28.1)	24 (35.8)	49 (31.4)
>=2	0	0	0
Number of Adjudicated Prior Therapies			
n	89	67	156
Mean (SD)	3.2 (1.62)	3.3 (1.71)	3.3 (1.65)
Median	3.0	3.0	3.0
Min, Max	1, 8	1, 9	1, 9
Prior Therapy Category, n (%)			
Anti-CTLA4	73 (82.0)	54 (80.6)	127 (81.4)
Anti-PD-1/PD-L1	89 (100)	67 (100)	156 (100)
Anti-PD-1/CTLA4 Combo	49 (55.1)	35 (52.2)	84 (53.8)
BRAF/MEK Inhibitor [1]	24 (27.0)	15 (22.4)	39 (25.0)
IL-2	6 (6.7)	7 (10.4)	13 (8.3)
Patients with > 1 prior line containing anti-PD-1/L1, n (%)	54 (60.7)	35 (52.2)	89 (57.1)
Resistance to prior anti-PD-1/L1 defined by SITC definition, n (%)			
All resistant	86 (96.6)	67 (100)	153 (98.1)
Primary resistance to prior anti-PD-1/L1 [2]	58 (65.2)	53 (79.1)	111 (71.2)
Secondary resistance to prior anti-PD-1/L1 [3]	28 (31.5)	14 (20.9)	42 (26.9)
Late Progressor	2 (2.2)	0	2 (1.3)
Not Evaluable	1 (1.1)	0	1 (0.6)
Cumulative Duration on Prior Anti-PD-1/ L1 (Months)			
n	89	67	156
Mean (SD)	12.829 (12.8706)	8.354 (8.8937)	10.907 (11.5181)
Median	10.021	5.027	6.932
Min, Max	0.66, 75.83	1.38, 51.12	0.66, 75.83
Stage at Study Entry, n (%)			
IIIC	1 (1.1)	9 (13.4)	10 (6.4)

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
IV	88 (98.9)	58 (86.6)	146 (93.6)
Disease metastasis at Study Entry, n (%)			
M0	0	NA	NA
M1a	11 (12.4)	NA	NA
M1b	12 (13.5)	NA	NA
M1c	55 (61.8)	NA	NA
M1d	10 (11.2)	NA	NA
Resected Tumour Site, n (%)			
Lymph Node	23 (25.8)	20 (29.9)	43 (27.6)
Other	12 (13.5)	26 (38.8)	38 (24.4)
Skin/Subcutaneous	22 (24.7)	9 (13.4)	31 (19.9)
Liver	7 (7.9)	5 (7.5)	12 (7.7)
Lung	11 (12.4)	1 (1.5)	12 (7.7)
Other Visceral	4 (4.5)	3 (4.5)	7 (4.5)
Peritoneal/Retroperitoneal	5 (5.6)	2 (3.0)	7 (4.5)
Breast	3 (3.4)	1 (1.5)	4 (2.6)
Musculoskeletal	2 (2.2)	0	2 (1.3)
Patients with Mucosal Melanoma, n (%)	7 (7.9)	3 (4.5)	10 (6.4)
% PD-L1 Tumour Proportion Score (TPS) per Central Laboratory, n (%)			
PD-L1 High/Positive (TPS >=1%)	39 (43.8)	37 (55.2)	76 (48.7)
PD-L1 Negative (TPS <1%)	21 (23.6)	12 (17.9)	33 (21.2)
PD-L1 Positive (TPS >=5%)	20 (22.5)	23 (34.3)	43 (27.6)
PD-L1 Negative (TPS <5%)	40 (44.9)	26 (38.8)	66 (42.3)
Missing	29 (32.6)	18 (26.9)	47 (30.1)
BRAF Status, n(%)			
Mutated (V600E or V600K)	24 (27.0)	17 (25.4)	41 (26.3)
Wild Type	60 (67.4)	46 (68.7)	106 (67.9)
Other	5 (5.6)	1 (1.5)	6 (3.8)
Unknown	0	3 (4.5)	3 (1.9)
Baseline Lactate Dehydrogenase (U/L), n (%)			
<=ULN	31 (34.8)	39 (58.2)	70 (44.9)
1-2 x ULN	36 (40.4)	19 (28.4)	55 (35.3)
>2 x ULN	22 (24.7)	9 (13.4)	31 (19.9)
Target Lesion Sum of Diameter Assessed by IRC (mm)			
n	88	63	151
Mean (SD)	126.30 (94.470)	108.66 (65.860)	118.94 (83.936)
Median	103.00	103.00	103.00
Min, Max	15.7, 552.9	13.5, 271.3	13.5, 552.9
Number of Baseline Target and Non-target Lesions Assessed by IRC			
n	89	65	154
Mean (SD)	6.3 (3.09)	5.4 (2.97)	5.9 (3.06)
Median	6.0	5.0	5.0
Min, Max	1, 16	1, 14	1, 16
Number of Baseline Target and Non-target Lesions Assessed by IRC, n (%)			
<=3	14 (15.7)	22 (32.8)	36 (23.1)

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
>3	75 (84.3)	43 (64.2)	118 (75.6)
Missing	0	2 (3.0)	2 (1.3)

[1] Includes patients who are BRAF V600E or V600K mutated and received BRAF Inhibitor +/- MEK Inhibitor.
[2] Includes primary resistance to prior anti-PD-1/PD-L1 in metastatic setting and primary resistance/early relapse to prior anti-PD-1/PD-L1 in adjuvant setting (Kluger 2020).
[3] Includes secondary resistance to prior anti-PD-1/PD-L1 in metastatic setting and late relapse in adjuvant setting (Kluger 2020).

Table 7 Summary of Baseline Brain and Other Visceral Lesion - Cohorts 2 and 4 Tumour Harvested Set

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Patients with Baseline Brain Lesion by investigator, n (%)	17 (15.3)	8 (10.3)	25 (13.2)
Patients with Baseline brain lesion only (no any other visceral lesions) by investigator, n (%)	1 (0.9)	3 (3.8)	4 (2.1)
Patients with Baseline Brain and Other Visceral Lesion (including liver) by investigator, n (%)	16 (14.4)	5 (6.4)	21 (11.1)
Patients with Baseline Brain and Liver Lesion by investigator, n (%)	11 (9.9)	3 (3.8)	14 (7.4)
Patients with Baseline Brain and Other Visceral Lesion (excluding liver) by investigator, n (%)	5 (4.5)	2 (2.6)	7 (3.7)
Patients with Baseline Liver Lesion by investigator, n (%)	42 (37.8)	26 (33.3)	68 (36.0)

Table 8 Prior Anticancer Therapies (Cohorts 2 and 4 Safety Analysis Set)

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Prior therapy treatment setting, n (%)			
Adjuvant/Neoadjuvant only	3 (3.4)	3 (4.5)	6 (3.8)
Metastatic only	51 (57.3)	44 (65.7)	95 (60.9)
Both Adjuvant/Neoadjuvant and Metastatic	35 (39.3)	20 (29.9)	55 (35.3)
Number of Prior Treatment Lines (per Adjudication)			
Mean (SD)	3.2 (1.62)	3.3 (1.71)	3.3 (1.65)
Median	3.0	3.0	3.0
Min, Max	1, 8	1, 9	1, 9

Table 9 Summary of Prior Radiotherapy (Cohorts 2 and 4 Safety Analysis Set)

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Number of Patients with Prior Radiotherapy, n (%)	44 (49.4)	35 (52.2)	79 (50.6)

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Prior Radiotherapy Adjudicated Radiation Site, n (%)			
Abdomen	11 (12.4)	5 (7.5)	16 (10.3)
Extremity	1 (1.1)	4 (6.0)	5 (3.2)
Head and Neck	24 (27.0)	20 (29.9)	44 (28.2)
Lumbar	2 (2.2)	0	2 (1.3)
Other	2 (2.2)	6 (9.0)	8 (5.1)
Pelvis	12 (13.5)	7 (10.4)	19 (12.2)
Thorax	11 (12.4)	10 (14.9)	21 (13.5)
Total Cumulative Dose, cGY [1]			
n [2]	32	26	58
Mean (SD)	5753.7 (17365.70)	16571.0 (31822.19)	10602.8 (25250.83)
Median	323.5	1318.0	800.0
Min, Max	8, 96000	18, 144000	8, 144000
Time from the last stop date of prior radiotherapy to Tumour Harvest (months)			
n	44	35	79
Mean (SD)	13.275 (17.3264)	13.469 (17.5076)	13.361 (17.2950)
Median	7.113	6.209	6.998
Min [3], Max	-0.69, 66.63	0.46, 81.74	-0.69, 81.74

Notes: Radiotherapy modality details were not collected in database.
[1] Total cumulative dose is calculated by the number of doses multiplied by radiation (cGY) per dose.
[2] Refers to the number of patients with non-missing number of doses and radiation per dose.
[3] The last day of prior radiotherapy was after TH for 1 patient.

Table 5 Most Common Concomitant Medications (≥ 40%) Reported (Safety Analysis Set)

ATC-2 Dictionary Level Preferred Name	Cohort 4 (N=89) n (%)	Cohort 2 (N=67) n (%)	Pooled Cohorts 2 and 4 (N=156) n (%)
ALL OTHER THERAPEUTIC PRODUCTS			
MESNA	89 (100)	67 (100)	156 (100)
ANALGESICS			
PARACETAMOL	85 (95.5)	60 (89.6)	145 (92.9)
PETHIDINE	30 (33.7)	27 (40.3)	57 (36.5)
PETHIDINE HYDROCHLORIDE	37 (41.6)	15 (22.4)	52 (33.3)
ANTIBACTERIALS FOR SYSTEMIC USE			
SULFAMETHOXAZOLE;TRIMETHOPRIM	56 (62.9)	47 (70.1)	103 (66.0)
VANCOMYCIN	36 (40.4)	31 (46.3)	67 (42.9)
CEFEPIME	33 (37.1)	31 (46.3)	64 (41.0)
ANTIEMETICS AND ANTINAUSEANTS			
ONDANSETRON	72 (80.9)	60 (89.6)	132 (84.6)
ANTIMYCOTICS FOR SYSTEMIC USE			
FLUCONAZOLE	82 (92.1)	57 (85.1)	139 (89.1)
ANTIVIRALS FOR SYSTEMIC USE			
ACICLOVIR	42 (47.2)	38 (56.7)	80 (51.3)
BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS			
PLATELETS	55 (61.8)	43 (64.2)	98 (62.8)
SODIUM CHLORIDE	44 (49.4)	43 (64.2)	87 (55.8)
POTASSIUM CHLORIDE	50 (56.2)	28 (41.8)	78 (50.0)
MAGNESIUM SULFATE	35 (39.3)	31 (46.3)	66 (42.3)
RED BLOOD CELLS, CONCENTRATED	38 (42.7)	20 (29.9)	58 (37.2)
DIURETICS			
FUROSEMIDE	74 (83.1)	43 (64.2)	117 (75.0)
DRUGS FOR ACID RELATED DISORDERS			
FAMOTIDINE	42 (47.2)	30 (44.8)	72 (46.2)
IMMUNOSTIMULANTS			
FILGRASTIM	71 (79.8)	52 (77.6)	123 (78.8)
MINERAL SUPPLEMENTS			
POTASSIUM CHLORIDE	38 (42.7)	31 (46.3)	69 (44.2)
PSYCHOLEPTICS			
LORAZEPAM	38 (42.7)	34 (50.7)	82 (52.6)

Abbreviations: ATC = Anatomical Therapeutic Chemical; NMA-LD = nonmyeloablative lymphodepletion; TIL = tumor-infiltrating lymphocytes; WHO = World Health Organization

Notes: Concomitant medications are defined as medications that are either initiated before and continued after the first dose of NMA-LD or initiated after the first dose of NMA-LD through 30 days post-TIL infusion, not including study regimen.

Coded using WHO Drug version B3 Global 2021Q1.

A patient with multiple incidences of a given preferred name is counted only once under the specific preferred name.

Source: C-144-01, Program: t14-1-9-2-2-conmed-40pt-c2c4-saf Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

BMI = Body Mass Index. SD = Standard Deviation.

Source: C-144-01, Program: t14-1-5-5-1-demo-c2c4-th.sas, Data: ADSL (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Numbers analysed

The Tumor Harvested Set is defined as all tumor-resected patients for production of LN-144, regardless of whether they have received LN-144 or not.
Cohort 2 N=78
Cohort 4 N= 111
Pooled cohorts 2+4 N=189

The Safety Analysis Set is defined as patients who have received any LN-144 infusion.
Cohort 2 N= 67
Cohort 4 N= 89
Pooled cohorts 2+4 N=156

The Full Analysis Set is defined as patients who have received LN-144 that meets the final manufacturing product
Specifications.
Cohort 2 N= 66
Cohort 4 N= 87
Pooled cohorts 2+4 N=153

Tumor Harvested (TH) Set is consider as the primary efficacy set and Safety Analysis Set is considered to be supportive.

Outcomes and estimation

Primary endpoint:

ORR by the IRC

Tumor harvest set:

Summary of Clinical Efficacy — Protocol: C-144-01

Table 2.7.3.3.2 Summary of Response (ORR, DCR, BOR) - by IRC per RECIST v1.1
Cohorts 2 and 4 Tumor Harvest Set

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Objective Response Rate, n (%) (95% CI)	25 (22.5) (15.1, 31.4)	23 (29.5) (19.7, 40.9)	48 (25.4) (19.4, 32.2)
Disease Control Rate, n (%) (95% CI)	72 (64.9) (55.2, 73.7)	48 (61.5) (49.8, 72.3)	120 (63.5) (56.2, 70.4)
Best Overall Response, n (%)			
CR	4 (3.6)	5 (6.4)	9 (4.8)
PR	21 (18.9)	18 (23.1)	39 (20.6)
SD	47 (42.3)	24 (30.8)	71 (37.6)
NN	0	1 (1.3)	1 (0.5)
PD	13 (11.7)	15 (19.2)	28 (14.8)
NE	26 (23.4)	15 (19.2)	41 (21.7)

BOR = Best Overall Response. CI = Confidence Interval. CR = Complete Response. DCR = Disease control rate. IRC = Independent Review Committee. NE = Not Evaluable. NN = Non-CR/Non-PD. ORR = Objective response rate. PD = Progressive Disease. PR = Partial Response. SD = Stable Disease.

Notes: Patients who had tumor harvested but did not receive TIL, 22 patients in Cohort 4 and 11 patients in Cohort 2, are considered as non-responders with BOR of NE.
Non-CR/Non-PD is for patients who did not have acceptable target lesions by IRC assessment.
Objective response refers to patients with best overall response of CR and PR.
Disease control refers to patients with best overall response of CR, PR, SD and NN.
95% CI is calculated using the Clopper-Pearson Exact test.

Source: C-144-01, Program: t2-7-3-3-2-rsp-irc-c2c4-th.sas, Data: ADSL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Safety analysis set:

Table 2.7.3.3.1 Summary of Response (ORR, DCR, BOR) - by IRC per RECIST v1.1
Cohorts 2 and 4 Safety Analysis Set

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Objective Response Rate, n (%) (95% CI)	25 (28.1) (19.1, 38.6)	23 (34.3) (23.2, 46.9)	48 (30.8) (23.6, 38.6)
Disease Control Rate, n (%) (95% CI)	72 (80.9) (71.2, 88.5)	48 (71.6) (59.3, 82.0)	120 (76.9) (69.5, 83.3)
Best Overall Response, n (%)			
CR	4 (4.5)	5 (7.5)	9 (5.8)
PR	21 (23.6)	18 (26.9)	39 (25.0)
SD	47 (52.8)	24 (35.8)	71 (45.5)
NN	0	1 (1.5)	1 (0.6)
PD	13 (14.6)	15 (22.4)	28 (17.9)
NE	4 (4.5)	4 (6.0)	8 (5.1)

BOR = Best Overall Response. CI = Confidence Interval. CR = Complete Response. DCR = Disease control rate. IRC = Independent Review Committee. NE = Not Evaluable. NN = Non-CR/Non-PD. ORR = Objective response rate. PD = Progressive Disease. PR = Partial Response. SD = Stable Disease.

Notes: Non-CR/Non-PD is for patients who did not have acceptable target lesions by IRC assessment.
Objective response refers to patients with best overall response of CR and PR.
Disease control refers to patients with best overall response of CR, PR, SD and NN.
95% CI is calculated using the Clopper-Pearson Exact test.

Source: C-144-01, Program: t2-7-3-3-1-rsp-irc-c2c4-saf.sas, Data: ADSL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

ORR by IL-2 doses, safety analysis set:

Table 2.7.3.8.4 Objective Response Rate by IL-2 doses - by IRC per RECIST v1.1
Cohorts 2 and 4 Safety Analysis Set

	Cohort 4 (N=89)		Cohort 2 (N=67)		Pooled Cohorts 2 and 4 (N=156)	
Objective Response Rate by Subgroup	n/N1 (%)	95% CI	n/N1 (%)	95% CI	n/N1 (%)	95% CI
IL-2 doses						
1 - 4	5/ 18 (27.8)	(9.7, 53.5)	9/ 24 (37.5)	(18.8, 59.4)	14/ 42 (33.3)	(19.6, 49.5)
5 - 6	20/ 69 (29.0)	(18.7, 41.2)	14/ 42 (33.3)	(19.6, 49.5)	34/111 (30.6)	(22.2, 40.1)
1 - 2	1/ 5 (20.0)	(0.5, 71.6)	5/ 11 (45.5)	(16.7, 76.6)	6/ 16 (37.5)	(15.2, 64.6)
3 - 4	4/ 13 (30.8)	(9.1, 61.4)	4/ 13 (30.8)	(9.1, 61.4)	8/ 26 (30.8)	(14.3, 51.8)
5 - 6	20/ 69 (29.0)	(18.7, 41.2)	14/ 42 (33.3)	(19.6, 49.5)	34/111 (30.6)	(22.2, 40.1)
Patients with prior IL-2 in metastatic setting [1]	0/ 1	(0, 97.5)	2/ 4 (50.0)	(6.8, 93.2)	2/ 5 (40.0)	(5.3, 85.3)

CI = Confidence Interval. IRC = Independent Review Committee. N1 = number of patients in the specific subgroup. % = n/N1*100.

Notes: 95% CI is calculated using the Clopper-Pearson Exact test.

[1] Not including investigational IL-2 agents administered as part of combination regimens.

Source: C-144-01, Program: t2-7-3-8-4-orr-il2-irc-c2c4-saf.sas, Data: ADSL, ADBL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

ORR by infused TIL viable cells:

Table 6_D120 Objective Response Rate and Clinical Benefit Rate by Subgroup - by IRC per RECIST v1.1
Cohorts 2 and 4 Tumor Harvested Set

	Cohort 4 (N=111)		Cohort 2 (N=78)		Pooled Cohorts 2 and 4 (N=189)	
	n/N1 (%)	95% CI	n/N1 (%)	95% CI	n/N1 (%)	95% CI
Objective Response Rate by Infused TIL viable cells [1]						
Patients who didn't receive TIL (0 viable cells)	0/ 22	-	0/ 11	-	0/ 33	-
<=Median	9/ 45 (20.0)	(9.6, 34.6)	6/ 34 (17.6)	(6.8, 34.5)	14/ 79 (17.7)	(10.0, 27.9)
>Median	16/ 44 (36.4)	(22.4, 52.2)	17/ 33 (51.5)	(33.5, 69.2)	34/ 77 (44.2)	(32.8, 55.9)
Clinical Benefit Rate by Infused TIL viable cells [1]						
Patients who didn't receive TIL (0 viable cells)	0/ 22	-	0/ 11	-	0/ 33	-
<=Median	21/ 45 (46.7)	(31.7, 62.1)	16/ 34 (47.1)	(29.8, 64.9)	35/ 79 (44.3)	(33.1, 55.9)
>Median	26/ 44 (59.1)	(43.2, 73.7)	20/ 33 (60.6)	(42.1, 77.1)	48/ 77 (62.3)	(50.6, 73.1)

CI = Confidence Interval. IRC = Independent Review Committee. N1 = number of patients in the specific subgroup. % = n/N1*100.

Notes: Objective response refers to patients with best overall response of CR or PR.
Clinical Benefit refers to patients with best overall response of CR, PR, or SD >= 2.8 months.

[1] Median was 20.50 x10^9, 24.03 x10^9, and 21.09 x10^9 Cells for cohort 4, cohort 2, and pooled cohorts 2 and 4 respectively.

Source: C-144-01, Program: t6-d120-orr-irc-sub-c2c4-saf.sas (Date of Report: 03Feb2025) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Secondary and other endpoints:

ORR by Inv

Table 2.7.3.9.2 Concordance of Objective Responses per RECIST v1.1 between IRC and Investigator Assessments
Cohorts 2 and 4 Tumor Harvest Set

	Objective Responses per Investigator Cohort 4		Objective Responses per Investigator Cohort 2		Objective Responses per Investigator Pooled Cohorts 2 and 4	
Objective Responses per IRC	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Responder	21	4	20	3	41	7
Non-responder	3	83	4	51	7	134

Table 2.7.3.9.2 Concordance of Objective Responses per RECIST v1.1 between IRC and Investigator Assessments
Cohorts 2 and 4 Tumor Harvest Set

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
ORR per IRC, n (%)	25 (22.5)	23 (29.5)	48 (25.4)
ORR per Investigator, n (%)	24 (21.6)	24 (30.8)	48 (25.4)
Concordance Rate	93.7%	91.0%	92.6%
Cohen's Kappa coefficient (95% CI)	0.82 (0.69, 0.95)	0.79 (0.64, 0.94)	0.80 (0.71, 0.90)
p-value	<0.0001	<0.0001	<0.0001

Safety analysis set (supportive)

Summary of Clinical Efficacy Protocol: C-144-01

Table 2.7.3.9.1 Concordance of Objective Responses per RECIST v1.1 between IRC and Investigator Assessments
Cohorts 2 and 4 Safety Analysis Set

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
ORR per IRC, n (%)	25 (28.1)	23 (34.3)	48 (30.8)
ORR per Investigator, n (%)	24 (27.0)	24 (35.8)	48 (30.8)
Concordance Rate	92.1%	89.6%	91.0%
Cohen's Kappa coefficient (95% CI)	0.80 (0.66, 0.94)	0.77 (0.61, 0.93)	0.79 (0.68, 0.89)
p-value	<0.0001	<0.0001	<0.0001

CI = Confidence Interval. IRC = Independent Review Committee. ORR = Objective Response Rate.

Source: C-144-01, Program: t2-7-3-9-1-orr-concor-c2c4-saf.sas, Data: ADSL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Table 2.7.3.9.1 Concordance of Objective Responses per RECIST v1.1 between IRC and Investigator Assessments
Cohorts 2 and 4 Safety Analysis Set

	Objective Responses per Investigator Cohort 4		Objective Responses per Investigator Cohort 2		Objective Responses per Investigator Pooled Cohorts 2 and 4	
Objective Responses per IRC	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Responder	21	4	20	3	41	7
Non-responder	3	61	4	40	7	101

CI = Confidence Interval. IRC = Independent Review Committee. ORR = Objective Response Rate.

Source: C-144-01, Program: t2-7-3-9-1-orr-concor-c2c4-saf.sas, Data: ADSL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Duration of response, time to first response and time to best response

DOR analyses only include responders and the responders are the same for all analysis sets.

Table 6 Duration of Response, Time to First Response, and Time to Best Response as Assessed by the IRC per RECIST v1.1 for Confirmed Responders (Full Analysis Set)

	Cohort 4 (N=25)	Cohort 2 (N=23)	Pooled Cohorts 2 and 4 (N=48)
DOR [1], months			
Median (95% CI)	10.4 (4.1, 26.2)	NR (NR, NR)	36.5 (8.3, NR)
Min, Max	1.4+, 45.8+	1.4+, 55.8+	1.4+, 55.8+
Probability of remaining in response at, % (95% CI) [1]			
12 Months	50.0 (29.1, 67.8)	85.0 (60.4, 94.9)	65.5 (49.4, 77.6)
24 Months	40.0 (20.4, 59.0)	79.3 (53.7, 91.7)	57.6 (41.2, 70.9)
36 Months	30.0 (12.8, 49.4)	79.3 (53.7, 91.7)	51.5 (35.1, 65.7)
48 Months	NR (NR, NR)	79.3 (53.7, 91.7)	48.1 (31.6, 62.8)
Follow-up time for Response [2], months			
Median (95% CI)	42.3 (12.5, NR)	51.9 (16.6, 54.2)	45.6 (21.5, 54.0)
Time to First Response, months			
Mean (SD)	1.915 (0.8970)	1.654 (0.6553)	1.790 (0.7932)
Median	1.478	1.446	1.446
Min, Max	1.28, 4.24	1.31, 4.11	1.28, 4.24
Time to Best Response, months			
Mean (SD)	3.463 (5.8361)	4.398 (7.4321)	3.911 (6.5932)
Median	1.544	1.446	1.478
Min, Max	1.28, 30.42	1.35, 29.63	1.28, 30.42
Patients who had Stable Disease and improved to confirmed Partial Response, n (%)	7 (28.0)	3 (13.0)	10 (20.8)
Patients who had Partial Response and improved to confirmed Complete Response, n (%)	4 (16.0)	3 (13.0)	7 (14.6)
Patients who had Response Starting on Day 42 visit, n (%)	19 (76.0)	20 (87.0)	39 (81.3)

Abbreviations: CI = confidence interval; DOR = duration of response; IRC = Independent Review Committee; max = maximum; min = minimum; NR = not reached; RECIST = Response Evaluation Criteria in Solid Tumors; SD = standard deviation
[1] Based on Kaplan-Meier estimates.
[2] Based on the reverse Kaplan-Meier method.
Source: C-144-01 CSR Addendum Table 14.2.1.3.2.1 and C-144-01 CSR Addendum Table 14.2.1.6.2.1

Updated follow-up data

Table 10 Summary Statistics for Study Follow-Up Time (Tumour Harvested Set)

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Study Follow-up Time until the last known alive date prior to the data cutoff date, months [1]			
Median	10.7	13.1	12.0
Min, Max	0.9, 49.7	0.7, 62.2	0.7, 62.2
Study Follow-up Time until the data cut-off date, months [2]			
Median	46.2	61.8	49.5
Min, Max	42.4, 52.1	53.4, 74.6	42.4, 74.6

[1] Defined as the time in months from the date of tumour harvested to the last known alive date, which is derived from the latest among dosing records, safety and any other assessment dates indicating that a patient is alive or death date if patient has died.
[2] Defined as the time in months from the date of tumour harvested to the data cutoff date.

Table 10 Duration of Response as Assessed by the IRC per RECIST v1.1 in Confirmed Responders (Full Analysis Set)

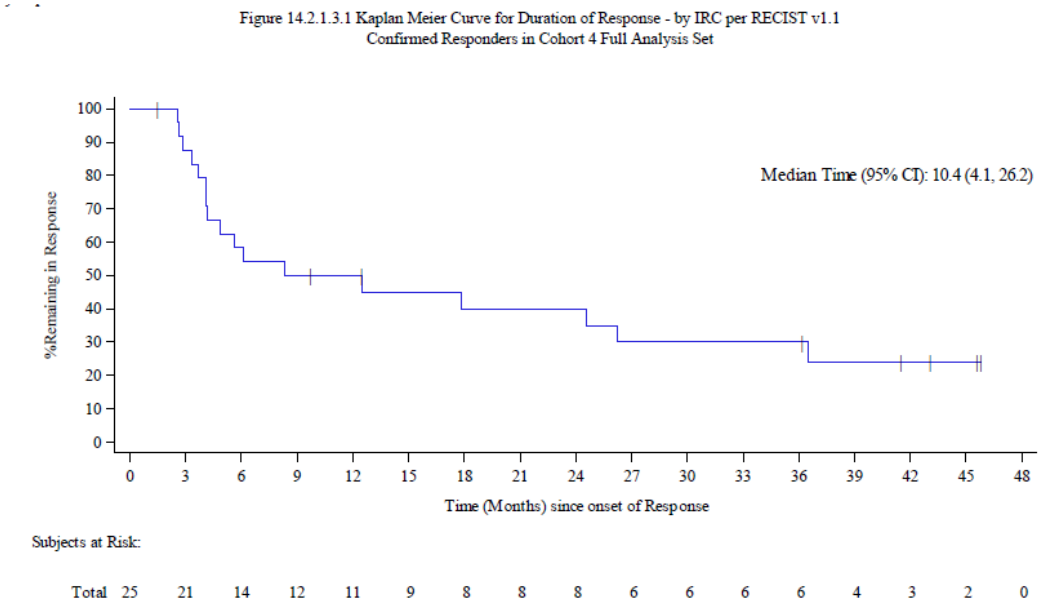
	Cohort 4 (N=25)	Cohort 2 (N=23)	Pooled Cohorts 2 and 4 (N=48)
Events, n (%)	17 (68.0)	4 (17.4)	21 (43.8)
Progressive disease	17	4	21
Death	0	0	0
Censored, n (%)	8 (32.0)	19 (82.6)	27 (56.3)
Primary Reason for Censoring			
Death or PD after 2 or more missed visits	2 (8.0)	0	2 (4.2)
Start of a new anti-cancer therapy	1 (4.0)	8 (34.8)	9 (18.8)
Discontinued assessment without PD or death	0	6 (26.1)	6 (12.5)
Ongoing without PD or death	5 (20.0)	5 (21.7)	10 (20.8)
DOR [1], months			
Median (95% CI)	10.4 (4.1, 26.2)	NR (NR, NR)	36.5 (8.3, NR)
Min, Max	1.4+, 45.8+	1.4+, 55.8+	1.4+, 55.8+
Probability of remaining in response at, % (95% CI) [1]			
12 months	50.0 (29.1, 67.8)	85.0 (60.4, 94.9)	65.5 (49.4, 77.6)
24 months	40.0 (20.4, 59.0)	79.3 (53.7, 91.7)	57.6 (41.2, 70.9)
36 months	30.0 (12.8, 49.4)	79.3 (53.7, 91.7)	51.5 (35.1, 65.7)
48 months	NE	79.3 (53.7, 91.7)	48.1 (31.6, 62.8)
DOR [2], n(%)			
>= 6 months	14 (56.0)	16 (69.6)	30 (62.5)
>= 9 months	12 (48.0)	15 (65.2)	27 (56.3)
>= 12 months	11 (44.0)	15 (65.2)	26 (54.2)
>= 15 months	9 (36.0)	15 (65.2)	24 (50.0)
>= 18 months	8 (32.0)	13 (56.5)	21 (43.8)
>= 24 months	8 (32.0)	11 (47.8)	19 (39.6)
>= 36 months	6 (24.0)	10 (43.5)	16 (33.3)
>= 42 months	3 (12.0)	10 (43.5)	13 (27.1)
>= 48 months	0	10 (43.5)	10 (20.8)
Follow-up time for Response [3], months			
Median (95% CI)	42.3 (12.5, NR)	51.9 (16.6, 54.2)	45.6 (21.5, 54.0)

Abbreviations: CI = confidence interval; DOR = duration of response; IRC = Independent Review Committee; max = maximum; min = minimum; NE = not evaluable; NR = not reached; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors
[1] Based on Kaplan-Meier product-limit estimates.
[2] Based on the observed rate.
[3] Based on the reverse Kaplan-Meier method.
Source: Table 14.2.1.3.2.1

Table 10 Summary Statistics for IRC Response Follow-Up Time (Responders in the Safety Analysis Set)

	Cohort 4 (N=25)	Cohort 2 (N=23)	Pooled Cohorts 2 and 4 (N=48)
Response Follow-up Time until PD or death or censoring prior to the data cutoff date, months [1]			
Median	8.3	21.5	13.8
Min, Max	1.4, 45.8	1.4, 55.8	1.4, 55.8
Response Follow-up Time until the data cut-off date, months [2]			
Median	42.3	57.9	48.8
Min, Max	38.5, 49.3	51.8, 72.0	38.5, 72.0

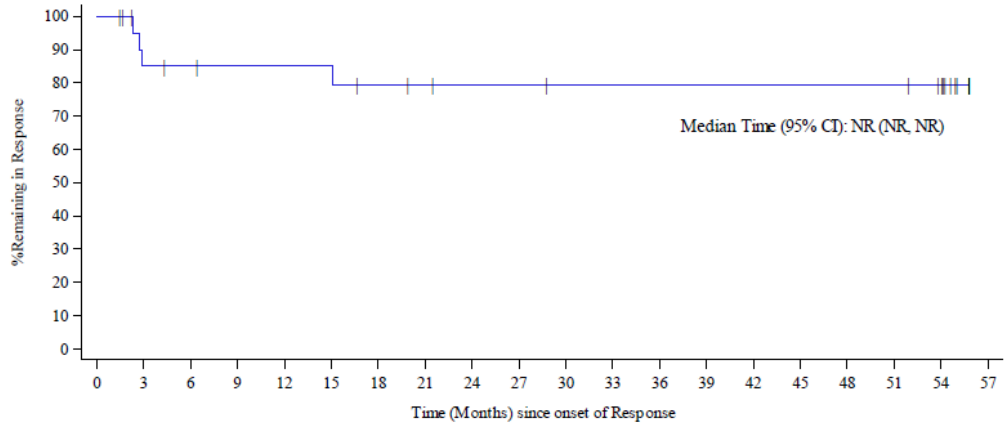
[1] Defined as the time in months from the onset of response to the date of the last adequate tumour assessment if patients did not experience progression or died, or the first date that progressive disease is objectively documented or the death date. If patients had new anticancer therapy, DOR was censored at the last adequate tumour assessment prior to new anticancer therapy. If patients had PD or death immediately after 2 or more consecutive missing tumour assessment visits, DOR was censored at the last adequate tumour assessment prior to the missing visits.
[2] Defined as the time in months from the onset date of response to the data cutoff date.



DoR = Duration of Response. CI = Confidence Interval.

Source: C-144-01, Program: f14-2-1-3-1-dor-irc-c4-fas.sas, Data: ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Figure 14.2.1.3.2 Kaplan Meier Curve for Duration of Response - by IRC per RECIST v1.1
Confirmed Responders in Cohort 2 Full Analysis Set



Subjects at Risk:

Total	23	17	16	15	15	15	13	12	11	11	10	10	10	10	10	10	10	8	0

DoR = Duration of Response. CI = Confidence Interval. NR = Not Reached.

Source: C-144-01, Program: f14-2-1-3-2-dor-irc-c2-fas.sas, Data: ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

DCR, BOR by IRC

Table 19 Disease Control Rate and Best Overall Response as Assessed by the IRC per RECIST v1.1 (Tumor Harvested Set)

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Disease Control Rate, n (%) (95% CI)	72 (64.9) (55.2, 73.7)	48 (61.5) (49.8, 72.3)	120 (63.5) (56.2, 70.4)
Best Overall Response, n (%)			
CR	4 (3.6)	5 (6.4)	9 (4.8)
PR	21 (18.9)	18 (23.1)	39 (20.6)
SD	47 (42.3)	24 (30.8)	71 (37.6)
NN	0	1 (1.3)	1 (0.5)
PD	13 (11.7)	15 (19.2)	28 (14.8)
NE	26 (23.4)	15 (19.2)	41 (21.7)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; IRC = Independent Review Committee; NE = not evaluable; NN = non-CR/non-PD; PD = progressive disease; PR = partial response; SD = stable disease
Notes: Non-CR/Non-PD is for patients who did not have acceptable target lesions by IRC assessment.
Disease control refers to patients with a BOR of CR, PR, SD, and NN.
95% CI was calculated using the Clopper-Pearson Exact test.
Source: Table 2.7.3.3.2

Table 15 Disease Control Rate and Best Overall Response as Assessed by the IRC per RECIST v1.1 (Safety Analysis Set)

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Disease Control Rate, n (%) (95% CI)	72 (80.9) (71.2, 88.5)	48 (71.6) (59.3, 82.0)	120 (76.9) (69.5, 83.3)
Best Overall Response, n (%)			
CR	4 (4.5)	5 (7.5)	9 (5.8)
PR	21 (23.6)	18 (26.9)	39 (25.0)
SD	47 (52.8)	24 (35.8)	71 (45.5)
NN	0	1 (1.5)	1 (0.6)
PD	13 (14.6)	15 (22.4)	28 (17.9)
NE	4 (4.5)	4 (6.0)	8 (5.1)

Abbreviations: BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; IRC = Independent Review Committee; NE = not evaluable; NN = non-CR/non-PD; PD = progressive disease; PR = partial response; SD = stable disease
Notes: Non-CR/Non-PD is for patients who did not have acceptable target lesions by IRC assessment.
Disease control refers to patients with a BOR of CR, PR, SD, and NN.
95% CI was calculated using the Clopper-Pearson Exact test.
Source: Table 2.7.3.3.1

PFS by IRC

Table 20 Progression-Free Survival (per EMA Guideline) as Assessed by the IRC per RECIST v1.1 (Tumor Harvested Set)

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Events, n (%)	95 (85.6)	62 (79.5)	157 (83.1)
Progressive disease	63	43	106
Death	32	19	51
Censored, n (%)	16 (14.4)	16 (20.5)	32 (16.9)
Primary Reason for Censoring			
Discontinued assessment without PD or death	3 (2.7)	9 (11.5)	12 (6.3)
Ongoing without PD or death	6 (5.4)	5 (6.4)	11 (5.8)
No baseline tumor assessment	7 (6.3)	2 (2.6)	9 (4.8)
Time to Event [1], months			
Median (95% CI)	4.9 (4.0, 5.8)	5.0 (3.7, 5.9)	5.0 (4.1, 5.4)
Progression-free Survival Rate (%) (95% CI) [1]			
at 12 months	19.7 (12.6, 27.9)	30.9 (20.9, 41.5)	24.4 (17.9, 31.4)
at 24 months	10.5 (5.5, 17.5)	21.5 (13.0, 31.4)	16.3 (10.9, 22.6)
at 36 months	8.4 (4.0, 14.9)	16.8 (9.2, 26.3)	12.0 (7.7, 17.4)
at 48 months	6.1 (2.5, 12.2)	16.8 (9.2, 26.3)	10.6 (6.5, 15.8)

Abbreviations: CI = confidence interval; EMA = European Medicines Agency; IRC = Independent Review Committee; PD = progressive disease; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors
[1] Based on Kaplan-Meier product-limit estimates.
PFS was defined as the time (in months) from the date of tumor resection to PD or death due to any cause, whichever occurred earlier. Patients not experiencing PD or not having died at the time of the data cut had their event times censored at the last adequate tumor assessment.
EMA censoring definition: For patients with PD or death after single missing tumor assessment visit, the PFS was considered as having an event at date of progression assessment or death. Missing assessments or initiation of new anticancer therapy did not result in censoring for PFS (EMA Guideline on the evaluation of anticancer medicinal products in man, 2017).
Source: Table 2.7.3.6.2

Table 2.7.3.5.2 Progression-free Survival - by IRC per RECIST v1.1 (per FDA guideline)
Cohorts 2 and 4 Tumor Harvest Set

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Events, n (%)	76 (68.5)	45 (57.7)	121 (64.0)
Progressive disease	57	37	94
Death	19	8	27
Censored, n (%)	35 (31.5)	33 (42.3)	68 (36.0)
Primary Reason for Censoring			
Death or PD after 2 or more missed visits	2 (1.8)	2 (2.6)	4 (2.1)
Start of a new anti-cancer therapy	11 (9.9)	12 (15.4)	23 (12.2)
Discontinued assessment without PD or death	1 (0.9)	7 (9.0)	8 (4.2)
Ongoing without PD or death	6 (5.4)	5 (6.4)	11 (5.8)
No baseline tumor assessment	15 (13.5)	7 (9.0)	22 (11.6)
Time to Event [1], months			
Median (95% CI)	4.4 (3.9, 5.5)	5.0 (3.6, 7.0)	4.4 (4.0, 5.4)
Progression-free Survival Rate (%) (95% CI) [1]			
Progression-free Survival at 3 months	75.5 (65.5, 83.0)	68.3 (55.9, 77.8)	72.4 (64.9, 78.6)
Progression-free Survival at 6 months	37.6 (27.4, 47.7)	38.4 (26.5, 50.1)	37.9 (30.1, 45.6)
Progression-free Survival at 9 months	26.3 (17.4, 36.1)	36.5 (24.8, 48.2)	30.3 (23.0, 37.9)
Progression-free Survival at 12 months	21.3 (13.2, 30.7)	34.3 (22.7, 46.2)	26.3 (19.3, 33.8)
Progression-free Survival at 18 months	15.5 (8.5, 24.5)	34.3 (22.7, 46.2)	22.9 (16.2, 30.3)
Progression-free Survival at 24 months	14.0 (7.3, 22.8)	30.0 (18.8, 42.0)	20.2 (13.8, 27.5)
Progression-free Survival at 30 months	10.9 (5.0, 19.2)	30.0 (18.8, 42.0)	18.2 (12.0, 25.4)
Progression-free Survival at 36 months	10.9 (5.0, 19.2)	30.0 (18.8, 42.0)	18.2 (12.0, 25.4)
Progression-free Survival at 42 months	9.1 (3.8, 17.3)	30.0 (18.8, 42.0)	17.1 (11.0, 24.2)
Progression-free Survival at 48 months	9.1 (3.8, 17.3)	30.0 (18.8, 42.0)	17.1 (11.0, 24.2)

CI = Confidence Interval. PD = Progressive Disease.

[1] Based on Kaplan-Meier product-limit estimates.

Source: C-144-01, Program: t2-7-3-5-2-pfs-irc-fda-c2c4-th.sas, Data: ADSL and ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Safety analysis dataset (supportive)

Table 2.7.3.6.1 Progression-free Survival - by IRC per RECIST v1.1 (per EMA guideline)
Cohorts 2 and 4 Safety Analysis Set

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Events, n (%)	80 (89.9)	53 (79.1)	133 (85.3)
Progressive disease	63	43	106
Death	17	10	27
Censored, n (%)	9 (10.1)	14 (20.9)	23 (14.7)
Primary Reason for Censoring			
Discontinued assessment without PD or death	3 (3.4)	9 (13.4)	12 (7.7)
Ongoing without PD or death	6 (6.7)	5 (7.5)	11 (7.1)
Time to Event [1], months			
Median (95% CI)	3.8 (2.8, 4.9)	4.1 (2.8, 6.1)	4.1 (2.8, 4.4)
Progression-free Survival Rate (%) (95% CI) [1]			
Progression-free Survival at 3 months	53.1 (42.2, 62.9)	55.0 (42.3, 66.0)	54.0 (45.8, 61.5)
Progression-free Survival at 6 months	32.3 (22.8, 42.2)	39.7 (28.0, 51.2)	35.5 (28.0, 43.1)
Progression-free Survival at 9 months	21.9 (13.9, 31.1)	35.1 (23.9, 46.6)	27.6 (20.8, 34.9)
Progression-free Survival at 12 months	19.6 (12.1, 28.6)	30.5 (19.9, 41.8)	24.4 (17.9, 31.4)
Progression-free Survival at 18 months	12.4 (6.5, 20.4)	24.4 (14.9, 35.3)	17.6 (12.0, 24.1)
Progression-free Survival at 24 months	11.2 (5.6, 18.9)	22.9 (13.7, 33.6)	16.3 (10.9, 22.6)
Progression-free Survival at 30 months	8.7 (3.9, 15.9)	21.1 (12.2, 31.7)	14.1 (9.0, 20.2)
Progression-free Survival at 36 months	8.7 (3.9, 15.9)	19.2 (10.6, 29.7)	13.3 (8.4, 19.3)
Progression-free Survival at 42 months	7.5 (3.1, 14.4)	19.2 (10.6, 29.7)	12.5 (7.7, 18.4)
Progression-free Survival at 48 months		19.2 (10.6, 29.7)	12.5 (7.7, 18.4)

CI = Confidence Interval. PD = Progressive Disease.

[1] Based on Kaplan-Meier product-limit estimates.

Source: C-144-01, Program: t2-7-3-6-1-pfs-irc-ema-c2c4-saf.sas, Data: ADSL and ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Table 2.7.3.5.1 Progression-free Survival - by IRC per RECIST v1.1 (per FDA guideline)
Cohorts 2 and 4 Safety Analysis Set

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Events, n (%)	69 (77.5)	40 (59.7)	109 (69.9)
Progressive disease	57	37	94
Death	12	3	15
Censored, n (%)	20 (22.5)	27 (40.3)	47 (30.1)
Primary Reason for Censoring			
Death or PD after 2 or more missed visits	2 (2.2)	2 (3.0)	4 (2.6)
Start of a new anti-cancer therapy	11 (12.4)	12 (17.9)	23 (14.7)
Discontinued assessment without PD or death	1 (1.1)	7 (10.4)	8 (5.1)
Ongoing without PD or death	6 (6.7)	5 (7.5)	11 (7.1)
No baseline tumor assessment	0	1 (1.5)	1 (0.6)
Time to Event [1], months			
Median (95% CI)	3.8 (2.8, 4.9)	4.1 (2.8, 8.4)	3.9 (2.8, 4.4)
Progression-free Survival Rate (%) (95% CI) [1]			
Progression-free Survival at 3 months	53.2 (41.9, 63.3)	54.4 (41.3, 65.7)	53.8 (45.3, 61.5)
Progression-free Survival at 6 months	32.8 (22.6, 43.3)	41.7 (29.2, 53.8)	36.5 (28.5, 44.6)
Progression-free Survival at 9 months	24.6 (15.6, 34.7)	37.3 (24.9, 49.7)	29.7 (22.1, 37.7)
Progression-free Survival at 12 months	21.8 (13.3, 31.6)	37.3 (24.9, 49.7)	27.9 (20.5, 35.9)
Progression-free Survival at 18 months	17.0 (9.3, 26.5)	32.7 (20.6, 45.2)	23.2 (16.1, 31.0)
Progression-free Survival at 24 months	15.3 (8.0, 24.7)	32.7 (20.6, 45.2)	22.2 (15.2, 29.9)
Progression-free Survival at 30 months	11.9 (5.5, 20.9)	32.7 (20.6, 45.2)	19.9 (13.2, 27.7)
Progression-free Survival at 36 months	11.9 (5.5, 20.9)	32.7 (20.6, 45.2)	19.9 (13.2, 27.7)
Progression-free Survival at 42 months	10.2 (4.4, 18.9)	32.7 (20.6, 45.2)	18.8 (12.2, 26.5)
Progression-free Survival at 48 months		32.7 (20.6, 45.2)	18.8 (12.2, 26.5)

CI = Confidence Interval. PD = Progressive Disease.

[1] Based on Kaplan-Meier product-limit estimates.

Source: C-144-01, Program: t2-7-3-5-1-pfs-irc-fda-c2c4-saf.sas, Data: ADSL and ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

OS

Table 2.7.3.11.2 Overall Survival
Cohorts 2 and 4 Tumor Harvest Set

	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Death, n (%)	84 (75.7)	58 (74.4)	142 (75.1)
Censored, n (%)	27 (24.3)	20 (25.6)	47 (24.9)
Time to Death [1], months			
Median (95% CI)	11.2 (8.8, 17.6)	14.4 (9.8, 19.2)	13.1 (9.9, 16.5)
Overall Survival Rate (%) (95% CI) [1]			
Overall Survival at 3 months	88.2 (80.5, 93.0)	89.6 (80.4, 94.7)	88.8 (83.3, 92.6)
Overall Survival at 6 months	70.4 (60.8, 78.1)	75.2 (63.9, 83.4)	72.4 (65.3, 78.3)
Overall Survival at 9 months	58.2 (48.3, 66.9)	63.3 (51.4, 73.0)	60.3 (52.9, 67.0)
Overall Survival at 12 months	49.7 (40.0, 58.8)	56.7 (44.9, 66.9)	52.6 (45.2, 59.6)
Overall Survival at 18 months	39.0 (29.7, 48.1)	44.6 (33.2, 55.3)	41.3 (34.1, 48.4)
Overall Survival at 24 months	30.0 (21.5, 38.9)	36.4 (25.7, 47.2)	32.7 (25.9, 39.6)
Overall Survival at 30 months	30.0 (21.5, 38.9)	30.8 (20.7, 41.4)	30.3 (23.7, 37.2)
Overall Survival at 36 months	27.0 (18.8, 35.8)	28.0 (18.3, 38.5)	27.4 (21.1, 34.1)
Overall Survival at 42 months	19.8 (12.7, 28.1)	23.8 (14.8, 34.0)	21.5 (15.8, 27.9)
Overall Survival at 48 months	19.8 (12.7, 28.1)	22.4 (13.7, 32.5)	20.8 (15.1, 27.1)
Study Follow-up time for OS [2], months			
Median (95% CI)	45.1 (43.0, 47.8)	57.0 (54.3, 57.6)	48.3 (45.4, 54.3)
Min, Max	0.9+, 49.7	0.7+, 62.2	0.7+, 62.2
Study Follow-up time for OS [3], months			
Median	10.7	13.1	12.0
Min, Max	0.9, 49.7	0.7, 62.2	0.7, 62.2

CI = Confidence Interval.

[1] Based on Kaplan-Meier product-limit estimates.
[2] Based on the reverse Kaplan-Meier method.
[3] Based on the summary statistics.

Source: C-144-01, Program: t2-7-3-11-2-os-c2c4-th.sas, Data: ADSL and ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Summary of Clinical Efficacy Protocol: C-144-01

Table 2.7.3.11.2 Overall Survival
Cohorts 2 and 4 Tumor Harvest Set

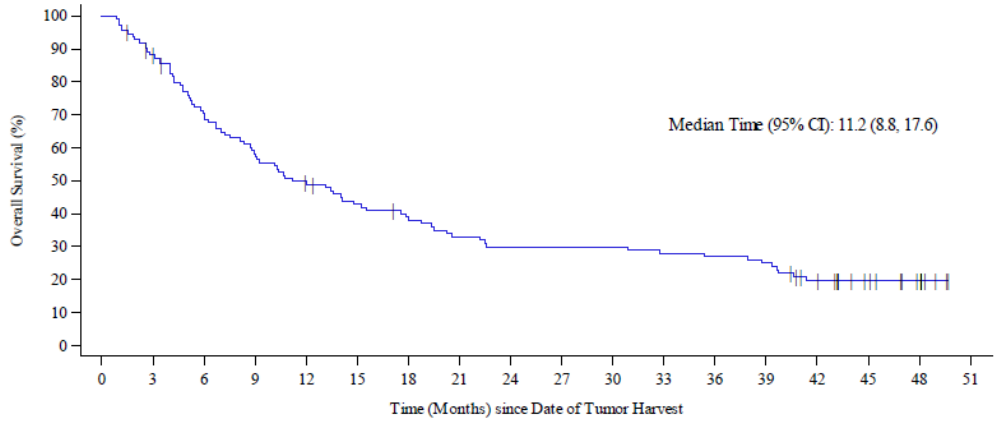
	Cohort 4 (N=111)	Cohort 2 (N=78)	Pooled Cohorts 2 and 4 (N=189)
Death, n (%)	84 (75.7)	58 (74.4)	142 (75.1)
Censored, n (%)	27 (24.3)	20 (25.6)	47 (24.9)
Time to Death [1], months			
Median (95% CI)	11.2 (8.8, 17.6)	14.4 (9.8, 19.2)	13.1 (9.9, 16.5)
Overall Survival Rate (%) (95% CI) [1]			
Overall Survival at 3 months	88.2 (80.5, 93.0)	89.6 (80.4, 94.7)	88.8 (83.3, 92.6)
Overall Survival at 6 months	70.4 (60.8, 78.1)	75.2 (63.9, 83.4)	72.4 (65.3, 78.3)
Overall Survival at 9 months	58.2 (48.3, 66.9)	63.3 (51.4, 73.0)	60.3 (52.9, 67.0)
Overall Survival at 12 months	49.7 (40.0, 58.8)	56.7 (44.9, 66.9)	52.6 (45.2, 59.6)
Overall Survival at 18 months	39.0 (29.7, 48.1)	44.6 (33.2, 55.3)	41.3 (34.1, 48.4)
Overall Survival at 24 months	30.0 (21.5, 38.9)	36.4 (25.7, 47.2)	32.7 (25.9, 39.6)
Overall Survival at 30 months	30.0 (21.5, 38.9)	30.8 (20.7, 41.4)	30.3 (23.7, 37.2)
Overall Survival at 36 months	27.0 (18.8, 35.8)	28.0 (18.3, 38.5)	27.4 (21.1, 34.1)
Overall Survival at 42 months	19.8 (12.7, 28.1)	23.8 (14.8, 34.0)	21.5 (15.8, 27.9)
Overall Survival at 48 months	19.8 (12.7, 28.1)	22.4 (13.7, 32.5)	20.8 (15.1, 27.1)
Study Follow-up time for OS [2], months			
Median (95% CI)	45.1 (43.0, 47.8)	57.0 (54.3, 57.6)	48.3 (45.4, 54.3)
Min, Max	0.9+, 49.7	0.7+, 62.2	0.7+, 62.2
Study Follow-up time for OS [3], months			
Median	10.7	13.1	12.0
Min, Max	0.9, 49.7	0.7, 62.2	0.7, 62.2

CI = Confidence Interval.

[1] Based on Kaplan-Meier product-limit estimates.
[2] Based on the reverse Kaplan-Meier method.
[3] Based on the summary statistics.

Source: C-144-01, Program: t2-7-3-11-2-os-c2c4-th.sas, Data: ADSL and ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Figure 2.7.3.6.4 Kaplan Meier Curve for Overall Survival
Cohort 4 Tumor Harvested Set



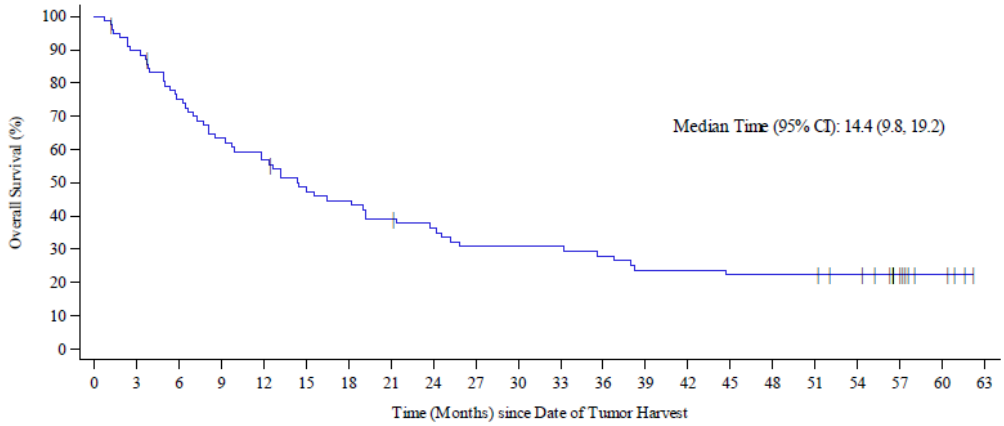
Subjects at Risk:

Total	111	95	75	62	52	44	39	33	30	30	30	28	27	25	17	11	6	0

CI = Confidence Interval.

Source: C-144-01, Program: f2-7-3-6-4-os-c4-th.sas, Data: ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Figure 2.7.3.6.5 Kaplan Meier Curve for Overall Survival
Cohort 2 Tumor Harvested Set



Subjects at Risk:

Total	78	69	57	48	43	36	33	29	26	22	22	22	20	17	17	16	16	16	14	9	4	0

CI = Confidence Interval.

Source: C-144-01, Program: f2-7-3-6-5-os-c2-th.sas, Data: ADTTE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Table 11 Overall Survival (Safety Analysis Set)

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Death, n (%)	69 (77.5)	49 (73.1)	118 (75.6)
Censored, n (%)	20 (22.5)	18 (26.9)	38 (24.4)
OS [1], months			
Median (95% CI)	12.3 (7.9, 17.1)	14.6 (10.7, 23.3)	13.4 (10.3, 17.8)
OS Rate (%) (95% CI) [1]			
at 12 months	50.6 (39.7, 60.5)	56.0 (43.2, 67.0)	52.9 (44.7, 60.5)
at 24 months	30.1 (20.7, 40.0)	37.4 (25.8, 48.9)	33.2 (25.8, 40.8)
at 36 months	26.5 (17.6, 36.2)	29.6 (19.0, 40.9)	27.8 (20.9, 35.1)
at 48 months	19.0 (11.4, 28.1)	24.9 (15.2, 35.9)	21.4 (15.2, 28.4)
Study Follow-up Time [2], months			
Median (95% CI)	44.0 (41.5, 46.9)	55.7 (54.3, 57.1)	48.1 (45.3, 55.2)

Abbreviations: CI = confidence interval
[1] Based on Kaplan-Meier estimates.
[2] Based on the reverse Kaplan-Meier method.

Subsequent therapies

TH dataset

Table 13_D120 New Anti-Cancer Therapy
Cohorts 2 and 4 Tumor Harvested Set

ATC-2 Dictionary Level Preferred Name	Cohort 4 (N=111) n (%)	Cohort 2 (N=78) n (%)	Pooled Cohorts 2 and 4 (N=189) n (%)
Patients with at least one new anti-cancer therapy	59 (53.2)	43 (55.1)	102 (54.0)
ANTINEOPLASTIC AGENTS	56 (50.5)	39 (50.0)	95 (50.3)
NIVOLUMAB	23 (20.7)	13 (16.7)	36 (19.0)
IPILIMUMAB	19 (17.1)	10 (12.8)	29 (15.3)
PEMBROLIZUMAB	14 (12.6)	14 (17.9)	28 (14.8)
CARBOPLATIN	10 (9.0)	6 (7.7)	16 (8.5)
BINIMETINIB	9 (8.1)	6 (7.7)	15 (7.9)
ENCORAFENIB	9 (8.1)	5 (6.4)	14 (7.4)
TRAMETINIB	8 (7.2)	6 (7.7)	14 (7.4)
PACLITAXEL	8 (7.2)	5 (6.4)	13 (6.9)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	7 (6.3)	5 (6.4)	12 (6.3)
DABRAFENIB	6 (5.4)	4 (5.1)	10 (5.3)
DACARBAZINE	5 (4.5)	3 (3.8)	8 (4.2)
TALIMOGENE LAHERPAREPVEC	3 (2.7)	5 (6.4)	8 (4.2)
MONOCLONAL ANTIBODIES	2 (1.8)	3 (3.8)	5 (2.6)
TEMOZOLOMIDE	3 (2.7)	2 (2.6)	5 (2.6)
CYCLOPHOSPHAMIDE	2 (1.8)	1 (1.3)	3 (1.6)
PACLITAXEL ALBUMIN	2 (1.8)	1 (1.3)	3 (1.6)
ANTINEOPLASTIC AGENTS			
RELATLIMAB	3 (2.7)	0	3 (1.6)
APG 115	2 (1.8)	0	2 (1.1)
BLEOMYCIN	1 (0.9)	1 (1.3)	2 (1.1)
CHIDAMIDE	1 (0.9)	1 (1.3)	2 (1.1)
CISPLATIN	2 (1.8)	0	2 (1.1)
DUBERMATINIB	2 (1.8)	0	2 (1.1)
FOTEMUSTINE	2 (1.8)	0	2 (1.1)
IRINOTECAN	2 (1.8)	0	2 (1.1)
MELPHALAN	1 (0.9)	1 (1.3)	2 (1.1)
MITOMYCIN	2 (1.8)	0	2 (1.1)
OTHER ANTINEOPLASTIC AGENTS	1 (0.9)	1 (1.3)	2 (1.1)
RIBOCICLIB	2 (1.8)	0	2 (1.1)
ANTINEOPLASTIC AGENTS	1 (0.9)	0	1 (0.5)
ATEZOLIZUMAB	0	1 (1.3)	1 (0.5)
BEVACIZUMAB	1 (0.9)	0	1 (0.5)
BI 754091	1 (0.9)	0	1 (0.5)
CABOZANTINIB S-MALATE	1 (0.9)	0	1 (0.5)
CARMUSTINE	1 (0.9)	0	1 (0.5)
ANTINEOPLASTIC AGENTS			
COBIMETINIB	1 (0.9)	0	1 (0.5)
CYCLOPHOSPHAMIDE;DOXORUBICIN HYDROCHLORIDE;PREDNISONE;RITUXIMAB;VINCRISTINE SULFATE	1 (0.9)	0	1 (0.5)
CYCLOPHOSPHAMIDE;DOXORUBICIN;PREDNISOLONE;RITUXIMAB;VINCRISTINE	0	1 (1.3)	1 (0.5)
DURVALUMAB	0	1 (1.3)	1 (0.5)
ERDAFITINIB	1 (0.9)	0	1 (0.5)
FLUDARABINE	1 (0.9)	0	1 (0.5)
FLUDARABINE PHOSPHATE	1 (0.9)	0	1 (0.5)
GLEMBATUMUMAB VEDOTIN	0	1 (1.3)	1 (0.5)
LENVATINIB	0	1 (1.3)	1 (0.5)
MITOGEN-ACTIVATED PROTEIN KINASE (MEK) INHIBITORS	0	1 (1.3)	1 (0.5)
NIVOLUMAB;RELATLIMAB	1 (0.9)	0	1 (0.5)
PROTEIN KINASE INHIBITORS	0	1 (1.3)	1 (0.5)
SENSITIZERS USED IN PHOTODYNAMIC/RADIATION THERAPY	1 (0.9)	0	1 (0.5)
SORAFENIB	1 (0.9)	0	1 (0.5)
TELAGLENASTAT	1 (0.9)	0	1 (0.5)
TREMELIMUMAB	0	1 (1.3)	1 (0.5)
TUMOR-INFILTRATING LYMPHOCYTES	1 (0.9)	0	1 (0.5)
URELUMAB	1 (0.9)	0	1 (0.5)

VARIOUS [1]	16 (14.4)	5 (6.4)	21 (11.1)
RADIOTHERAPY	16 (14.4)	5 (6.4)	21 (11.1)
IMMUNOSTIMULANTS	3 (2.7)	4 (5.1)	7 (3.7)
INTERLEUKIN-2	1 (0.9)	2 (2.6)	3 (1.6)
ACTIVATED T-LYMPHOCYTES	1 (0.9)	0	1 (0.5)
ALDESLEUKIN	1 (0.9)	0	1 (0.5)
EDODEKIN ALFA	0	1 (1.3)	1 (0.5)
IMCGP 100	0	1 (1.3)	1 (0.5)
IMMUNOTHERAPY	1 (0.9)	0	1 (0.5)
ALL OTHER NON-THERAPEUTIC PRODUCTS	0	5 (6.4)	5 (2.6)
ALL OTHER NON-THERAPEUTIC PRODUCTS	0	5 (6.4)	5 (2.6)
INVESTIGATIONAL DRUG	3 (2.7)	2 (2.6)	5 (2.6)
INVESTIGATIONAL DRUG	3 (2.7)	0	3 (1.6)
CABIRALIZUMAB	0	1 (1.3)	1 (0.5)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	0	1 (1.3)	1 (0.5)
IMMUNOSUPPRESSANTS	0	2 (2.6)	2 (1.1)
INFLIXIMAB DYYB	0	1 (1.3)	1 (0.5)
TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	0	1 (1.3)	1 (0.5)
ALL OTHER THERAPEUTIC PRODUCTS	1 (0.9)	0	1 (0.5)
ALL OTHER THERAPEUTIC PRODUCTS	1 (0.9)	0	1 (0.5)

ATC = Anatomical Therapeutic Chemical.

Notes: Coded using WHO Drug version B3 Global 2021Q1.
A patient with multiple occurrences of a drug class or drug is counted only once in the specific ATC classification or preferred name, respectively.

[1] Based on ATC-1 level as ATC-2 level is missing.

Source: C-144-01, Program: t13-d120-posttx-c2c4-th.sas (Date of Report: 13Jan2025) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Table 14.1.10.2.1 New Anti-Cancer Therapy
Cohorts 2 and 4 Safety Analysis Set

ATC-2 Dictionary Level Preferred Name	Cohort 4 (N=89) n (%)	Cohort 2 (N=67) n (%)	Pooled Cohorts 2 and 4 (N=156) n (%)
Patients with at least one new anti-cancer therapy	46 (51.7)	37 (55.2)	83 (53.2)
ANTINEOPLASTIC AGENTS	43 (48.3)	33 (49.3)	76 (48.7)
NIVOLUMAB	18 (20.2)	12 (17.9)	30 (19.2)
PEMBROLIZUMAB	13 (14.6)	14 (20.9)	27 (17.3)
IPILIMUMAB	14 (15.7)	8 (11.9)	22 (14.1)
BINIMETINIB	7 (7.9)	5 (7.5)	12 (7.7)
CARBOPLATIN	6 (6.7)	5 (7.5)	11 (7.1)
ENCORAFENIB	7 (7.9)	4 (6.0)	11 (7.1)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	6 (6.7)	5 (7.5)	11 (7.1)
TRAMETINIB	7 (7.9)	3 (4.5)	10 (6.4)
PACLITAXEL	5 (5.6)	4 (6.0)	9 (5.8)
DABRAFENIB	5 (5.6)	3 (4.5)	8 (5.1)
TALIMOGENE LAHERPAREPVEC	2 (2.2)	5 (7.5)	7 (4.5)
DACARBAZINE	3 (3.4)	2 (3.0)	5 (3.2)
MONOCLONAL ANTIBODIES	2 (2.2)	3 (4.5)	5 (3.2)
TEMOZOLOMIDE	3 (3.4)	2 (3.0)	5 (3.2)
APG 115	2 (2.2)	0	2 (1.3)
BLEOMYCIN	1 (1.1)	1 (1.5)	2 (1.3)
ANTINEOPLASTIC AGENTS			
CISPLATIN	2 (2.2)	0	2 (1.3)
DUBERMATINIB	2 (2.2)	0	2 (1.3)
IRINOTECAN	2 (2.2)	0	2 (1.3)
MELPHALAN	1 (1.1)	1 (1.5)	2 (1.3)
MITOMYCIN	2 (2.2)	0	2 (1.3)
PACLITAXEL ALBUMIN	1 (1.1)	1 (1.5)	2 (1.3)
RIBOCICLIB	2 (2.2)	0	2 (1.3)
ATEZOLIZUMAB	0	1 (1.5)	1 (0.6)
BEVACIZUMAB	1 (1.1)	0	1 (0.6)
BI 754091	1 (1.1)	0	1 (0.6)
CABOZANTINIB S-MALATE	1 (1.1)	0	1 (0.6)
CARMUSTINE	1 (1.1)	0	1 (0.6)
CHIDAMIDE	0	1 (1.5)	1 (0.6)
COBIMETINIB	1 (1.1)	0	1 (0.6)
CYCLOPHOSPHAMIDE	0	1 (1.5)	1 (0.6)
DURVALUMAB	0	1 (1.5)	1 (0.6)
ERDAFITINIB	1 (1.1)	0	1 (0.6)
FOTEMUSTINE	1 (1.1)	0	1 (0.6)

ANTINEOPLASTIC AGENTS			
GLEMBATUMUMAB VEDOTIN	0	1 (1.5)	1 (0.6)
LENVATINIB	0	1 (1.5)	1 (0.6)
MITOGEN-ACTIVATED PROTEIN KINASE (MEK) INHIBITORS	0	1 (1.5)	1 (0.6)
NIVOLUMAB;RELATLIMAB	1 (1.1)	0	1 (0.6)
OTHER ANTINEOPLASTIC AGENTS	0	1 (1.5)	1 (0.6)
PROTEIN KINASE INHIBITORS	0	1 (1.5)	1 (0.6)
RELATLIMAB	1 (1.1)	0	1 (0.6)
SENSITIZERS USED IN PHOTODYNAMIC/RADIATION THERAPY	1 (1.1)	0	1 (0.6)
SORAFENIB	1 (1.1)	0	1 (0.6)
TELAGLENASTAT	1 (1.1)	0	1 (0.6)
TREMELIMUMAB	0	1 (1.5)	1 (0.6)
URELUMAB	1 (1.1)	0	1 (0.6)
VARIOUS [1]	13 (14.6)	5 (7.5)	18 (11.5)
RADIOTHERAPY	13 (14.6)	5 (7.5)	18 (11.5)
ALL OTHER NON-THERAPEUTIC PRODUCTS	0	5 (7.5)	5 (3.2)
ALL OTHER NON-THERAPEUTIC PRODUCTS	0	5 (7.5)	5 (3.2)
IMMUNOSTIMULANTS	1 (1.1)	4 (6.0)	5 (3.2)
INTERLEUKIN-2	0	2 (3.0)	2 (1.3)
IMMUNOSTIMULANTS			
EDODEKIN ALFA	0	1 (1.5)	1 (0.6)
IMCGP 100	0	1 (1.5)	1 (0.6)
IMMUNOTHERAPY	1 (1.1)	0	1 (0.6)
INVESTIGATIONAL DRUG	3 (3.4)	2 (3.0)	5 (3.2)
INVESTIGATIONAL DRUG	3 (3.4)	0	3 (1.9)
CABIRALIZUMAB	0	1 (1.5)	1 (0.6)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	0	1 (1.5)	1 (0.6)
IMMUNOSUPPRESSANTS	0	2 (3.0)	2 (1.3)
INFLIXIMAB DYYB	0	1 (1.5)	1 (0.6)
TUMOR NECROSIS FACTOR ALPHA (TNF-) INHIBITORS	0	1 (1.5)	1 (0.6)
ALL OTHER THERAPEUTIC PRODUCTS	1 (1.1)	0	1 (0.6)
ALL OTHER THERAPEUTIC PRODUCTS	1 (1.1)	0	1 (0.6)

ATC = Anatomical Therapeutic Chemical.

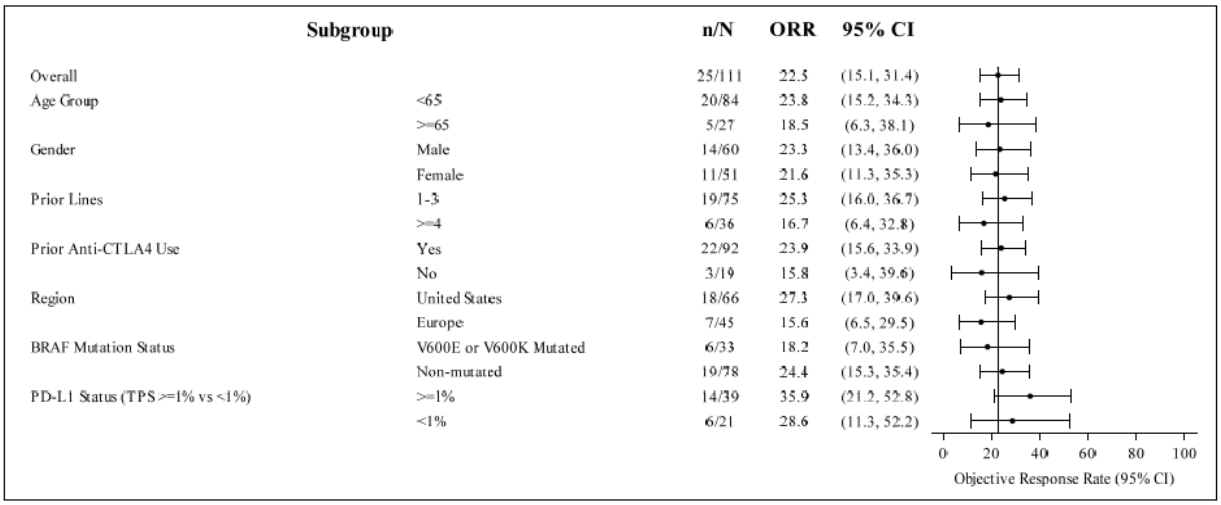
Notes: Coded using WHO Drug version B3 Global 2021Q1.
A patient with multiple occurrences of a drug class or drug is counted only once in the specific ATC classification or preferred name, respectively.

[1] Based on ATC-1 level as ATC-2 level is missing.

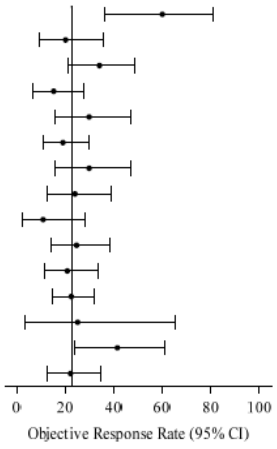
Source: C-144-01, Program: t14-1-10-2-1-posttx-c2c4-saf.sas, Data: ADSL and ADCM (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Ancillary analyses

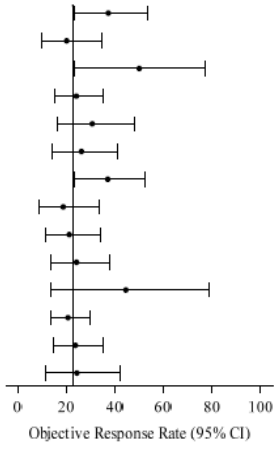
Figure 2.7.3.5.4 Forest Plot for ORR by Subgroup - by IRC per RECIST v1.1
Cohort 4 Tumor Harvested Set



Subgroup		n/N	ORR	95% CI
PD-L1 Status (TPS >=5% vs <5%)	>=5%	12/20	60.0	(36.1, 80.9)
	<5%	8/40	20.0	(9.1, 35.6)
Baseline ECOG	0	17/50	34.0	(21.2, 48.8)
	>=1	8/53	15.1	(6.7, 27.6)
Baseline Lactate Dehydrogenase	<=ULN	11/37	29.7	(15.9, 47.0)
	>ULN	14/74	18.9	(10.7, 29.7)
Baseline Lactate Dehydrogenase	<=ULN	11/37	29.7	(15.9, 47.0)
	1-2 x ULN	11/46	23.9	(12.6, 38.8)
	>2 x ULN	3/28	10.7	(2.3, 28.2)
Primary Refractory to Anti-PD-1/PD-L1	Yes	13/53	24.5	(13.8, 38.3)
	No	12/58	20.7	(11.2, 33.4)
Contract Manufacturing Organization	WuXi	23/103	22.3	(14.7, 31.6)
	Lonza	2/8	25.0	(3.2, 65.1)
Baseline Target Lesion Sum of Diameters	<70 mm	12/29	41.4	(23.5, 61.1)
	>=70 mm	13/59	22.0	(12.3, 34.7)



Subgroup		n/N	ORR	95% CI
Subgroup of Baseline Target Lesion Sum of Diameters	<Median (99.5 mm)	16/43	37.2	(23.0, 53.3)
	>=Median (99.5 mm)	9/45	20.0	(9.6, 34.6)
Number of Baseline Target and Non-target Lesions	<=3	7/14	50.0	(23.0, 77.0)
	>3	18/75	24.0	(14.9, 35.3)
Patients with Baseline Liver Lesions		11/36	30.6	(16.3, 48.1)
Patients with Baseline Brain and/or Liver Lesions		12/46	26.1	(14.3, 41.1)
Time from Stop of Anti-PD-1/PD-L1 to TIL Infusion	<=Median (4.44 months)	17/46	37.0	(23.2, 52.5)
	>Median (4.44 months)	8/43	18.6	(8.4, 33.4)
Cumulative Time on Prior Anti-PD-1/PD-L1	<=Median (10.02 months)	12/57	21.1	(11.4, 33.9)
	>Median (10.02 months)	13/54	24.1	(13.5, 37.6)
Mucosal Melanoma	Yes	4/9	44.4	(13.7, 78.8)
	No	21/102	20.6	(13.2, 29.7)
Resistance Type by SITC definition	Primary resistance to prior anti-PD1/L1	17/72	23.6	(14.4, 35.1)
	Secondary resistance to prior anti-PD1/L1	8/33	24.2	(11.1, 42.3)

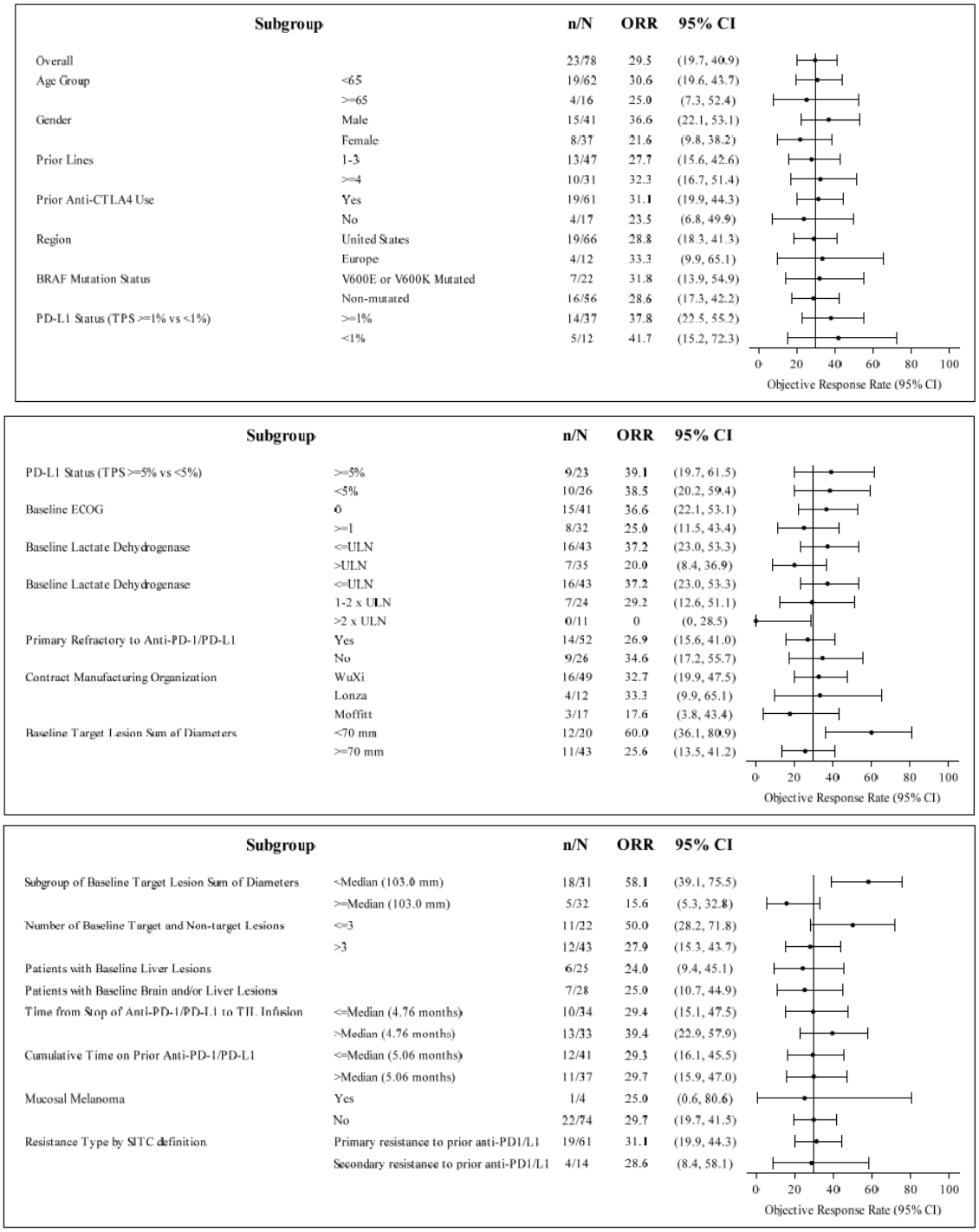


CI = Confidence Interval. ULN = Upper Limit Normal.

Notes: Patients who had tumor harvested but did not receive TIL are considered as non-responders with BOR of NE.
PD-L1 status is from central laboratory.
Baseline target lesion sum of diameters and number of baseline target and non-target lesions are based on IRC assessment.
95% CI is calculated using the Clopper-Pearson Exact test.
Includes primary resistance to prior anti-PD1/PD-L1 in metastatic setting and primary resistance/early relapse to prior anti-PD1/PD-L1 in adjuvant setting.
Includes secondary resistance to prior anti-PD1/PD-L1 in metastatic setting and late relapse in adjuvant setting.

Source: C-144-01, Program: f2-7-3-5-4-forest-orr-irc-sub-c4-th.sas, Data: ADSL, ADBL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Figure 2.7.3.5.5 Forest Plot for ORR by Subgroup - by IRC per RECIST v1.1
Cohort 2 Tumor Harvested Set



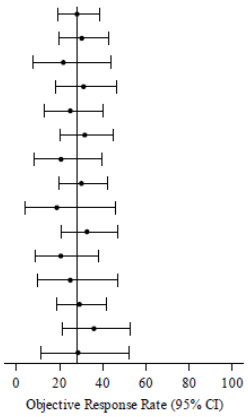
CI = Confidence Interval. ULN = Upper Limit Normal.

Notes: : Patients who had tumor harvested but did not receive TIL are considered as non-responders with BOR of NE.
PD-L1 status is from central laboratory.
Baseline target lesion sum of diameters and number of baseline target and non-target lesions are based on IRC assessment.
95% CI is calculated using the Clopper-Pearson Exact test.
Includes primary resistance to prior anti-PD1/PD-L1 in metastatic setting and primary resistance/early relapse to prior anti-PD1/PD-L1 in adjuvant setting.
Includes secondary resistance to prior anti-PD1/PD-L1 in metastatic setting and late relapse in adjuvant setting.

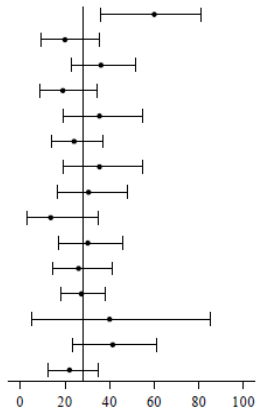
Source: C-144-01, Program: f2-7-3-5-5-forest-orr-irc-sub-c2-th.sas, Data: ADSL, ADBL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Figure 2.7.3.5.1 Forest Plot for ORR by Subgroup - by IRC per RECIST v1.1
Cohort 4 Safety Analysis Set

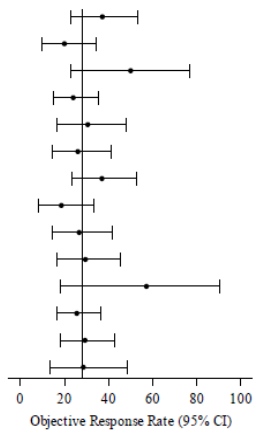
Subgroup		n/N	ORR	95% CI
Overall		25/89	28.1	(19.1, 38.6)
Age Group	<65	20/66	30.3	(19.6, 42.9)
	>=65	5/23	21.7	(7.5, 43.7)
Gender	Male	14/45	31.1	(18.2, 46.6)
	Female	11/44	25.0	(13.2, 40.3)
Prior Lines	1-3	19/60	31.7	(20.3, 45.0)
	>=4	6/29	20.7	(8.0, 39.7)
Prior Anti-CTLA4 Use	Yes	22/73	30.1	(19.9, 42.0)
	No	3/16	18.8	(4.0, 45.6)
Region	United States	18/55	32.7	(20.7, 46.7)
	Europe	7/34	20.6	(8.7, 37.9)
BRAF Mutation Status	V600E or V600K Mutated	6/24	25.0	(9.8, 46.7)
	Non-mutated	19/65	29.2	(18.6, 41.8)
PD-L1 Status (TPS>=1% vs <1%)	>=1%	14/39	35.9	(21.2, 52.8)
	<1%	6/21	28.6	(11.3, 52.2)



Subgroup		n/N	ORR	95% CI
PD-L1 Status (TPS>=5% vs <5%)	>=5%	12/20	60.0	(36.1, 80.9)
	<5%	8/40	20.0	(9.1, 35.6)
Baseline ECOG	0	17/47	36.2	(22.7, 51.5)
	>=1	8/42	19.0	(8.6, 34.1)
Baseline Lactate Dehydrogenase	<=ULN	11/31	35.5	(19.2, 54.6)
	>ULN	14/58	24.1	(13.9, 37.2)
Baseline Lactate Dehydrogenase	<=ULN	11/31	35.5	(19.2, 54.6)
	1-2 x ULN	11/36	30.6	(16.3, 48.1)
	>2 x ULN	3/22	13.6	(2.9, 34.9)
Primary Refractory to Anti-PD-1/PD-L1	Yes	13/43	30.2	(17.2, 46.1)
	No	12/46	26.1	(14.3, 41.1)
Contract Manufacturing Organization	WuXi	23/84	27.4	(18.2, 38.2)
	Lonza	2/5	40.0	(5.3, 85.3)
Baseline Target Lesion Sum of Diameters	<70 mm	12/29	41.4	(23.5, 61.1)
	>=70 mm	13/59	22.0	(12.3, 34.7)



Subgroup		n/N	ORR	95% CI
Subgroup of Baseline Target Lesion Sum of Diameters	<Median (99.5 mm)	16/43	37.2	(23.0, 53.3)
	>=Median (99.5 mm)	9/45	20.0	(9.6, 34.6)
Number of Baseline Target and Non-target Lesions	<=3	7/14	50.0	(23.0, 77.0)
	>3	18/75	24.0	(14.9, 35.3)
Patients with Baseline Liver Lesions		11/36	30.6	(16.3, 48.1)
Patients with Baseline Brain and/or Liver Lesions		12/46	26.1	(14.3, 41.1)
Time from Stop of Anti-PD-1/PD-L1 to TIL Infusion	<=Median (4.44 months)	17/46	37.0	(23.2, 52.5)
	>Median (4.44 months)	8/43	18.6	(8.4, 33.4)
Cumulative Time on Prior Anti-PD-1/PD-L1	<=Median (10.02 months)	12/45	26.7	(14.6, 41.9)
	>Median (10.02 months)	13/44	29.5	(16.8, 45.2)
Mucosal Melanoma	Yes	4/7	57.1	(18.4, 90.1)
	No	21/82	25.6	(16.6, 36.4)
Resistance Type by SITC definition	Primary resistance to prior anti-PD1/L1	17/58	29.3	(18.1, 42.7)
	Secondary resistance to prior anti-PD1/L1	8/28	28.6	(13.2, 48.7)



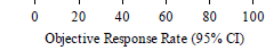
CI = Confidence Interval. ULN = Upper Limit Normal.

Notes: PD-L1 status is from central laboratory.
Baseline target lesion sum of diameters and number of baseline target and non-target lesions are based on IRC assessment.
95% CI is calculated using the Clopper-Pearson Exact test.
Includes primary resistance to prior anti-PD1/PD-L1 in metastatic setting and primary resistance/early relapse to prior anti-PD1/PD-L1 in adjuvant setting.
Includes secondary resistance to prior anti-PD1/PD-L1 in metastatic setting and late relapse in adjuvant setting.

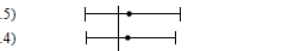
Source: C-144-01, Program: f2-7-3-5-1-forest-orr-irc-sub-c4-saf.sas, Data: ADSL, ADBL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Figure 2.7.3.5.2 Forest Plot for ORR by Subgroup - by IRC per RECIST v1.1
Cohort 2 Safety Analysis Set

Subgroup		n/N	ORR	95% CI
Overall		23/67	34.3	(23.2, 46.9)
Age Group	<65	19/53	35.8	(23.1, 50.2)
	>=65	4/14	28.6	(8.4, 58.1)
Gender	Male	15/39	38.5	(23.4, 55.4)
	Female	8/28	28.6	(13.2, 48.7)
Prior Lines	1-3	13/41	31.7	(18.1, 48.1)
	>=4	10/26	38.5	(20.2, 59.4)
Prior Anti-CTLA4 Use	Yes	19/54	35.2	(22.7, 49.4)
	No	4/13	30.8	(9.1, 61.4)
Region	United States	19/56	33.9	(21.8, 47.8)
	Europe	4/11	36.4	(10.9, 69.2)
BRAF Mutation Status	V600E or V600K Mutated	7/17	41.2	(18.4, 67.1)
	Non-mutated	16/50	32.0	(19.5, 46.7)
PD-L1 Status (TPS >=1% vs <1%)	>=1%	14/37	37.8	(22.5, 55.2)
	<1%	5/12	41.7	(15.2, 72.3)



Subgroup		n/N	ORR	95% CI
PD-L1 Status (TPS >=5% vs <5%)	>=5%	9/23	39.1	(19.7, 61.5)
	<5%	10/26	38.5	(20.2, 59.4)
Baseline ECOG	0	15/38	39.5	(24.0, 56.6)
	>=1	8/29	27.6	(12.7, 47.2)
Baseline Lactate Dehydrogenase	<=ULN	16/39	41.0	(25.6, 57.9)
	>ULN	7/28	25.0	(10.7, 44.9)
Baseline Lactate Dehydrogenase	<=ULN	16/39	41.0	(25.6, 57.9)
	1-2 x ULN	7/19	36.8	(16.3, 61.6)
	>2 x ULN	0/9	0	(0, 33.6)
Primary Refractory to Anti-PD-1/PD-L1	Yes	14/43	32.6	(19.1, 48.5)
	No	9/24	37.5	(18.8, 59.4)
Contract Manufacturing Organization	WuXi	16/41	39.0	(24.2, 55.5)
	Lonza	4/11	36.4	(10.9, 69.2)
	Moffitt	3/15	20.0	(4.3, 48.1)
Baseline Target Lesion Sum of Diameters	<70 mm	12/20	60.0	(36.1, 80.9)
	>=70 mm	11/43	25.6	(13.5, 41.2)



Subgroup		n/N	ORR	95% CI
Subgroup of Baseline Target Lesion Sum of Diameters	<Median (103.0 mm)	18/31	58.1	(39.1, 75.5)
	>=Median (103.0 mm)	5/32	15.6	(5.3, 32.8)
Number of Baseline Target and Non-target Lesions	<=3	11/22	50.0	(28.2, 71.8)
	>3	12/43	27.9	(15.3, 43.7)
Patients with Baseline Liver Lesions		6/25	24.0	(9.4, 45.1)
Patients with Baseline Brain and/or Liver Lesions		7/28	25.0	(10.7, 44.9)
Time from Stop of Anti-PD-1/PD-L1 to TIL Infusion	<=Median (4.76 months)	10/34	29.4	(15.1, 47.5)
	>Median (4.76 months)	13/33	39.4	(22.9, 57.9)
Cumulative Time on Prior Anti-PD-1/PD-L1	<=Median (5.06 months)	12/34	35.3	(19.7, 53.5)
	>Median (5.06 months)	11/33	33.3	(18.0, 51.8)
Mucosal Melanoma	Yes	1/3	33.3	(0.8, 90.6)
	No	22/64	34.4	(22.9, 47.3)
Resistance Type by SITC definition	Primary resistance to prior anti-PD1/L1	19/53	35.8	(23.1, 50.2)
	Secondary resistance to prior anti-PD1/L1	4/14	28.6	(8.4, 58.1)

CI = Confidence Interval. ULN = Upper Limit Normal.

Notes: PD-L1 status is from central laboratory.
Baseline target lesion sum of diameters and number of baseline target and non-target lesions are based on IRC assessment.
95% CI is calculated using the Clopper-Pearson Exact test.
Includes primary resistance to prior anti-PD1/PD-L1 in metastatic setting and primary resistance/early relapse to prior anti-PD1/PD-L1 in adjuvant setting.
Includes secondary resistance to prior anti-PD1/PD-L1 in metastatic setting and late relapse in adjuvant setting.

Source: C-144-01, Program: f2-7-3-5-2-forest-orr-irc-sub-c2-saf.sas, Data: ADSL, ADBL and ADRS (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Exploratory analyses: Persistence of Lifileucel and Immune Correlates

The persistence of lifileucel was characterized. Potential immune correlates of response, outcome, and toxicity of the treatment were not evaluated.

In Cohort 4, TIL products were available for all patients in the FAS (N = 87), with a median number of 2,792 (min = 491; max = 14,904) clonotypes per product. A total of 292,050 clones were identified across all TIL products. Of these clones, 281,134 (96.3%) were patient-specific. Six weeks post-infusion (ie, Day 42 visit), PBMC samples were available for 74 patients (85.1%). Lifileucel TIL clones were detected in 100% (74/74) of these patients at Day 42 and in 100% (11/11) of patients who had PBMC samples available at Month 12.

In Cohort 2, TIL products were available for 64 of the 66 patients in the FAS, with a median number of 5,287 (min = 959; max = 21,187) clonotypes per product. A total of 366,441 clones were identified across all TIL products. Of these clones, 349,221 (95.3%) were patient-specific. Six weeks post-infusion (ie, Day 42 visit), PBMC samples were available for 46 patients (69.7%). Lifileucel TIL clones were detected in 100% (46/46) of these patients at Day 42 and in 100% (11/11) of patients who had PBMC samples available at Month 12.

3.3.4.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12 Summary of efficacy for study C-144-01

Title: A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144; Lifileucel) for Treatment of Patients with Metastatic Melanoma		
Study identifier	Protocol C-144-01 EudraCT: 2017-000760-15 NCT: 02360579	
Design	Study C-144-01 is an ongoing Phase 2, prospective, interventional, multicenter study evaluating the efficacy and safety of lifileucel in adult patients with unresectable or metastatic melanoma who progressed following treatment 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 mitogen-activated extracellular signal regulated kinase (MEK) inhibitor.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment and follow up: up to 5 years not applicable not applicable
Hypothesis	Statistical hypothesis testing of the primary efficacy endpoint was performed for the Full Analysis Set (FAS; defined as patients who had received lifileucel that met the manufacturing product specification) of Cohort 4 using a null hypothesis (H_{01}) of an objective response rate (ORR) ≤ 10% versus H_{a1} of an ORR > 10%. The null hypothesis was to be rejected, and the study was considered to have met its primary objective, if the lower bound of the 2-sided 95% Clopper Pearson confidence interval (CI) for the primary efficacy endpoint was > 10%. If the null hypothesis for Cohort 4 (H_{01}) was rejected, a second hypothesis testing of the	

Title: A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144; Lifileucel) for Treatment of Patients with Metastatic Melanoma			
	primary efficacy endpoint was to be performed based on the Pooled Cohorts 2 and 4 data, H_{02} of an ORR ≤ 10% versus H_{a2} of an ORR > 10%. Analyses were performed on Pooled Cohorts 2 and 4 because Cohort 2 and Cohort 4 patients met the same primary eligibility criteria, had the same assessments, received the same lifileucel regimen, and received the same cryopreserved lifileucel that was produced using the same TIL manufacturing process, specification, and product formulation.		
Treatments groups	Cohort 4		Cryopreserved lifileucel product, single dose N =111 (TH Set)
Endpoints and definitions Endpoints and definitions (continued)	Primary endpoint	Objective response rate (ORR) by IRC	The proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) as assessed by the Independent Review Committee (IRC) per the Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1 The ORR was based on confirmed responses (ie, a PR or CR that was confirmed by a consecutive tumor assessment at least 4 weeks later).
	Secondary endpoints	Duration of response (DOR)	The time (in months) from the time point at which the initial measurement criteria per RECIST v1.1 are met for a CR or PR as assessed by the IRC, whichever response is observed first, until the first date that progressive disease (PD) is objectively documented, or death occurs.
		Disease control rate (DCR)	The proportion of patients with a BOR of CR, PR, stable disease (SD), or non-CR/non-PD (only for patients without target lesions) as assessed by the IRC per RECIST v1.1. The DCR was based on confirmed responses (ie, a PR or CR that was confirmed by a consecutive tumor assessment at least 4 weeks later).
		Overall survival (OS)	The time (in months) from the start date of lifileucel infusion to death due to any cause.
Database lock	21 Dec 2023		
Results and Analysis			
Analysis description	**Primary Analysis (based on IRC assessments; data cutoff 30 Jun 2023)** **Primary Endpoint**		
Analysis population and time point description	Tumor Harvested set: all tumor-resected patients for production of LN-144, regardless of whether they have received LN-144 or not.		
Descriptive statistics and	Treatment group	Cohort 4	
	Number of subjects	111	

Title: A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144; Lifileucel) for Treatment of Patients with Metastatic Melanoma		
estimated variability	ORR by IRC n (%) (95% CI)	25 (22.5) (15.1, 31.4)
Analysis description	**Primary Analysis (based on IRC assessments; data cutoff 30 Jun 2023)** **Secondary Endpoints**	
Analysis population and time point description	Only in responders	
Descriptive statistics and estimated variability	Treatment group	Cohort 4
	Number of subjects	111
	DOR (months) by IRC Median (95% CI)	n=25 responders 10.4 (4.1, 26.2) *8.3 months (initiation of new anti-cancer therapy was used as event)

3.3.4.4. Clinical studies in special populations

Table 13 Clinical studies in special populations

	Controlled Trials	Non-controlled Trials
Renal impairment* patients (Subjects number /total number)	Not applicable	Not applicable
Hepatic impairment** patients (Subjects number /total number)	Not applicable	Not applicable
Paediatric patients <18 years (Subjects number /total number)	Not applicable	Not applicable
Age 65-74 (Subjects number /total number)	Not applicable	C-144-01: 41/189
Age 75-84 (Subjects number /total number)	Not applicable	C-144-01: 2/189
Age 85+ (Subjects number /total number)	Not applicable	Not applicable
Other (Subjects number /total number)	Not applicable	Not applicable

* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
** Hepatic impairment is defined as having Child-Pugh score B or C

3.3.4.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

3.3.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

3.3.4.7. Supportive study(ies)

Not applicable.

3.3.5. Discussion on clinical efficacy

Lifileucel [autologous tumor infiltrating lymphocytes; Amtagvi] is a preparation of autologous, non-genetically modified tumor infiltrating lymphocytes (TIL). TIL recognise the tumour-specific neoantigens via T-Cell receptor (TCR)-peptide human leukocyte antigen (pHLA) engagement. The TCR-pHLA interaction induces T cell activation and T cell-mediated tumour killing via secretion of cytokines and cytolytic enzymes, which form pores and disrupt the integrity of the tumour cell membrane and mediate tumour cell lysis.

The indication applied for is:

AMTAGVI is 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.

Design and conduct of clinical studies

The pivotal study for efficacy in this application for a conditional marketing authorisation (CMA) is Study C-144-01, which is a phase 2, global, multicentre, multicohort single-arm, open-label study evaluating the anti-tumor activity of Lifileucel in adult patients with advanced melanoma in the 2L+ setting. Patients were enrolled in one of 4 cohorts. Cohort 3 was the only re-treatment cohort, where patients from the other cohorts could be offered a second infusion with lifileucel. Cohort 2 (supportive) and 4 (pivotal) form the basis for this application. In context of a CMA, the provided non-comparative data is considered sufficient to assess the benefit-risk balance for the applied indication.

The clinical development program of Lifileucel included multiple phase 2 studies across different tumours types. The most relevant SA pertaining to the current submission was given in 2022 (EMA/SA/0000100171), where issues regarding CMA and confirmatory phase 3 study (IOV-MEL-301, referred now as TILVANCE-301) design were discussed. There was somewhat agreement on the planned strategy, however some caveats on the design of the study TILVANCE-301 were pointed out. Since the applicant planned on submitting data from limited number of patients (n=156) treated across two cohorts, the CHMP asked the applicant to provide differences between these cohorts i in order to evaluate if pooling of data would be allowed. The applicant states that the across protocol amendments during the course of both cohorts were mostly regarding clarifying eligibility criteria (f.e.g requirement of BRAF+/- MEK therapy, inclusion of patients with brain metastases, permitted dose of steroids). The applicant believes that pooling of data from cohorts should be allowed, as protocol amendments should not have resulted in major differences in baseline characteristics of the study population enrolled into these two cohorts and represent the expected population of patients with advanced melanoma. This is partially agreed. The baseline characteristics of the pooled cohorts reflect

the most fit population of patients with advanced melanoma with limited treatment options, however the higher proportions of patients with brain and/or liver metastases, higher baseline LDH and tumor burden in cohort 4 lead to conclusion that patients in cohort 4 had inferior prognosis compared to cohort 2 and this can also partially explain the observed differences in the ORR and DOR of the respective cohorts. The rationale for amendments during the course of cohort 2 are understood, nevertheless the main issue is that only cohort 4 had a pre-defined SAP at the time of inclusion and therefore pooling of results from these two cohorts is not accepted. Regarding the design of confirmatory study some caveats considering study population, treatment, endpoints and use of crossover were pointed out during SA and pre-submission meeting. The proposed **confirmatory study IOV-MEL-301** (referred now as TILVANCE-301), which is an open-label, randomized, mulitcenter phase 3 study, investigates the efficacy and safety of Amtagvi plus pembrolizumab over pembrolizumab monotherapy as first-line treatment in patients with previously untreated unresectable or metastatic melanoma. The final results of the confirmatory study have a tentative submission date of 31 Mar 2031. However, considering the statistical plan's hierarchical testing, and likelihood of difficulties in interpreting the OS data due to crossover the applicant is asked to further specify the predicted OS maturity at the IA analysis and discuss the option of an earlier submission of the SOB.

The TILVANCE-301 study will condense the NMA-LD regiment to 5 days and initiate both agents simultaneously with the same doses as used in Study C-144-01. The IL-2 dose is maintained but administration will be restricted to max twice per day, max 6 doses and is not to be administrated after day 4 post lifileucel infusion. Lifileucel dose is 1.8-100x10^9 total viable cells. Pembrolizumab will be initiated after randomization and resection of tumour for lifileucel production. A dose for the lifileucel-arm will be given just before initiation of NMA-LD and then every 6 weeks until progression. The dosing schedule for pembrolizumab is the same for both treatment arms. 600 patients naïve for ICI are planned to be randomised 1:1 and an additional 70 non-ICI naïve patients are also planned to be randomised 1:1. Randomization is stratified by BRAF V600 mutation status (V600 mutation vs no V600 mutation); Disease stage at screening (Stage III/M1a or b vs M1c or d); Prior adjuvant/neoadjuvant ICI use (prior ICI use vs no prior ICI use); Region (North America vs Europe vs rest of world) as well as Lactate dehydrogenase (LDH) level at baseline (≤upper limit of normal [ULN] vs >ULN). Primary endpoint in the EMA hierarchical testing strategy will be PFS by BICR in the ICI-naïve population. This will be followed by PFS in the overall population and OS in the ICI naïve and overall population respectively. Crossover will be allowed from pembrolizumab to lifileucel following BICR and confirmed progression. Crossover will affect the interpretability of the OS results. A sensitivity analysis as a 2-stage method, or the inverse probability of censoring weighting (IPCW) method [Robins 2000] may be performed according to the protocol. A draft SAP has been provided for agency review, stating that it will be finalized before the first interim analysis, ensuring that the analysis plan is pre-specified and not influenced by accumulated data. The delay in completing the SAP until prior to the planned first interim analysis is not accepted. The SAP for open-label studies with regards to the primary and important secondary analyses would ideally be finalised before the first participant is randomised or allocated to study intervention (EMA/CHMP/ICH/544570/1998). The first planned interim analysis is the final PFS analysis. The applicant is urged to see to that a final version of the SAP is issued according to EMA recommendations considering this is a SOB mandatory considering the CMA currently under assessment. The main points of the statistical analysis plan are presented in the protocol. The justification on performing the confirmatory study in the earlier setting is accepted as Lifileucel will be used in the same disease and there is a scientific rationale that it will be also effective in the earlier line setting as well. Moreover, it has previously been accepted by the CHMP that efficacy of new drug established in the latter line, allows for the assumption of its efficacy in prior lines, also as add-on treatment to SoC. Overall, the proposed SOB is acceptable. The applicant committed to include the confirmatory study in Annex II with a defined timeframe for the fulfilment of the SOB**.**

The in- and exclusion criteria in Study C-144-01 are adequate and reflect the target population of 2L+ setting. Patients, who progressed on/after ICI and BRAF/MEK inhibitors (if BRAF-mutated), have limited treatment options and need new efficacious therapies.

The treatment period was 11 or 12 days in total and consisted of NMA-LD, Lifileucel and IL-2. Treatment with Amtagvi start with resection of a lesion (or aggregates of lesions) for production, defined as at least 1.5 cm in diameter post-resection. No bridging therapy was allowed during the production time. 7 days before lifileucel was planned, non-myeloablative lymphodepletion (NMA-LD) was initiated with 2 days of cyclophosphamide 60mg/kg/day (including mesna) followed by 5 days of fludarabine 25 mg/m^2/day. The dose of Lifileucel was patient-specific and ranged from 1 × 10^9 to 150 × 10^9 viable cells suspended in a cryopreservation medium. The dose-selection strategy in the study programme is inadequate and the protocol definition of study doses was an even wider range than what is currently proposed for commercial use. The actual range of studied doses in the study programme is more reflective of the currently proposed range. Based on the provided data, there is substantial uncertainty on the efficacy of Amtagvi at lower doses infused. To define the lower limit of the dose range, the applicant should consider the lowest dose in the patient(s) who had an objective response. Lifileucel was given as a one-time infusion after lymphodepleting regimen. IL-2 was infused within 3-24hr afterwards. The hospitalization was only mandatory during Lifleucel and IL-2 infusions, however the majority of patients across both cohorts received NMA-LD in inpatient setting. Therefore, a recommendation in SmPC is needed (SmPC OC). The manufacturing process of TIL was expected to be about 22 days from enrolment/ tumor harvest to the treatment period. A washout period of 28 days before start of NMA-LD regimen was required. Therefore, it would be expected that some patients would not receive the planned treatment, as their disease might progress during the manufacturing process.

The intended target population is described sufficiently in the proposed indication.

Statistical methods: Cohort 2 was added three years after the initiation of the original protocol in 2014, its primary endpoint was modified in the same year, shifting from a safety profile to the ORR. Additionally, its sample size was increased twice, followed by another expansion in 2018, during which the endpoint was further clarified to be assessed by the Investigator. Later in 2018, Cohort 4 was introduced, with its primary endpoint, ORR, assessed by an IRC. The multiple amendments in Cohort 2, along with the reliance on Investigator-based assessments, raised concerns about the study's integrity. As a result, Cohort 2 and the combined analysis of Cohorts 2 and 4 are considered supportive, while Cohort 4 alone is regarded as the pivotal dataset.

Data restriction and confidentiality procedures were applied to Cohort 4 to maintain study integrity, with oversight provided by an IDMC. The IDMC was established in protocol version 9. The applicant confirmed that similar data restriction and confidentiality procedures were applied to Cohort 2 as to Cohort 4, including restricted access to IRC data, secure storage, and oversight by a restricted team to ensure data integrity. While an Independent Data Monitoring Committee (IDMC) was established only for Cohort 4 due to the expansion of international study sites, both Cohort 2 and Cohort 4 efficacy data were reviewed by the IRC.

The primary endpoint, ORR in FAS by IRC per RECIST v1.1, was introduced in protocol version 8 with the addition of cohort 4. According to SAP v.3, the primary analysis was to be performed after confirmed responders had at least 6 months of follow-up, as agreed with the FDA. However, there is no information on how study integrity was maintained during the determination of the timing for this primary analysis, raising concerns about potential bias or unblinding.

Secondary endpoints, including DOR, DCR, PFS, and OS, were analysed using Kaplan-Meier estimates. Given the single-arm design, the applicant relied on median estimates with 95% CIs. For PFS, 3

participants were censored due to discontinuation without experiencing progression or death, and 7 participants without baseline tumor assessment were also censored. These participants should have been classified as progression events in a sensitivity analysis.

Subgroup analyses of ORR and DCR, stratified by factor of manufacturing site (WuXi, Lonza, and Moffitt), showed no statistically significant results. The narrower confidence intervals observed for the WuXi site are likely attributable to the larger sample size at this site compared to Lonza and Moffitt, resulting in greater precision of the estimates. While this improves the reliability of the WuXi site's data, the smaller sample sizes at Lonza and Moffitt inherently limit the ability to draw definitive conclusions about site-specific differences.

Results: The applicant proposes pooling of data from cohort 2 and 4 based on similarity of included population, recipient of the cryopreserved TIL, treatment regimen and observed ORR results which are similar in both cohorts and are over 10%. However, in view of the methodological concerns regarding study integrity in cohort 2, pooling of data from the cohorts is not agreed upon. In addition, due to the numerous protocol amendments cohort 4 is considered to be the pivotal part of Study C-144-01 where potentially a reasonable level of pre-definition has been in place before inclusion of patients. Cohort 2 may be considered supportive provided conclusion on comparability of product based on quality. The analyses sets were pre-defined in the SAP. Primary efficacy endpoint was assessed using the Full analysis set (FAS), defined as patients who received lifileucel (LN-144) that met the final manufacturing product specifications. Considering that the production is initiated with lesion resection, the decision of treatment is made at resection not when the patient receives the product. According to Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application [EMA/CHMP/458061/2024], all subjects who initiated treatment should be used for the primary analysis, therefore the exclusion of 33 subjects from the primary analysis has not been clearly motivated. However, the fact that a sensitivity analysis based on the TH set (patients who had tumour resected for the production of lifileucel) for the primary endpoint (ORR as assessed by the IRC using RECIST v1.1) was pre-specified in the SAP and done in accordance with the pre-specification is appreciated. In addition, results from the safety analysis dataset would be considered supportive.

The original protocol was amended 9 times. The majority of changes involved clarification of inclusion/exclusion criteria, study design/objectives and safety procedures. It is noted that the first DCO for the primary endpoint was Sept 2021. The original protocol included only one cohort (cohort 1). The addition of Cohort 2 and 3 (re-treatment cohort) was implemented with amendment 4 (protocol version 5) in order to investigate cryopreserved Lifileucel. Cohort 4 was added with amendment 7 (nearly 2 years after addition of cohorts 2 and 3) based on the feedback received from FDA. Primary endpoint of ORR per RECIST v1.1 was changed: to be assessed by IRC, not investigator. Analysis population TH set, Enrolled set as well as FAS were also added during protocol version 8. The rationale for these changes during protocol amendment was to align with regulatory guidance to support product registration. The reason given for these major changes seem to be rational, nevertheless, the fact that major changes were made after study start is concerning, especially since this is a single arm trial. Due to the unblinded nature of this single arm trial, claims on existing firewalls can hardly overcome concerns on potential data knowledge and any amendment is considered potentially data driven. The fact that major changes were made after trial initiation poses a large impact on the reliability of the results and the assessment of this single arm trial [EMA/CHMP/458061/2024]. At the time of protocol amendment 8, Cohort 2 was closed to enrolment, but a few patients were being screened at the time of the study closing for enrolment, therefore these patients were still to be enrolled and/or treated. It is therefore understood that a majority of patients in cohort 2 were enrolled under different terms compared to those in cohort 4. The relevance of pooling the results from cohorts 2 and 4 for efficacy is therefore questionable. Important protocol deviations were overall infrequent in both datasets. Altogether, the important protocol deviations are

not expected to have an impact on overall study integrity. The enrolment of the pivotal study is complete with the first patient infused with Lifileucel in January 2016 and the last one in January 2020. As expected, the majority of not enrolled patients were screening failures, whereas the rest were not included due to death, subject withdrawing IC or other reasons. Overall, the treatment compliance seems balanced and acceptable for a reliable assessment of the study results.

The Tumor Harvested Dataset included 111 patients in **cohort 4**. The majority of enrolled patients in cohort 4 were white, American, males who had ECOG PS 0, metastatic disease and a median age of 55 years at the study entry. 43% of patients with liver and/or brain metastases were enrolled in the cohort 4. The median baseline LDH level was 316 (min, max:138, 1825). Given that brain metastases and high baseline LDH are well-known to be negative prognostic factors, the greater proportions of patients with liver and/or brain metastases (43.2% vs. 39.7%) and higher baseline LDH (316 vs. 258 U/L) compared to cohort 2 suggest that the cohort 4 included patients with an expected worse prognosis. (van Duin et al., 2024; https://doi.org/10.1002/ijc.34853). Median previous number of therapies were 3 (min 1, max 8). Most patients in cohort 4 (TH dataset) received prior anticancer therapy in the metastatic only setting. The median and mean target lesion diameter as assessed by INV was 84 mm and 103.4 mm (SD 71.0; min, max: 10, 325) respectively. 33 out of 111 (30%) patients had BRAF mutation and all were exposed to BRAF/MEK inhibitor. All patients received prior anti-PD-1/PDL-1 therapy, the combination with CTLA-4 inhibitor was utilized for 57% of the study population. The percentage of patients in cohort 4 who had primary refractory disease to PD-1/PDL-1 inhibitors was 48%. Median time from the prior therapy to tumor harvest was 1.8 months. The most common sites resected for manufacturing of TIL were skin/subcutaneous lesions (28%), lymph nodes (24%) and lung (13%).

A limited number of patients from Europe were included in the pivotal study (45 out of 156 patients in Safety analysis dataset) across both cohorts. This is to be expected, as there were only few European study centres participating in the study C-144-01. Even with a predominance of patients from USA, the assessment of B/R for Lifileucel is possible, as there is no biologic rationale to assume a difference in response between Europeans and Americans.

Since high toxicity is anticipated with TIL treatment, it would be foreseen that the study population would represent the most fit patients. The lower median age and high percentage of patients with ECOG PS 0 enrolled in the study C-144-01 are indicative of this. The proportion of patients with BRAF mutation is lower than anticipated (~<30% of enrolled population regardless of dataset employed) in the real world, where BRAF mutation can be detected in around 50% of melanomas (Gonzalez et al, 2013 doi: 10.1111/bjd.12248). This is considered acceptable and will not be pursued further. Overall, demographic and disease characteristics are considered to be representative of younger and fit European population of patients with advanced melanoma with limited treatment options.

Efficacy data and additional analyses

Primary endpoint

Overall response in the TH population was achieved in 25 of 111 patients corresponding to an ORR of 22.5% (95% CI 15.1, 31.4). Four (3.6%) patients achieved CR and 21 (18.9%) PR. 22/111 did not receive lifileucel. Primary reasons for not receiving included AEs 2 (1.8%), death 2 (2.7%), partial withdrawal of consent 1 (0.9%), TIL not available 6 (5.4%), progressive disease 5 (4.5%), start of new anti-cancer therapy 2 (1.8%) and other 3 (2.7%). The activity of 22.5% (95% CI 15.1, 31.4) for ORR is not sufficient to conclude on clinical benefit. In the absence of a randomised trial, it cannot be concluded that the benefits of Amtagvi outweigh the risks. Furthermore, the benefits to public health of the immediate availability of Amtagvi is not justified with the presented ORR of 22.5% which is not sufficient to conclude on clinical benefit. In the light of this level of antitumoral activity, the

toxicity profile of Amtagvi is not acceptable. Since efficacy has not been demonstrated, B/R has not been shown to be positive.

Secondary and other endpoints

Analyses of duration of response **(DOR),** time to first response **(TFR)** and time to best response **(TBR)** by IRC were performed only on responders, which were the same for all analysis sets. Median DOR was **10.4 months** (95% CI 4.1, 26.2; min, max: 1.4+, 45.8+) in cohort 4. With alternative censoring where initiation of new anti-cancer therapy was set as an event, the median DOR was 8.3 months (min 1.4, max 45.8; 95% CI not provided)

In conclusion, results from secondary and exploratory endpoints are supportive of Lifileucel activity in the present last line setting of advanced melanoma treatment.
The ORR results by Investigator in TH dataset show a high concordance rate, and ORR results are almost identical with IRC analyses. Acknowledging the caveats of time-to-event endpoints in an uncontrolled trial, a brief analysis of these is presented. Time to event endpoints such as OS and PFS cannot be contextualised in uncontrolled trials and the drug effect is not isolated. No efficacy claims can be based on PFS and OS results from the pivotal study. The mPFS for cohort 4 was 4.9 months (95% CI 4.0, 5.8). 16 patients were censored with 6 ongoing without PD or death. Overall, the applicant presented the PFS analysis per EMA guidelines, which is endorsed. Median OS in the TH set was 11.2 months (95% CI 8.8, 17.6). In the OS analysis, 24.3% of patients were censored. Of notice, median follow-up time is based on the reverse KM method and therefore is longer than median OS. The applicant provided the actual median survival follow up, per CHMP request, which was 10.7 months (min, max: 0.9, 49.7).
Regardless of dataset employed, the results of ORR in **prespecified subgroups** were consistent compared to the overall study populations this includes patients receiving fewer IL-2 doses and lifileucel doses produced at different facilities. But it has to be acknowledged that in cohort 4 for IL-2 doses this is based on 18 patients and for production facilities 5 patients. Due to limited sample size of subgroups, no conclusions can be drawn based on observed results of specific subgroups i.e. improved ORR in patients with PD-L1 TPS status>=5%.

Supportive data:

TH dataset: Most patients included in **cohort 2** were white, American, males, had baseline EGOG PS 0 and metastatic disease. The median age of the study population was 55 years old. The median baseline LDH level was 258 U/L. Patients had a median of three prior therapies; all were treated with anti-PD-1/PDL-1, and 51% also received it in combination with CTLA-4 inhibitor. The majority (67%) were primary refractory to PD-1/PDL-1 inhibitors. 22(28% of cohort 2 population) patients had BRAF mutation and nearly all (except for 2 patients) received BRAF/MEK inhibitor. Although the enrolment of BRAF/MEK naïve patients did not comply with the inclusion criteria (inclusion b, see section 3.3.1.1.1), this is still acceptable because the assessment of B/R of Lifileucel would unlikely be affected by these 2 BRAF/MEKi naïve patients and inclusion b was first added with the amendment 5. Median time from the prior therapy to tumor harvest was 2 months. The most common sites resected for manufacturing of TIL were other lesions (37%), lymph nodes (30%) and skin/subcutaneous (15%). In cohort 2, 11/78 patients did not receive lifileucel. ORR was achieved by 23/78 (29.5%; 95% CI 19.7, 40.9) in the TH set. DOR by IRC was NR months (95% CI NR, NR; min, max: 1.4+, 55.8+) in the cohort 2 with a possible median follow-up time of 51.9 months (95% CI 16.6, 54.2). The median follow-up time for response and mDOR for cohort 2 were 21.5 months (min, max: 1.4, 55.8) with alternative censoring where initiation of new anti-cancer therapy was set as an event. 19/23 patients were censored in the analysis, 0 due to death or PD after 2 or more missed visits, 8 due to start of new anti-cancer therapy, 6 discontinued assessment without PD or death and 5 are ongoing without PD or death. With the heavy censoring of DoR in cohort 2 a reliable estimate on median DoR is not considered to be presented.

Overall, the results in cohort 2 appears similar as the results in cohort 4. The cohort 2 results are considered supportive provided conclusion on comparability of product based on quality.

Safety analysis dataset

Cohort 4 consists of 89 patients with a nearly 1:1 ratio of females and males included. Demographics and disease characteristics of cohort 4 were similar to those described for TH dataset. ORR by IRC was 28.1% (95%CI: 19.1, 38.6) in cohort 4, meeting the statistical significance. The results of ORR by Investigator were overall correspondent to those reported by ICR. With maturity of ~90 %, median progression free survival (PFS) was 3.8 months (95%CI: 2.8, 4.9) in cohort 4. With median follow-up of 44 months and maturity of 77%, treatment with Amtagvi resulted in median overall survival (OS) of 12.3 (95%CI 7.9, 17.1) in cohort 4. Subsequent therapies were given to a majority of patients in cohorts 4 (51.7%), most received nivolumab (20.2% of patients), pembrolizumab (14.6% of patients) and ipilimumab (15.7%). The use of chemotherapy or IL-2 was limited. This is acceptable and represents clinical practice.

Among the 67 patients in Cohort 2 in the safety analysis dataset, most patients were American, white males with a median age of 55 and had baseline ECOG PS 0; 87% had a metastatic disease with liver and/or brain lesions (28/67 patients; 42%). With actual median follow-up for survival of 14 months for cohort 2 the study met its primary endpoint with objective response rate (ORR) by the IRC of 34.3% (95%CI: 23.2, 46.9).

Additional efficacy data needed in the context of a conditional MA

The following measures are necessary to address the missing efficacy data in the context of a conditional MA:

Final efficacy and safety results from the confirmatory phase 3 study TILVANCE-301, which investigates the efficacy and safety of Amtagvi plus pembrolizumab versus pembrolizumab monotherapy in the first line setting of recurrent or metastatic melanoma. The data should be provided as a specific obligation for the CMA, please refer also to section 6.2: Proposed list of post-authorisation measures.

3.3.6. Conclusions on clinical efficacy

Efficacy results of the pivotal study of Amtagvi monotherapy for the treatment of advanced melanoma show a low overall response rate and are considered insufficient to substantiate a CMA. The benefit/risk is negative. In addition, several OCs have been identified, which also need to be addressed by the applicant.

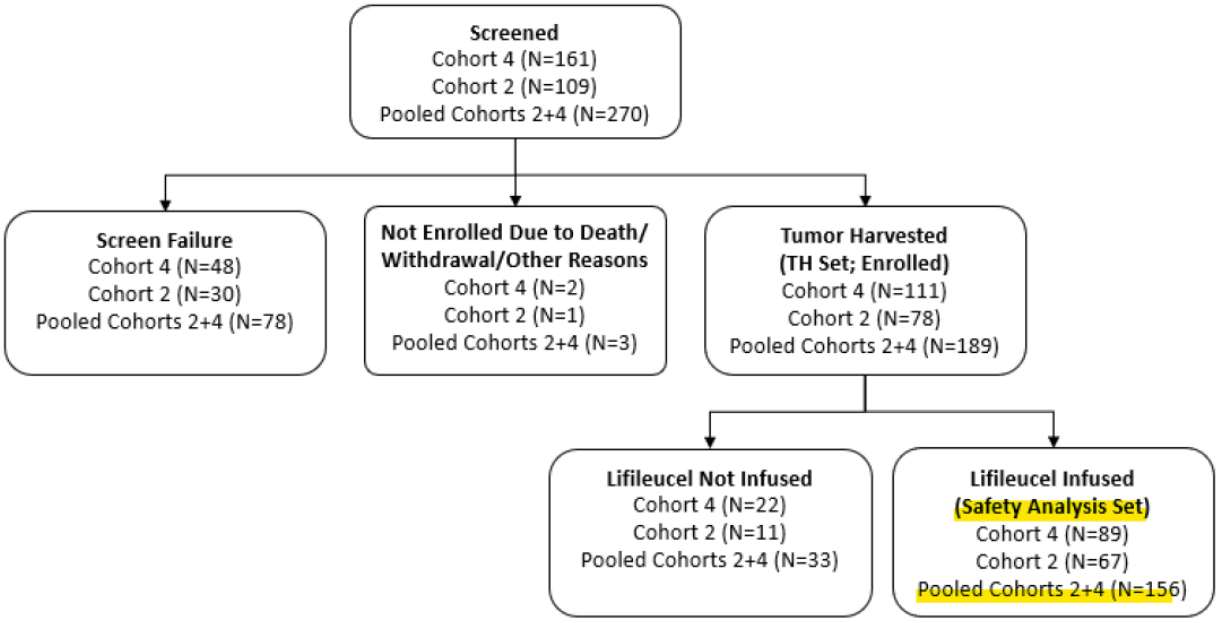
3.3.7. Clinical safety

The main safety database are those patients that received lifileucel (n=156), corresponding to the Safety Analysis Set (Cohort 2+4).

A supplementary assessment of patients that went through tumor harvesting but did not proceed to NMA-LD and in particular patients receiving NMA-LD but who did not proceed to lifileucel treatment will also be included.

Data Cutoff Date: 30 Jun 2023

Figure 1 Patient Disposition Flow Chart for All Screened Patients



Abbreviations: TH = tumor harvested
Source: C-144-01 CSR Addendum Table 14.1.1.2.1 (screening disposition) and C-144-01 CSR Addendum Table 14.1.2.2.1 (post-screening disposition)

3.3.7.1. Patient exposure

Exposure includes the various treatments given within 11 to 12 days:

NMA-LD Day -7 to Day -1: Cyclophosphamide IV (60 mg/kg × 2 doses) over 2 days with mesna followed by fludarabine IV (25 mg/m^2 × 5 doses) over 5 days.

Lifileucel Day 0; infusion as soon as possible after 24 hours have elapsed following the last dose of fludarabine, but no later than 4 days. The median dose of lifileucel in the Safety Analysis Set was 20.87 × 10^9 viable cells which fell within the manufacturing product specifications of between 1 × 10^9 and 150 × 10^9 viable cells (min, max: 0.4 × 10^9, 99.5 × 10^9), with a median relative infusion of 100%.

IL-2 (aldesleukin=Proleukin®) Day 0 up to Day 4: 600,000 IU/kg approximately every 8-12 hours (maximum of 6 doses) with the first dose within 3-24 hours after the completion of the lifileucel infusion.

Table 14.3.1.1.2.2 Study Regimen Administration
Cohorts 2 and 4 Safety Analysis Set

	Parameters	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Cyclophosphamide	Number of patients received Cyclophosphamide, n (%)	89 (100)	67 (100)	156 (100)
	Total Number of Infusions Received			
	n	89	67	156
	Mean (SD)	2.0 (0.00)	2.0 (0.12)	2.0 (0.08)
	Median	2.0	2.0	2.0
	Min, Max	2, 2	1, 2	1, 2
	Total Cumulative Dose (mg/kg)			
	n	89	67	156
	Mean (SD)	119.23 (4.844)	116.21 (11.567)	117.93 (8.518)
	Median	120.00	120.00	120.00
	Min, Max	87.6, 128.0	60, 130.1	60, 130.1
	Relative Dose Intensity (%) [2]			
	n	89	67	156
	Mean (SD)	99.36 (4.037)	96.84 (9.639)	98.28 (7.098)
	Median	100.00	100.00	100.00
	Min, Max	73.0, 106.6	50, 108.4	50, 108.4

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Table 14.3.1.1.2.2 Study Regimen Administration
Cohorts 2 and 4 Safety Analysis Set

	Parameters	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Fludarabine	Number of patients received Fludarabine, n (%)	89 (100)	67 (100)	156 (100)
	Planned dose, n (%)			
	$15mg/m^2$	6 (6.7)	0	6 (3.8)
	$20mg/m^2$	13 (14.6)	0	13 (8.3)
	$25mg/m^2$	76 (85.4)	67 (100)	143 (91.7)
	Total Number of Infusions Received			
	n	89	67	156
	Mean (SD)	4.0 (1.29)	4.8 (0.63)	4.4 (1.12)
	Median	5.0	5.0	5.0
	Min, Max	2, 5	2, 5	2, 5
	Total Cumulative Dose (mg/m^2)			
	n	89	67	156
	Mean (SD)	97.43 (33.535)	119.37 (17.719)	106.85 (29.848)
	Median	122.13	125.38	123.68
	Min, Max	23.2, 130.1	50.3, 134.1	23.2, 134.1
	Relative Dose Intensity (%) [3]			
	n	89	67	156
	Mean (SD)	81.12 (25.800)	95.50 (14.175)	87.29 (22.682)
	Median	98.36	100.31	99.03
	Min, Max	31.0, 104.1	40.3, 107.3	31.0, 107.3

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Table 14.3.1.1.2.2 Study Regimen Administration
Cohorts 2 and 4 Safety Analysis Set

	Parameters	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
LN-144 Infusion	Total Infused Cells ($x10^9$)			
	n	89	67	156
	Mean (SD)	23.30 (15.108)	26.90 (20.395)	24.85 (17.604)
	Median	20.50	23.28	20.87
	Min, Max	1.3, 72	0.4, 99.5	0.4, 99.5
	Relative Infusion (%) [1]			
	n	89	67	156
	Mean (SD)	99.05 (5.281)	93.96 (18.564)	96.87 (12.999)
	Median	100.00	100.00	100.00
	Min, Max	66.7, 100	3.5, 100	3.5, 100
	Number of patients received full dose of LN-144, n (%)	86 (96.6)	59 (88.1)	145 (92.9)

Table 14.3.1.1.2.2 Study Regimen Administration
Cohorts 2 and 4 Safety Analysis Set

	Parameters	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
IL-2	Number of patients received IL-2, n (%)	87 (97.8)	66 (98.5)	153 (98.1)
	Total Number of Infusions Received			
	n	89	67	156
	Mean (SD)	5.1 (1.46)	4.6 (1.76)	4.9 (1.61)
	Median	6.0	5.0	6.0
	Min, Max	0, 6	0, 6	0, 6
	Total Cumulative Dose (x10^3 IU/kg)			
	n	89	66	155
	Mean (SD)	3079.66 (894.389)	2704.40 (1113.804)	2919.87 (1007.656)
	Median	3584.17	3161.82	3537.30
	Min, Max	0, 3844.1	0, 3825.3	0, 3844.1
	Relative Dose Intensity (%) [4]			
	n	89	66	155
	Mean (SD)	97.75 (15.148)	96.21 (17.324)	97.09 (16.074)
	Median	100.00	100.00	100.00
	Min, Max	0, 106.8	0, 108.6	0, 108.6

[1] Actual infused viable cells/the total manufactured and released viable cells*100%.
[2] Relative to 2 planned doses of cyclophosphamide.
[3] Relative to 5 planned doses of fludarabine.
[4] Up to maximum of 6 doses of IL-2 at 600,000 IU/kg/dose.

Source: C-144-01, Program: t14-3-1-1-2-2-ex-c2c4-saf.sas, Data: ADSL, ADES and ADEX (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Table 14 Summary Statistics for Study Follow-Up Time (Safety Analysis Set)

	Cohort 4 (N=89)	Cohort 2 (N=67)	Pooled Cohorts 2 and 4 (N=156)
Study Follow-up Time until the last known alive date prior to the data cutoff date, months [1]			
Median	10.6	14.0	12.1
Min, Max	0.4, 48.1	0.2, 61.2	0.2, 61.2
Study Follow-up Time until the data cut-off date, months [2]			
Median	45.0	60.8	48.7
Min, Max	41.5, 51.2	51.7, 73.5	41.5, 73.5

[1] Defined as the time in months from the date of lifileucel infusion to the last known alive date, which is derived from the latest among dosing records, safety and any other assessment dates indicating that a patient is alive or death date if patient has died.
[2] Defined as the time in months from the date of lifileucel infusion to the data cutoff date.

3.3.7.2. Adverse events

The AE analyses were performed for the following study periods:

- **Tumor Harvested (TH) Period**: from Tumor Harvest up to the start of NMA-LD. For patients who did not receive NMA-LD, AEs up to 30 days following the date of the tumor harvest were included.
- **NMA-LD Period:** from the start of NMA-LD up to the start of the lifileucel infusion. For patients who did not receive lifileucel, AEs up to 30 days from the last dose of NMA-LD were included.
- **Treatment-emergent Period**: from the start of the lifileucel infusion on Day 0 up to 30 days after the lifileucel infusion (ie, TEAEs)

- **Post-treatment-emergent Period:** from 30 days following the lifileucel infusion on Day 0 and up to 6 months after the lifileucel infusion or until the start of a new anti-cancer therapy, whichever occurred first.

Table 16 Adverse Event Summary

Number of patients with at least one of the following events	Cohort 4 N1	Cohort 4 Any Grade n (%)	Cohort 4 Grade 3/4 n (%)	Cohort 4 Grade 5 n (%)	Cohort 2 N1	Cohort 2 Any Grade n (%)	Cohort 2 Grade 3/4 n (%)	Cohort 2 Grade 5 n (%)	Pooled Cohorts 2 and 4 N1	Pooled Cohorts 2 and 4 Any Grade n (%)	Pooled Cohorts 2 and 4 Grade 3/4 n (%)	Pooled Cohorts 2 and 4 Grade 5 n (%)
For the TH Set [1]												
Tumor-Harvest AE	111	78 (70.3)	21 (18.9)	0	78	48 (61.5)	17 (21.8)	0	189	126 (66.7)	38 (20.1)	0
Tumor-Harvest SAE	111	15 (13.5)	10 (9.0)	0	78	9 (11.5)	9 (11.5)	0	189	24 (12.7)	19 (10.1)	0
For Patients who Received NMA-LD [2]												
AE during NMA-LD period	91	91 (100)	77 (84.6)	1 (1.1)	69	69 (100)	65 (94.2)	1 (1.4)	160	160 (100)	142 (88.8)	2 (1.3)
SAE during NMA-LD period	91	6 (6.6)	6 (6.6)	1 (1.1)	69	9 (13.0)	6 (8.7)	1 (1.4)	160	15 (9.4)	12 (7.5)	2 (1.3)
For the Safety Analysis Set [3]												
TEAE	89	89 (100)	86 (96.6)	2 (2.2)	67	67 (100)	65 (97.0)	2 (3.0)	156	156 (100)	151 (96.8)	4 (2.6)
TEAE related to lifileucel [4]	89	70 (78.7)	32 (36.0)	0	67	50 (74.6)	28 (41.8)	1 (1.5)	156	120 (76.9)	60 (38.5)	1 (0.6)
TEAE related to lifileucel only [5]	89	30 (33.7)	4 (4.5)	0	67	27 (40.3)	4 (6.0)	0	156	57 (36.5)	8 (5.1)	0
TEAE leading to lifileucel discontinuation	89	0	0	0	67	2 (3.0)	2 (3.0)	0	156	2 (1.3)	2 (1.3)	0
Post-treatment-emergent AE	89	44 (49.4)	18 (20.2)	3 (3.4)	67	53 (79.1)	19 (28.4)	3 (4.5)	156	97 (62.2)	37 (23.7)	6 (3.8)
Treatment-emergent SAE	89	31 (34.8)	29 (32.6)	2 (2.2)	67	23 (34.3)	22 (32.8)	2 (3.0)	156	54 (34.6)	51 (32.7)	4 (2.6)
Treatment-emergent SAE related to lifileucel [4]	89	2 (2.2)	1 (1.1)	0	67	6 (9.0)	5 (7.5)	1 (1.5)	156	8 (5.1)	6 (3.8)	1 (0.6)
Treatment-emergent SAE related to lifileucel only [5]	89	1 (1.1)	0	0	67	3 (4.5)	2 (3.0)	0	156	4 (2.6)	2 (1.3)	0
Post-treatment-emergent SAE	89	13 (14.6)	8 (9.0)	3 (3.4)	67	16 (23.9)	12 (17.9)	3 (4.5)	156	29 (18.6)	20 (12.8)	6 (3.8)

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NMA-LD = nonmyeloablative lymphodepletion; N1 = number of patients in the specific patient population; % = n/N1*100; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TH Set = Tumor Harvested Set

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03. Patients with multiple events are counted only once using the maximum grade. Tumor-Harvest AEs refer to AEs that started after the tumor harvest and before the start of the NMA-LD. For patients who did not receive NMA-LD, AEs up to 30 days from tumor harvest are included.

AEs during the NMA-LD period include AEs that occurred from the start of NMA-LD and before the start of the lifileucel infusion. For patients who did not receive a lifileucel infusion, AEs up to 30 days from the last dose of NMA-LD are included.

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.

[1] Percentage is calculated based on number of patients in TH Set.

[2] Percentage is calculated based on number of patients who received NMA-LD.

[3] Percentage is calculated based on number of patients in Safety Analysis Set.

[4] Related to lifileucel regardless of a relationship to other components of the treatment regimen (ie, cyclophosphamide, fludarabine, or IL-2).

[5] Related to lifileucel only and not related to other components of the treatment regimen (ie, cyclophosphamide, fludarabine, or IL-2).

Source: Table 14.3.1.2.2.1

Adverse Events: All and Grade 3/4:

The most clinically important AEs during the **Tumor harvest period** (TH-period, n=188) occurring in more than one patient were three cases of pulmonary embolism (all grade 3-4). No patients died due to an AE. Thirty-three patients from TH Set were not infused with lifileucel mainly due to progression, death, and unavailability of TIL (see the efficacy section).

As expected based on the chemotherapy given (high-dose cyclophosphamide and fludarabine), cytopenias and gastrointestinal symptoms were the most common AEs (all and grade 3-4) in the **NMA-LD treatment period** (n=160). Two patients died in this period due to acute kidney injury and septic shock, which given the relatively harsh chemotherapy used, is considered a known risk.

The applicant has presented very few overview tables in the SCS and the CSR but instead referred to tables in section 14 of the CSR that are 20-100 pages long. This is not acceptable as per the guidance. Please present an updated SCS with overview tables for each subheading in addition to the text presented that are suitable for the AR and eventually the EPAR – Public Assessment Report; there are many publicly available good examples.

AEs during the treatment-emergent period:

Table 3 TEAEs Reported at an Incidence of ≥ 20% in Pooled Cohorts 2 and 4 Presented by SOC, PT, and Grade (Safety Analysis Set)

System Organ Class Preferred Term	Cohort 4 (N=89) Any Grade n (%)	Cohort 4 (N=89) Grade 3/4 n (%)	Cohort 4 (N=89) Grade 5 n (%)	Cohort 2 (N=67) Any Grade n (%)	Cohort 2 (N=67) Grade 3/4 n (%)	Cohort 2 (N=67) Grade 5 n (%)	Pooled Cohorts 2 and 4 (N=156) Any Grade n (%)	Pooled Cohorts 2 and 4 (N=156) Grade 3/4 n (%)	Pooled Cohorts 2 and 4 (N=156) Grade 5 n (%)
Number of patients reporting at least one TEAE	89 (100)	86 (96.6)	2 (2.2)	67 (100)	65 (97.0)	2 (3.0)	156 (100)	151 (96.8)	4 (2.6)
Blood and lymphatic system disorders							145 (92.9)	143 (91.7)	0
Thrombocytopenia [1]	73 (82.0)	68 (76.4)	0	60 (89.6)	55 (82.1)	0	133 (85.3)	123 (78.8)	0
Anaemia	54 (60.7)	42 (47.2)	0	46 (68.7)	38 (56.7)	0	100 (64.1)	80 (51.3)	0
Neutropenia [2]	31 (34.8)	20 (22.5)	0	37 (55.2)	26 (38.8)	0	68 (43.6)	46 (29.5)	0
Febrile neutropenia	29 (32.6)	29 (32.6)	0	36 (53.7)	36 (53.7)	0	65 (41.7)	65 (41.7)	0
Leukopenia [3]	29 (32.6)	21 (23.6)	0	28 (41.8)	23 (34.3)	0	57 (36.5)	44 (28.2)	0
Lymphopenia [4]	28 (31.5)	19 (21.3)	0	23 (34.3)	21 (31.3)	0	51 (32.7)	40 (25.6)	0
Cardiac disorders							74 (47.4)	10 (6.4)	0
Tachycardia	22 (24.7)	3 (3.4)	0	23 (34.3)	1 (1.5)	0	45 (28.8)	4 (2.6)	0
Gastrointestinal disorders							102 (65.4)	10 (6.4)	1 (0.6)
Diarrhoea	29 (32.6)	1 (1.1)	0	19 (28.4)	1 (1.5)	0	48 (30.8)	2 (1.3)	0
Nausea	21 (23.6)	3 (3.4)	0	16 (23.9)	0	0	37 (23.7)	3 (1.9)	0
Vomiting	20 (22.5)	1 (1.1)	0	14 (20.9)	0	0	34 (21.8)	1 (0.6)	0
General disorders and administration site conditions							145 (92.9)	34 (21.8)	0
Chills	64 (71.9)	4 (4.5)	0	53 (79.1)	4 (6.0)	0	117 (75.0)	8 (5.1)	0
Pyrexia	42 (47.2)	6 (6.7)	0	39 (58.2)	11 (16.4)	0	81 (51.9)	17 (10.9)	0
Fatigue	25 (28.1)	6 (6.7)	0	26 (38.8)	1 (1.5)	0	51 (32.7)	7 (4.5)	0
Oedema peripheral	15 (16.9)	1 (1.1)	0	17 (25.4)	1 (1.5)	0	32 (20.5)	2 (1.3)	0
Investigations							96 (61.5)	29 (18.6)	0
Aspartate aminotransferase increased	14 (15.7)	4 (4.5)	0	19 (28.4)	0	0	33 (21.2)	4 (2.6)	0
Metabolism and nutrition disorders							109 (69.9)	54 (34.6)	0
Hypophosphataemia	28 (31.5)	18 (20.2)	0	30 (44.8)	23 (34.3)	0	58 (37.2)	41 (26.3)	0
Hypokalaemia	26 (29.2)	4 (4.5)	0	17 (25.4)	2 (3.0)	0	43 (27.6)	6 (3.8)	0
Respiratory, thoracic and mediastinal disorders							101 (64.7)	35 (22.4)	1 (0.6)
Hypoxia	19 (21.3)	9 (10.1)	0	16 (23.9)	10 (14.9)	0	35 (22.4)	19 (12.2)	0
Skin and subcutaneous tissue disorders							99 (63.5)	24 (15.4)	0
Rash	23 (25.8)	3 (3.4)	0	17 (25.4)	3 (4.5)	0	40 (25.6)	6 (3.8)	0
Alopecia	19 (21.3)	0	0	19 (28.4)	0	0	38 (24.4)	0	0
Vascular disorders							84 (53.8)	37 (23.7)	0
Hypotension	28 (31.5)	10 (11.2)	0	24 (35.8)	7 (10.4)	0	52 (33.3)	17 (10.9)	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03. Patients with multiple events for a given PT are counted only once using the maximum grade under each PT.

AEs are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in the Pooled Cohorts 2 and 4 group. TEAEs include all AEs that began starting from the lifileucel infusion to 30 days post lifileucel infusion.

[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.

Source: C-144-01 CSR Addendum Table 14.3.1.3.1.2.2

Table 2.7.4.1 TEAEs within Grouped Terms by Preferred Term
Cohorts 2 and 4 Safety Analysis Set

Grouped Term Preferred Term	Cohort 4 (N=89) Any Grade n (%)	Cohort 4 (N=89) Grade 3/4 n (%)	Cohort 4 (N=89) Grade 5 n (%)	Cohort 2 (N=67) Any Grade n (%)	Cohort 2 (N=67) Grade 3/4 n (%)	Cohort 2 (N=67) Grade 5 n (%)	Pooled Cohorts 2 and 4 (N=156) Any Grade n (%)	Pooled Cohorts 2 and 4 (N=156) Grade 3/4 n (%)	Pooled Cohorts 2 and 4 (N=156) Grade 5 n (%)
Cytopenia	77 (86.5)	73 (82.0)	0	61 (91.0)	59 (88.1)	0	138 (88.5)	132 (84.6)	0
Thrombocytopenia [1]	73 (82.0)	68 (76.4)	0	60 (89.6)	55 (82.1)	0	133 (85.3)	123 (78.8)	0
Neutropenia [2]	31 (34.8)	20 (22.5)	0	37 (55.2)	26 (38.8)	0	68 (43.6)	46 (29.5)	0
Leukopenia [3]	29 (32.6)	21 (23.6)	0	28 (41.8)	23 (34.3)	0	57 (36.5)	44 (28.2)	0
Lymphopenia [4]	28 (31.5)	19 (21.3)	0	23 (34.3)	21 (31.3)	0	51 (32.7)	40 (25.6)	0
Cardiac arrhythmia terms [5]	38 (42.7)	8 (9.0)	1 (1.1)	36 (53.7)	3 (4.5)	0	74 (47.4)	11 (7.1)	1 (0.6)
Tachycardia	22 (24.7)	3 (3.4)	0	23 (34.3)	1 (1.5)	0	45 (28.8)	4 (2.6)	0
Sinus tachycardia	13 (14.6)	2 (2.2)	0	10 (14.9)	0	0	23 (14.7)	2 (1.3)	0
Atrial fibrillation	3 (3.4)	2 (2.2)	0	1 (1.5)	0	0	4 (2.6)	2 (1.3)	0
Electrocardiogram QT prolonged	2 (2.2)	0	0	2 (3.0)	2 (3.0)	0	4 (2.6)	2 (1.3)	0

Grouped Term Preferred Term	Cohort 4 (N=89) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Cohort 2 (N=67) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Pooled Cohorts 2 and 4 (N=156) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)
Cardiac arrhythmia terms [5]									
Supraventricular tachycardia	1 (1.1)	1 (1.1)	0	3 (4.5)	0	0	4 (2.6)	1 (0.6)	0
Ventricular tachycardia	1 (1.1)	0	0	2 (3.0)	0	0	3 (1.9)	0	0
Arrhythmia	1 (1.1)	0	1 (1.1)	0	0	0	1 (0.6)	0	1 (0.6)
Atrial flutter	0	0	0	1 (1.5)	0	0	1 (0.6)	0	0
Atrioventricular block second degree	0	0	0	1 (1.5)	0	0	1 (0.6)	0	0
Bradycardia	1 (1.1)	0	0	0	0	0	1 (0.6)	0	0
Vascular hypotensive disorders [6]	37 (41.6)	15 (16.9)	0	27 (40.3)	8 (11.9)	0	64 (41.0)	23 (14.7)	0
Hypotension	28 (31.5)	10 (11.2)	0	24 (35.8)	7 (10.4)	0	52 (33.3)	17 (10.9)	0
Capillary leak syndrome	12 (13.5)	6 (6.7)	0	8 (11.9)	1 (1.5)	0	20 (12.8)	7 (4.5)	0
Orthostatic hypotension	2 (2.2)	0	0	0	0	0	2 (1.3)	0	0
Noninfectious encephalopathy/delirium [7]	27 (30.3)	8 (9.0)	0	23 (34.3)	6 (9.0)	0	50 (32.1)	14 (9.0)	0

Grouped Term Preferred Term	Cohort 4 (N=89) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Cohort 2 (N=67) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Pooled Cohorts 2 and 4 (N=156) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)
Noninfectious encephalopathy/delirium [7]									
Confusional state	5 (5.6)	1 (1.1)	0	9 (13.4)	1 (1.5)	0	14 (9.0)	2 (1.3)	0
Delirium	6 (6.7)	3 (3.4)	0	4 (6.0)	0	0	10 (6.4)	3 (1.9)	0
Encephalopathy	4 (4.5)	3 (3.4)	0	5 (7.5)	4 (6.0)	0	9 (5.8)	7 (4.5)	0
Muscular weakness	3 (3.4)	1 (1.1)	0	3 (4.5)	1 (1.5)	0	6 (3.8)	2 (1.3)	0
Somnolence	2 (2.2)	0	0	3 (4.5)	1 (1.5)	0	5 (3.2)	1 (0.6)	0
Hallucination	2 (2.2)	1 (1.1)	0	2 (3.0)	0	0	4 (2.6)	1 (0.6)	0
Agitation	1 (1.1)	0	0	2 (3.0)	1 (1.5)	0	3 (1.9)	1 (0.6)	0
Depressed level of consciousness	0	0	0	3 (4.5)	1 (1.5)	0	3 (1.9)	1 (0.6)	0
Aphasia	0	0	0	2 (3.0)	0	0	2 (1.3)	0	0
Disorientation	2 (2.2)	1 (1.1)	0	0	0	0	2 (1.3)	1 (0.6)	0
Disturbance in attention	2 (2.2)	0	0	0	0	0	2 (1.3)	0	0

Grouped Term Preferred Term	Cohort 4 (N=89) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Cohort 2 (N=67) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Pooled Cohorts 2 and 4 (N=156) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)
Noninfectious encephalopathy/delirium [7]									
Dysarthria	1 (1.1)	0	0	1 (1.5)	1 (1.5)	0	2 (1.3)	1 (0.6)	0
Dysphagia	1 (1.1)	0	0	1 (1.5)	0	0	2 (1.3)	0	0
Tremor	2 (2.2)	0	0	0	0	0	2 (1.3)	0	0
Bradyphrenia	1 (1.1)	0	0	0	0	0	1 (0.6)	0	0
Delusion	0	0	0	1 (1.5)	0	0	1 (0.6)	0	0
Hallucination, visual	1 (1.1)	0	0	0	0	0	1 (0.6)	0	0
Immune effector cell-associated neurotoxicity syndrome	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Lethargy	0	0	0	1 (1.5)	0	0	1 (0.6)	0	0
Memory impairment	0	0	0	1 (1.5)	0	0	1 (0.6)	0	0
Mental status changes	0	0	0	1 (1.5)	0	0	1 (0.6)	0	0
Restlessness	1 (1.1)	0	0	0	0	0	1 (0.6)	0	0

Grouped Term Preferred Term	Cohort 4 (N=89) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Cohort 2 (N=67) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Pooled Cohorts 2 and 4 (N=156) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)
Noninfectious encephalopathy/delirium [7]									
Seizure	1 (1.1)	0	0	0	0	0	1 (0.6)	0	0
Immune-mediated/autoimmune disorders [8]	3 (3.4)	0	0	7 (10.4)	0	0	10 (6.4)	0	0
Vitiligo	3 (3.4)	0	0	6 (9.0)	0	0	9 (5.8)	0	0
Cutaneous vasculitis	0	0	0	1 (1.5)	0	0	1 (0.6)	0	0

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Adverse Events are sorted by decreasing frequency of grouped PT, and of PT within grouped PT per any grade in Pooled Cohorts 2 and 4 group.
Treatment-Emergent Adverse Events refer to all AEs starting from LN-144 infusion to 30 days post LN-144 infusion.

[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] MedDRA 24.0 SMQ of Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) and Preferred terms of Bradycardia and Tachycardia.
[6] MedDRA 24.0 HLT of Vascular hypotensive disorders.
[7] MedDRA 24.0 SMQ of Noninfectious encephalopathy/delirium.
[8] Narrow MedDRA 24.0 SMQ of Immune-mediated/autoimmune disorders.

Source: C-144-01, Program: t2-7-4-1-teae-gpt-pt-c2c4-saf.sas, Data: ADSL and ADAE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

With a median study follow up of 12.1 months, the most common **post-treatment-emergent** AEs were anaemia (17.9%), the grouped terms of thrombocytopenia (12.8%) and neutropenia (7.1%), fatigue (7.7%), and vomiting (5.8%). One patient died due to septic shock.

Table 18 **Post-treatment-emergent AEs at an Incidence of ≥ 5% of Patients in Pooled Cohorts 2 and 4 Presented by SOC, PT, and Grade (Safety Analysis Set)**

	Cohort 4 (N=89)			Cohort 2 (N=67)			Pooled Cohorts 2 and 4 (N=156)		
System Organ Class Preferred Term	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders									
Anaemia	11 (12.4)	6 (6.7)	0	17 (25.4)	8 (11.9)	0	28 (17.9)	14 (9.0)	0
Thrombocytopenia [1]	9 (10.1)	5 (5.6)	0	11 (16.4)	3 (4.5)	0	20 (12.8)	8 (5.1)	0
Neutropenia [2]	7 (7.9)	5 (5.6)	0	4 (6.0)	0	0	11 (7.1)	5 (3.2)	0
Leukopenia [3]	4 (4.5)	2 (2.2)	0	6 (9.0)	2 (3.0)	0	10 (6.4)	4 (2.6)	0
Lymphopenia [4]	5 (5.6)	1 (1.1)	0	5 (7.5)	3 (4.5)	0	10 (6.4)	4 (2.6)	0
Gastrointestinal disorders									
Vomiting	2 (2.2)	1 (1.1)	0	7 (10.4)	0	0	9 (5.8)	1 (0.6)	0
General disorders and administration site conditions									
Fatigue	5 (5.6)	1 (1.1)	0	7 (10.4)	1 (1.5)	0	12 (7.7)	2 (1.3)	0

Abbreviations: AE = adverse event; CSR = clinical study report; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PD = progressive disease; PT = Preferred Term; SOC = System Organ Class
Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.
Patients with multiple events for a given PT are counted only once using the maximum grade under each PT.
AEs are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in the Pooled Cohorts 2 and 4 group.
Post Treatment-Emergent AEs refer to AEs that started 30 days post lifileucel infusion and through 6 months after the lifileucel infusion or up to the start of a new anti-cancer therapy, whichever occurred first.
[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.
Source: C-144-01, Program: t14-3-1-8-2-2-pteae-soc-5pt-c2c4-saf Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Adverse drug reactions

There are currently 3 risks for lifileucel that have been identified by the Sponsor:

- Hypersensitivity reactions, including infusion-related reactions (n=9; 5.8%, anaphylaxis (n=2; 1.3%), and hypersensitivity (n=1; 0.6%)
- Uveitis (n=6; 3.8%)
- Vitiligo (n=9; 5.8%)

Hypersensitivity reaction is a broad term. Cytokine release syndrome (CRS) is commonly seen with infusion of cells. Furthermore, capillary leak syndrome is a potentially life-threatening AE considered related to treatment with IL-2. Several OCs have been raised regarding these issues.

Table 20 TEAEs Reported as Related to Lifileucel at an Incidence of ≥ 10% of Patients in Pooled Cohorts 2 and 4 (Safety Analysis Set)

	Cohort 4 (N=89)			Cohort 2 (N=67)			Pooled Cohorts 2 and 4 (N=156)		
System Organ Class Preferred Term	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders									
Thrombocytopenia [1]	13 (14.6)	10 (11.2)	0	11 (16.4)	10 (14.9)	0	24 (15.4)	20 (12.8)	0
Anaemia	8 (9.0)	5 (5.6)	0	11 (16.4)	9 (13.4)	0	19 (12.2)	14 (9.0)	0
Febrile neutropenia	6 (6.7)	6 (6.7)	0	10 (14.9)	10 (14.9)	0	16 (10.3)	16 (10.3)	0
General disorders and administration site conditions									
Chills	24 (27.0)	2 (2.2)	0	23 (34.3)	2 (3.0)	0	47 (30.1)	4 (2.6)	0
Pyrexia	20 (22.5)	3 (3.4)	0	16 (23.9)	3 (4.5)	0	36 (23.1)	6 (3.8)	0
Fatigue	7 (7.9)	0	0	12 (17.9)	0	0	19 (12.2)	0	0
Skin and subcutaneous tissue disorders									
Rash	12 (13.5)	2 (2.2)	0	6 (9.0)	0	0	18 (11.5)	2 (1.3)	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE = treatment-emergent adverse event
Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.
Patients with multiple events for a given PT are counted only once using the maximum grade under each PT.
AEs are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in the Pooled Cohorts 2 and 4 group.
TEAEs refer to all AEs starting from the lifileucel infusion to 30 days post lifileucel infusion.
[1] AE grouped terms of platelet count decreased and thrombocytopenia.
Source: C-144-01, Program: t14-3-1-9-2-2-teae-reltil-soc-10pt-c2c4-saf Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

Treatment-related AEs should be presented for the entire treatment [NMA-LD period and treatment-emergent period (lifileucel & IL-2)] and not only for lifileucel, as presented in Table 20/CSR, as this forms the basis for the ADR table in the SmPC, as the applicant rightly states in that table (*Adverse reactions are defined as adverse events at least possibly related to any component of the AMTAGVI regimen (cyclophosphamide, fludarabine, lifileucel, IL-2) that occurred up to 6 months (182 days) post AMTAGVI or up to the start of a new anti-cancer therapy, whichever occurs first).*

The following terms are described separately in section 4.4 and/or 4.8 of the SmPC, as these are serious and to a large extent caused by the treatment regimen:

1. Infections (serious)
2. Cytopenias (grouped term; GT); neutropenia, febrile neutropenia and thrombocytopenia including prolonged cytopenias
3. Immune system disorders; hypersensitivity in particular CRS.
4. Nervous system disorders; encephalopathy (GT): TEAE 32.1% (all), 9.0% (grade 3-4)
5. Cardiac disorders; arrhythmia (GT): TEAE 47.4% (all), 7.1% (grade 3-4), and grade 5 in 1 patient.
6. Vascular disorders; haemorrhage: No information found re. TEAE frequency but at least one death; hypotension (GT): TEAE 41.0% (all), 14.7 % (grade 3-4); capillary leak syndrome (GT) 12.8% (all), 4.5% (grade 3-4)

3.3.7.3. Serious adverse events, deaths, and other significant events

Deaths

The applicant states that several deaths were due to the preparative (lympho-depleting) regimen. This may be so, but this treatment is part of the entire treatment-regimen (and a prerequisite for lifileucel infusion), and thus safety is assessed for the TEAE regardless of which part of the regimen is considered the causal agent.

Two patients died due to SAEs during the NMA-LD preparative regimen administration of acute kidney injury and septic shock; these are considered related to the treatment-regimen.

Table 4 Deaths that Occurred After the Lifileucel Infusion (Safety Analysis Set)

	Cohort 4 (N=89) n (%)	Cohort 2 (N=67) n (%)	Pooled Cohorts 2 and 4 (N=156) n (%)
Number of deaths that occurred after the lifileucel infusion	69 (77.5)	49 (73.1)	118 (75.6)
Number of deaths that occurred after the lifileucel infusion to 30 days post lifileucel infusion	4 (4.5)	2 (3.0)	6 (3.8)
Primary cause of death			
Adverse Event	2 (2.2)	2 (3.0)	4 (2.6)
Progressive Disease	2 (2.2)	0	2 (1.3)
Number of deaths that occurred after 30 days post lifileucel infusion	65 (73.0)	47 (70.1)	112 (71.8)
Primary cause of death			
Adverse Event	4 (4.5)	4 (6.0)	8 (5.1)
Progressive Disease	56 (62.9)	39 (58.2)	95 (60.9)
Other	5 (5.6)	4 (6.0)	9 (5.8)

Source: C-144-01 CSR Addendum Table 14.3.2.13.2.1

Serious adverse events

SAEs During the Tumor Harvest Period

Clinical Study Report Addendum — Protocol: C-144-01

Table 14.3.2.8.2.1 Tumor-Harvest SAEs for TH Set by System Organ Class and Preferred Term
Cohorts 2 and 4 Tumor Harvested Set

System Organ Class Preferred Term	Cohort 4 (N=111) Any Grade n (%)	Cohort 4 (N=111) Grade 3/4 n (%)	Cohort 4 (N=111) Grade 5 n (%)	Cohort 2 (N=78) Any Grade n (%)	Cohort 2 (N=78) Grade 3/4 n (%)	Cohort 2 (N=78) Grade 5 n (%)	Pooled Cohorts 2 and 4 (N=189) Any Grade n (%)	Pooled Cohorts 2 and 4 (N=189) Grade 3/4 n (%)	Pooled Cohorts 2 and 4 (N=189) Grade 5 n (%)
Number of patients reporting at least one Tumor-Harvest SAE for TH set	15 (13.5)	10 (9.0)	0	9 (11.5)	9 (11.5)	0	24 (12.7)	19 (10.1)	0
Infections and infestations	3 (2.7)	3 (2.7)	0	2 (2.6)	2 (2.6)	0	5 (2.6)	5 (2.6)	0
Cellulitis	1 (0.9)	1 (0.9)	0	1 (1.3)	1 (1.3)	0	2 (1.1)	2 (1.1)	0
Erysipelas	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Gastroenteritis Escherichia coli	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Sepsis	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Wound infection	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders	2 (1.8)	2 (1.8)	0	3 (3.8)	3 (3.8)	0	5 (2.6)	5 (2.6)	0
Pulmonary embolism	0	0	0	2 (2.6)	2 (2.6)	0	2 (1.1)	2 (1.1)	0
Dyspnoea	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Hypoxia	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Pleural effusion	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Gastrointestinal disorders	3 (2.7)	3 (2.7)	0	1 (1.3)	1 (1.3)	0	4 (2.1)	4 (2.1)	0
Ileus	2 (1.8)	1 (0.9)	0	0	0	0	2 (1.1)	1 (0.5)	0
Dysphagia	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Nausea	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Small intestinal obstruction	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.8)	2 (1.8)	0	2 (2.6)	2 (2.6)	0	4 (2.1)	4 (2.1)	0
Tumour pain	2 (1.8)	2 (1.8)	0	2 (2.6)	2 (2.6)	0	4 (2.1)	4 (2.1)	0
Injury, poisoning and procedural complications	1 (0.9)	0	0	2 (2.6)	2 (2.6)	0	3 (1.6)	2 (1.1)	0
Hip fracture	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Postoperative ileus	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Wound secretion	1 (0.9)	0	0	0	0	0	1 (0.5)	0	0
Metabolism and nutrition disorders	2 (1.8)	0	0	1 (1.3)	1 (1.3)	0	3 (1.6)	1 (0.5)	0
Hyponatraemia	2 (1.8)	0	0	0	0	0	2 (1.1)	0	0
Dehydration	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0

Hypovolaemia	1 (0.9)	0	0	0	0	0	1 (0.5)	0	0
Blood and lymphatic system disorders	1 (0.9)	0	0	1 (1.3)	1 (1.3)	0	2 (1.1)	1 (0.5)	0
Anaemia	1 (0.9)	0	0	1 (1.3)	1 (1.3)	0	2 (1.1)	1 (0.5)	0
General disorders and administration site conditions	1 (0.9)	0	0	1 (1.3)	1 (1.3)	0	2 (1.1)	1 (0.5)	0
Fatigue	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Pyrexia	1 (0.9)	0	0	0	0	0	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders	1 (0.9)	0	0	1 (1.3)	1 (1.3)	0	2 (1.1)	1 (0.5)	0
Muscular weakness	1 (0.9)	0	0	0	0	0	1 (0.5)	0	0
Rhabdomyolysis	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Renal and urinary disorders	2 (1.8)	2 (1.8)	0	0	0	0	2 (1.1)	2 (1.1)	0
Haematuria	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Urinary tract obstruction	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Psychiatric disorders	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Mental status changes	0	0	0	1 (1.3)	1 (1.3)	0	1 (0.5)	1 (0.5)	0
Surgical and medical procedures	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Brain tumour operation	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0
Internal fixation of fracture	1 (0.9)	1 (0.9)	0	0	0	0	1 (0.5)	1 (0.5)	0

SAE = Serious Adverse Event. TH set = Tumor Harvested Set.

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Adverse Events are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in Pooled Cohorts 2 and 4 group.
Tumor-Harvest Adverse Events refer to AEs that start after Tumor Harvest and before the start of NMA-LD. For patients who didn't receive NMA-LD, AEs up to 30 days from tumor harvest will be included.

Source: C-144-01, Program: t14-3-2-8-2-1-thae-sae-soc-pt-c2c4-th.sas, Data: ADSL and ADAE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

SAEs During the NMA-LD Period

In the **NMA-LD period** 9.4% experienced at least one SAE. SAEs that were reported in more than one patient were febrile neutropenia (3), and pyrexia, neutropenia (GT), acute kidney injury and pleural effusion where reported in 2 patients each. Cytopenias are expected to occur with a higher frequency from D8-10 and onwards. Two patients had fatal SAEs (see previous section).

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Table 14.3.2.8.5.1 SAEs during NMA-LD Period by System Organ Class and Preferred Term
Cohorts 2 and 4 Patients who received NMA-LD

	Cohort 4 (N=91)			Cohort 2 (N=69)			Pooled Cohorts 2 and 4 (N=160)		
System Organ Class Preferred Term	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Number of patients reporting at least one SAE during NMA-LD period	6 (6.6)	6 (6.6)	1 (1.1)	9 (13.0)	6 (8.7)	1 (1.4)	15 (9.4)	12 (7.5)	2 (1.3)
Blood and lymphatic system disorders	1 (1.1)	1 (1.1)	0	4 (5.8)	4 (5.8)	0	5 (3.1)	5 (3.1)	0
Febrile neutropenia	0	0	0	3 (4.3)	3 (4.3)	0	3 (1.9)	3 (1.9)	0
Neutropenia [1]	1 (1.1)	1 (1.1)	0	1 (1.4)	1 (1.4)	0	2 (1.3)	2 (1.3)	0
Renal and urinary disorders	3 (3.3)	2 (2.2)	0	2 (2.9)	1 (1.4)	1 (1.4)	5 (3.1)	3 (1.9)	1 (0.6)
Acute kidney injury	1 (1.1)	0	0	1 (1.4)	0	1 (1.4)	2 (1.3)	0	1 (0.6)
Cystitis haemorrhagic	0	0	0	1 (1.4)	1 (1.4)	0	1 (0.6)	1 (0.6)	0
Renal tubular necrosis	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Urinary tract obstruction	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	3 (3.3)	3 (3.3)	0	1 (1.4)	0	0	4 (2.5)	3 (1.9)	0
Pleural effusion	1 (1.1)	1 (1.1)	0	1 (1.4)	0	0	2 (1.3)	1 (0.6)	0
Acute respiratory failure	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0

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Table 14.3.2.8.5.1 SAEs during NMA-LD Period by System Organ Class and Preferred Term
Cohorts 2 and 4 Patients who received NMA-LD

	Cohort 4 (N=91)			Cohort 2 (N=69)			Pooled Cohorts 2 and 4 (N=160)		
System Organ Class Preferred Term	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Number of patients reporting at least one SAE during NMA-LD period	6 (6.6)	6 (6.6)	1 (1.1)	9 (13.0)	6 (8.7)	1 (1.4)	15 (9.4)	12 (7.5)	2 (1.3)
Blood and lymphatic system disorders	1 (1.1)	1 (1.1)	0	4 (5.8)	4 (5.8)	0	5 (3.1)	5 (3.1)	0
Febrile neutropenia	0	0	0	3 (4.3)	3 (4.3)	0	3 (1.9)	3 (1.9)	0
Neutropenia [1]	1 (1.1)	1 (1.1)	0	1 (1.4)	1 (1.4)	0	2 (1.3)	2 (1.3)	0
Renal and urinary disorders	3 (3.3)	2 (2.2)	0	2 (2.9)	1 (1.4)	1 (1.4)	5 (3.1)	3 (1.9)	1 (0.6)
Acute kidney injury	1 (1.1)	0	0	1 (1.4)	0	1 (1.4)	2 (1.3)	0	1 (0.6)
Cystitis haemorrhagic	0	0	0	1 (1.4)	1 (1.4)	0	1 (0.6)	1 (0.6)	0
Renal tubular necrosis	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Urinary tract obstruction	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	3 (3.3)	3 (3.3)	0	1 (1.4)	0	0	4 (2.5)	3 (1.9)	0
Pleural effusion	1 (1.1)	1 (1.1)	0	1 (1.4)	0	0	2 (1.3)	1 (0.6)	0
Acute respiratory failure	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Blood pressure decreased	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Metabolism and nutrition disorders	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Metabolic acidosis	1 (1.1)	1 (1.1)	0	0	0	0	1 (0.6)	1 (0.6)	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (1.4)	0	0	1 (0.6)	0	0
Muscular weakness	0	0	0	1 (1.4)	0	0	1 (0.6)	0	0

NMA-LD = Non-myeloablative Lymphodepletion. SAE = Serious Adverse event.

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Adverse Events are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in Pooled Cohorts 2 and 4 group.
AEs During NMA-LD period include AEs that occur from the start of NMA-LD and before the start of LN-144 infusion. For patients who didn't receive LN-144 infusion, AEs up to 30 days from the last dose of NMA-LD will be included.

[1] AE grouped terms of neutrophil count decreased and neutropenia.

Source: C-144-01, Program: t14-3-2-8-5-1-ldae-sae-soc-pt-c2c4-nmald.sas, Data: ADSL and ADAE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

SAEs during the treatment-emergent period

In the **treatment-emergent period** 54 patients (34.6%) experienced at least one SAE.

The most frequent preferred terms/grouped terms were observed in the SOCs

- Blood and lymphatic system disorders (10.9%); cytopenias, febrile neutropenia

- Respiratory, thoracic and mediastinal disorders (8.3%); hypoxia, oedema, dyspnoea, pulmonary oedema, acute respiratory failure, pleural effusion
- Infections and infestations (6.4%); pneumonia, sepsis
- Nervous system disorders (5.1%); encephalopathy
- Vascular disorders (5.1%): hypotension, capillary leak syndrome

There were two SAEs of anaphylaxis and one SAE due to uveitis; these are considered directly related to lifileucel.

All SAEs presented in Table 10/uSCS are considered treatment-related. There were four fatal SAEs in this period (D0-30); see the previous section.

Table 10 Treatment-emergent SAEs Reported in ≥ 2 Patients in Pooled Cohorts 2 and 4 by Preferred Term (Safety Analysis Set)

	Cohort 4 (N=89)			Cohort 2 (N=67)			Pooled Cohorts 2 and 4 (N=156)		
System Organ Class Preferred Term	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders	6 (6.7)	6 (6.7)	0	11 (16.4)	11 (16.4)	0	17 (10.9)	17 (10.9)	0
Febrile neutropenia	2 (2.2)	2 (2.2)	0	6 (9.0)	6 (9.0)	0	8 (5.1)	8 (5.1)	0
Thrombocytopenia [1]	3 (3.4)	3 (3.4)	0	4 (6.0)	4 (6.0)	0	7 (4.5)	7 (4.5)	0
Neutropenia [2]	2 (2.2)	2 (2.2)	0	1 (1.5)	1 (1.5)	0	3 (1.9)	3 (1.9)	0
Respiratory, thoracic and mediastinal disorders	9 (10.1)	9 (10.1)	0	4 (6.0)	3 (4.5)	1 (1.5)	13 (8.3)	12 (7.7)	1 (0.6)
Acute respiratory failure	1 (1.1)	1 (1.1)	0	2 (3.0)	1 (1.5)	1 (1.5)	3 (1.9)	2 (1.3)	1 (0.6)
Hypoxia	3 (3.4)	3 (3.4)	0	0	0	0	3 (1.9)	3 (1.9)	0
Pulmonary oedema	3 (3.4)	3 (3.4)	0	0	0	0	3 (1.9)	3 (1.9)	0
Dyspnoea	1 (1.1)	1 (1.1)	0	1 (1.5)	1 (1.5)	0	2 (1.3)	2 (1.3)	0
Pleural effusion	2 (2.2)	2 (2.2)	0	0	0	0	2 (1.3)	2 (1.3)	0
Infections and infestations	6 (6.7)	4 (4.5)	1 (1.1)	4 (6.0)	4 (6.0)	0	10 (6.4)	8 (5.1)	1 (0.6)
Pneumonia	2 (2.2)	1 (1.1)	1 (1.1)	2 (3.0)	2 (3.0)	0	4 (2.6)	3 (1.9)	1 (0.6)
Sepsis	1 (1.1)	1 (1.1)	0	1 (1.5)	1 (1.5)	0	2 (1.3)	2 (1.3)	0
Nervous system disorders	4 (4.5)	4 (4.5)	0	4 (6.0)	4 (6.0)	0	8 (5.1)	8 (5.1)	0
Encephalopathy	0	0	0	2 (3.0)	2 (3.0)	0	2 (1.3)	2 (1.3)	0
Vascular disorders	5 (5.6)	4 (4.5)	0	3 (4.5)	2 (3.0)	0	8 (5.1)	6 (3.8)	0
Hypotension	2 (2.2)	2 (2.2)	0	1 (1.5)	1 (1.5)	0	3 (1.9)	3 (1.9)	0
Capillary leak syndrome	2 (2.2)	1 (1.1)	0	0	0	0	2 (1.3)	1 (0.6)	0
General disorders and administration site conditions	2 (2.2)	2 (2.2)	0	2 (3.0)	1 (1.5)	0	4 (2.6)	3 (1.9)	0
Pyrexia	1 (1.1)	1 (1.1)	0	2 (3.0)	1 (1.5)	0	3 (1.9)	2 (1.3)	0

System Organ Class Preferred Term	Cohort 4 (N=89)			Cohort 2 (N=67)			Pooled Cohorts 2 and 4 (N=156)		
	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Psychiatric disorders	3 (3.4)	2 (2.2)	0	1 (1.5)	1 (1.5)	0	4 (2.6)	3 (1.9)	0
Delirium	2 (2.2)	1 (1.1)	0	0	0	0	2 (1.3)	1 (0.6)	0
Renal and urinary disorders	2 (2.2)	0	0	2 (3.0)	1 (1.5)	0	4 (2.6)	1 (0.6)	0
Acute kidney injury	2 (2.2)	0	0	2 (3.0)	1 (1.5)	0	4 (2.6)	1 (0.6)	0
Immune system disorders	1 (1.1)	1 (1.1)	0	2 (3.0)	2 (3.0)	0	3 (1.9)	3 (1.9)	0
Anaphylactic reaction	0	0	0	2 (3.0)	2 (3.0)	0	2 (1.3)	2 (1.3)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.1)	1 (1.1)	0	2 (3.0)	2 (3.0)	0	3 (1.9)	3 (1.9)	0
Tumour pain	0	0	0	2 (3.0)	2 (3.0)	0	2 (1.3)	2 (1.3)	0
Investigations	1 (1.1)	1 (1.1)	0	1 (1.5)	1 (1.5)	0	2 (1.3)	2 (1.3)	0
Aspartate aminotransferase increased	1 (1.1)	1 (1.1)	0	1 (1.5)	0	0	2 (1.3)	1 (0.6)	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event
Notes: SAEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.

Patients with multiple events for a given PT are counted only once using the maximum grade under each PT.

SAEs are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in the Pooled Cohorts 2 and 4 group.

TE SAEs include all SAEs that began starting from the lifileucel infusion to 30 days post lifileucel infusion.

[1] AE grouped terms of platelet count decreased and thrombocytopenia

[2] AE grouped terms of neutrophil count decreased and neutropenia

Source: C-144-01 CSR Addendum Table 14.3.2.1.1.2.1

Post-treatment-emergent SAEs

In the **post-treatment period** 18.6% experienced at least one SAE; six were grade 5 (see previous section). As shown in Table 23/CSR infection and cytopenias and SAEs related to this were the main adverse events, which is expected particularly given the harsh conditioning regimen.

Looking at Listing 16.2.7.8 (SAEs during the NMA-LD period), Listing 16.2.7.9 (Treatment-emergent SAEs), and Listing 16.2.7.10 (Post-treatment SAEs) there were 12 fatal SAEs.

Table 14.3.2.6.2.2 Post treatment-emergent SAEs Reported in >= 2 Patients by System Organ Class and Preferred Term
Cohorts 2 and 4 Safety Analysis Set

System Organ Class Preferred Term	Cohort 4 (N=89) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Cohort 2 (N=67) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)	Pooled Cohorts 2 and 4 (N=156) Any Grade n (%)	 Grade 3/4 n (%)	 Grade 5 n (%)
Blood and lymphatic system disorders									
Anaemia	1 (1.1)	1 (1.1)	0	3 (4.5)	3 (4.5)	0	4 (2.6)	4 (2.6)	0
Thrombocytopenia [1]	1 (1.1)	1 (1.1)	0	1 (1.5)	1 (1.5)	0	2 (1.3)	2 (1.3)	0
Infections and infestations									
Sepsis	1 (1.1)	1 (1.1)	0	4 (6.0)	3 (4.5)	1 (1.5)	5 (3.2)	4 (2.6)	1 (0.6)
Cellulitis	0	0	0	2 (3.0)	2 (3.0)	0	2 (1.3)	2 (1.3)	0
Herpes zoster	1 (1.1)	1 (1.1)	0	1 (1.5)	1 (1.5)	0	2 (1.3)	2 (1.3)	0
Nervous system disorders									
Aphasia	0	0	0	2 (3.0)	0	0	2 (1.3)	0	0
Cerebral haemorrhage	1 (1.1)	0	1 (1.1)	1 (1.5)	1 (1.5)	0	2 (1.3)	1 (0.6)	1 (0.6)
Respiratory, thoracic and mediastinal disorders									
Dyspnoea	2 (2.2)	1 (1.1)	0	2 (3.0)	2 (3.0)	0	4 (2.6)	3 (1.9)	0

SAE = Serious Adverse Event.

Notes: AEs are coded based on MedDRA version 24.0. Grades are based on CTCAE version 4.03.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Adverse Events are sorted by decreasing frequency of SOC, and of PT within SOC per any grade in Pooled Cohorts 2 and 4 group.
Post Treatment-Emergent Adverse Events refer to AEs that start 30 days post LN-144 infusion and through 6 months after LN-144 infusion or up to the start of a new anti-cancer therapy, whichever occurs first.

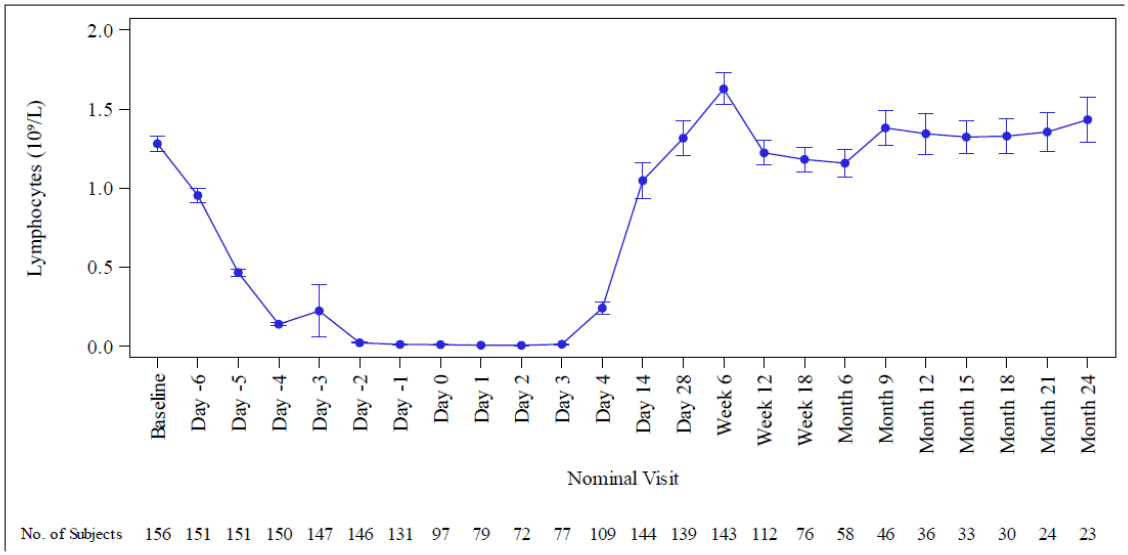
[1] AE grouped terms of platelet count decreased and thrombocytopenia.

Source: C-144-01, Program: t14-3-2-6-2-2-pteae-sae-soc-2pt-c2c4-saf.sas, Data: ADSL and ADAE (Date of Report: 22Jan2024) Data Extraction Date: 21Dec2023, Data Cut Date: 30Jun2023

3.3.7.4. Laboratory findings

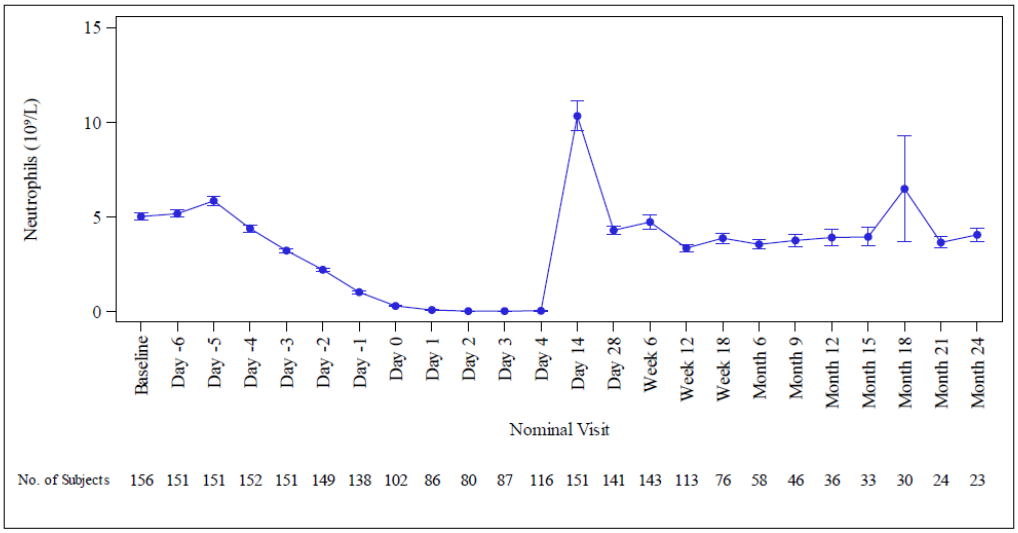
Haematology:

Figure 3 **Absolute Lymphocytes Values (Mean ± SEM) from the Initiation of NMA-LD (Baseline) to Month 24 for Pooled Cohorts 2 and 4 (Safety Analysis Set)**



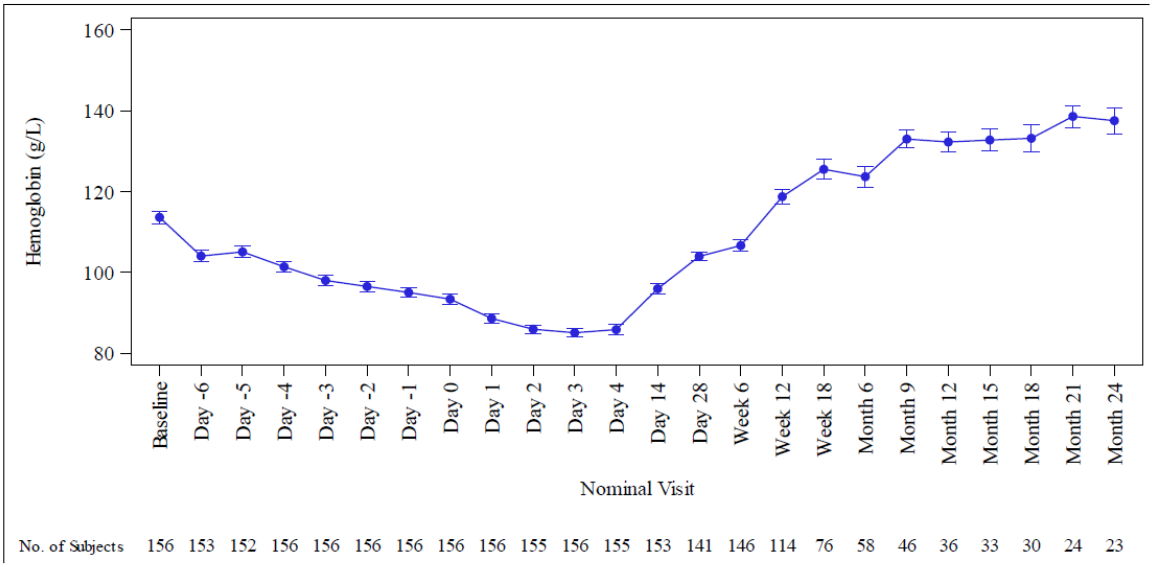
Abbreviations: NMA-LD = nonmyeloablative lymphodepletion; No. = number; SEM = standard error of the mean
Note: Includes visits with assessments of at least 5 patients.
Source: C-144-01 CSR Addendum Figure 14.3.4.1.2.1

Figure 5 **Absolute Neutrophil Values (Mean ± SEM) from the Initiation of NMA-LD (Baseline) to Month 24 for Pooled Cohorts 2 and 4 (Safety Analysis Set)**



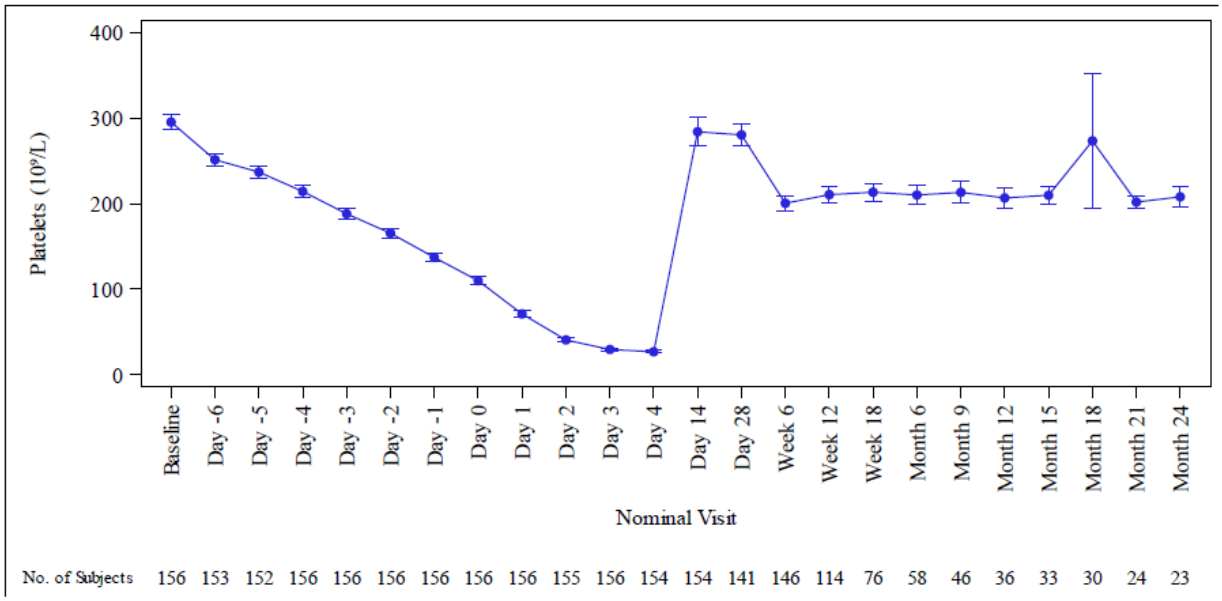
Abbreviations: NMA-LD = nonmyeloablative lymphodepletion; No. = number; SEM = standard error of the mean
Note: Includes visits with assessments of at least 5 patients.
The increase in mean neutrophils at Month 18 were driven by one patient: the patient had medical history of polycythemia; due to complications post splenectomy, had neutrophils of 87.4×10^9/L at Month 18.
Source: C-144-01 CSR Addendum Figure 14.3.4.1.2.1

Figure 6 **Hemoglobin Values (Mean ± SEM) from the Initiation of NMA-LD (Baseline) to Month 24 for Pooled Cohorts 2 and 4 (Safety Analysis Set)**



Abbreviations: NMA-LD = nonmyeloablative lymphodepletion; No. = number; SEM = standard error of the mean
Note: Includes visits with assessments of at least 5 patients.
Source: C-144-01 CSR Addendum Figure 14.3.4.1.2.1

Figure 7 **Platelet Counts (Mean ± SEM) from the Initiation of NMA-LD (Baseline) to Month 24 for Pooled Cohorts 2 and 4 (Safety Analysis Set)**



Abbreviations: NMA-LD = nonmyeloablative lymphodepletion; No. = number; SEM = standard error of the mean

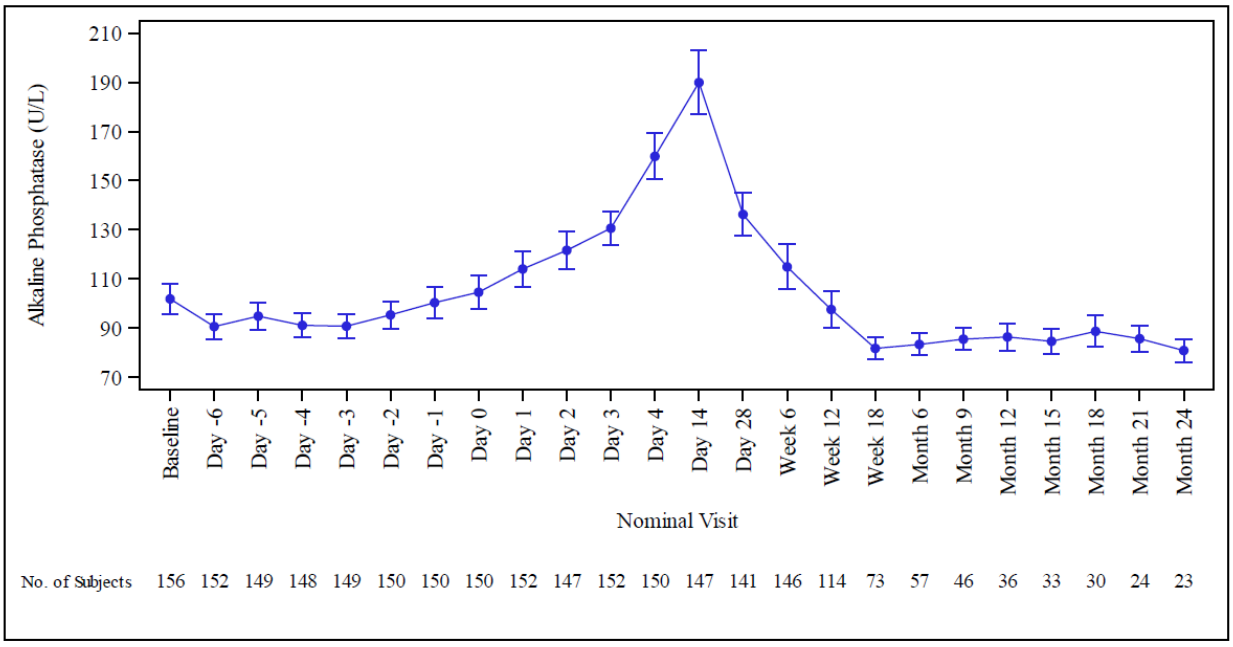
Note: Includes visits with assessments of at least 5 patients.

The increase in mean platelets at Month 18 were driven by 1 patient who had a medical history of polycythemia; due to complications post splenectomy, the patient had platelets of 2524 ×10⁹/L at Month 18.

Source: C-144-01 CSR Addendum Figure 14.3.4.1.2.1

Clinical chemistry:

Figure 9 **Alkaline Phosphatase Values (Mean ± SEM) from the Initiation of NMA-LD (Baseline) to Month 24 for Pooled Cohorts 2 and 4 (Safety Analysis Set)**



Abbreviations: NMA-LD = nonmyeloablative lymphodepletion; No. = number; SEM = standard error of the mean

Source: Figure 2.7.4.1

It is agreed with the applicant, that "Overall, changes in laboratory parameters were consistent with those expected due to the NMA-LD preparative regimen or IL-2".

3.3.7.5. In vitro biomarker test for patient selection for safety

Not applicable.

3.3.7.6. Safety in special populations

Age: There were 119 patients < 65 and 37 patients ≥ 65 years of age.

When comparing patients between the age groups< 65 and ≥ 65 years of age, the overall incidence of TEAEs and Grade 3 or higher TEAEs was similar between the age subgroups, while the incidence of treatment emergent SAE was higher in the older patient's subgroup over 65 years of age than in those younger of 65 years of age (45.9 % vs 31%). Higher incidence in the patient subgroup ≥ 65 years was reported for the overall TEAES included under Respiratory, thoracic and mediastinal disorders and for Vascular disorders. An age specific pattern was identified only for some TEAES with a higher incidence with age for asthenia (27.0% vs 10.1%), hypertension (32.4% vs 11.8%), encephalopathy (13.5% vs 3.4%), and hallucination (8.1% vs 0.8%).This is somewhat expected considering the risk for neurological toxicity and cytopenia with lifileucel regimen in the context of potential increasing incidence for risk factors for asthenia and hypertension with age. **Sex:** It is considered, that no clinically meaningful differences were observed.

Table 15 Adverse Event Summary by Age Group

	Cohort 4		Cohort 2		Pooled Cohorts 2 and 4	
	Age < 65 (N=66) n (%)	Age ≥ 65 (N=23) n (%)	Age < 65 (N=53) n (%)	Age ≥ 65 (N=14) n (%)	Age < 65 (N=119) n (%)	Age ≥ 65 (N=37) n (%)
Total TEAEs	66 (100)	23 (100)	53 (100)	14 (100)	119 (100)	37 (100)
Grade 3 or higher TEAEs	64 (97.0)	23 (100)	52 (98.1)	13 (92.9)	116 (97.5)	36 (97.3)
Treatment-emergent SAEs [1]	18 (27.3)	13 (56.5)	19 (35.8)	4 (28.6)	37 (31.1)	17 (45.9)
TEAE leading to TIL discontinuation	0	0	2 (3.8)	0	2 (1.7)	0
Number of patients with at least one TEAE in the following System Organ Class						
Blood and lymphatic system disorders	60 (90.9)	20 (87.0)	51 (96.2)	14 (100)	111 (93.3)	34 (91.9)
General disorders and administration site conditions	62 (93.9)	20 (87.0)	50 (94.3)	13 (92.9)	112 (94.1)	33 (89.2)
Respiratory, thoracic and mediastinal disorders	41 (62.1)	17 (73.9)	32 (60.4)	11 (78.6)	73 (61.3)	28 (75.7)
Metabolism and nutrition disorders	43 (65.2)	15 (65.2)	42 (79.2)	9 (64.3)	85 (71.4)	24 (64.9)
Vascular disorders	34 (51.5)	15 (65.2)	27 (50.9)	8 (57.1)	61 (51.3)	23 (62.2)
Gastrointestinal disorders	43 (65.2)	12 (52.2)	37 (69.8)	10 (71.4)	80 (67.2)	22 (59.5)
Investigations	38 (57.6)	11 (47.8)	36 (67.9)	11 (78.6)	74 (62.2)	22 (59.5)
Cardiac disorders	30 (45.5)	9 (39.1)	26 (49.1)	9 (64.3)	56 (47.1)	18 (48.6)
Nervous system disorders	25 (37.9)	11 (47.8)	24 (45.3)	6 (42.9)	49 (41.2)	17 (45.9)
Skin and subcutaneous tissue disorders	44 (66.7)	8 (34.8)	39 (73.6)	8 (57.1)	83 (69.7)	16 (43.2)
Infections and infestations	20 (30.3)	10 (43.5)	19 (35.8)	5 (35.7)	39 (32.8)	15 (40.5)
Psychiatric disorders	24 (36.4)	7 (30.4)	19 (35.8)	8 (57.1)	43 (36.1)	15 (40.5)
Renal and urinary disorders	16 (24.2)	9 (39.1)	19 (35.8)	5 (35.7)	35 (29.4)	14 (37.8)

	Cohort 4		Cohort 2		Pooled Cohorts 2 and 4	
	Age < 65 (N=66) n (%)	Age ≥ 65 (N=23) n (%)	Age < 65 (N=53) n (%)	Age ≥ 65 (N=14) n (%)	Age < 65 (N=119) n (%)	Age ≥ 65 (N=37) n (%)
Musculoskeletal and connective tissue disorders	14 (21.2)	5 (21.7)	19 (35.8)	7 (50.0)	33 (27.7)	12 (32.4)
Injury, poisoning and procedural complications	11 (16.7)	3 (13.0)	3 (5.7)	3 (21.4)	14 (11.8)	6 (16.2)
Eye disorders	12 (18.2)	2 (8.7)	9 (17.0)	1 (7.1)	21 (17.6)	3 (8.1)
Hepatobiliary disorders	4 (6.1)	2 (8.7)	2 (3.8)	1 (7.1)	6 (5.0)	3 (8.1)
Reproductive system and breast disorders	4 (6.1)	2 (8.7)	3 (5.7)	1 (7.1)	7 (5.9)	3 (8.1)
Immune system disorders	3 (4.5)	2 (8.7)	3 (5.7)	0	6 (5.0)	2 (5.4)
Ear and labyrinth disorders	4 (6.1)	1 (4.3)	1 (1.9)	0	5 (4.2)	1 (2.7)
Endocrine disorders	2 (3.0)	0	0	0	2 (1.7)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.5)	0	2 (3.8)	0	3 (2.5)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TIL = tumor-infiltrating lymphocytes

Notes: AEs are coded based on MedDRA version 24.0.

[1] SAE subcategories were not collected in Cohort 2 database thus not summarized in the table.

TEAEs refer to all AEs starting from lifileucel infusion to 30 days post lifileucel infusion.

Source: Table 2.7.4.10

3.3.7.7. Immunological events

In terms of the MoA, the therapy with autologous TILs is expected to potentially trigger the immune-mediated anti-tumour response, such the immunological events are anticipated. CRS, uveitis and vitiligo have been observed in the clinical study. None of these were SAEs or had severity more than grade 3. In addition, cutaneous vasculitis and one event of Haemophagocytic lymphohistiocytosis have been reported. The narrative and causality discussion should be provided for the case of Haemophagocytic lymphohistiocytosis. Taking into account the plausible biological rationale and the seriousness of the reported conditions (e.g. Haemophagocytic lymphohistiocytosis) that were identified in a relatively limited size study population of 156 patients, it is considered that the risk for Immune-mediated disorders needs further monitoring in postmarketing as RMP Important Potential risks. **(OC)**

3.3.7.8. Safety related to drug-drug interactions and other interactions

No drug-drug interaction or food effect studies were performed. Drug-drug interaction studies are not relevant; see the pharmacology section.

3.3.7.9. Discontinuation due to adverse events

Discontinuation in the common sense is not meaningful, as this is one treatment consisting of three parts, though.

Discontinuation relates to the entire treatment period, not only to the lifileucel infusion as presented by the applicant.

In the NMA-LD treatment period two patients discontinued: one patient due to gastrointestinal haemorrhage, and the other patient due to pleural effusion.

Three (1.9%) patients did not receive the planned IL2.

Post marketing experience

Lifileucel has been approved by the FDA since February 2024. No post marketing data are available. Post marketing data, based on 15 Feb 2025 data cut, is requested in the next round.

3.3.8. Discussion on clinical safety

The safety data for AMTAGVI stem from the analysis of a single study (Study C-144-01) that is pivotal.

To characterize the safety profile of lifileucel, analyses were performed on the safety data from Cohort 2 (N=67) and 4 (N=89) in patients that received cryopreserved lifileucel product, collected till the cut off 30 June 2023.

The median study follow-up for safety (cutoff date of 30 Jun 2023) was 12.1 months.

The safety analyses were performed separately for Cohort 2 and 4, as well on the pooled safety population from the two cohorts and provided as such by the company. For a comprehensive safety analysis and evaluation of ADRs, the safety analyses performed on the pooled safety data for Cohort 2+4 (n=156, corresponding to the Safety Analysis Set) was primarily taken into consideration.

The lifileucel regimen involves a preparative regimen of NMA-LD (nonmyeloablative lymphodepletion, ie, cyclophosphamide with mesna and fludarabine), followed by a single infusion of lifileucel, and post-infusion administration of IL-2 (up to 6 doses); all given within a period of 11-12 days.

During the NMA-LD period the patients experienced mostly haematological toxicities (neutropenia 63.1%, anaemia 56.9%, leukopenia (44.4%, thrombocytopenia (40.0%), lymphopenia 38.8%). These toxicities are well known for both cyclophosphamide and fludarabin. Among the non-haematological toxicities, the most frequently reported were nausea (66.9%), vomiting (34.4%), diarrhoea (32.5%), fatigue (30.0%), and pyrexia (30.0%).

Grade 3 and higher AEs were reported in 87.5% of patients, however the SAE incidence was only 9.4%.

Distribution of Onset Dates of Adverse Events from the Start of NMA-LD figures suggest that the incidence of AEs peaked around the third and fourth day of the NMA-LD preparative regimen then gradually decreased until the day following the lifileucel infusion when a second peak was observed corresponding to the IL-2 administration period and the expected cytopenia through after cyclophosphamide-fludara conditioning.

Treatment-related adverse events are considered those caused by the entire treatment regimen and not only lifileucel, as NMA-LD and IL-2 are prerequisites for the treatment with lifileucel. This is also noted by the applicant in the SmPC: Adverse reactions are defined as adverse events at least possibly related to any component of the AMTAGVI regimen (cyclophosphamide, fludarabine, lifileucel, IL-2) that occurred up to 6 months (182 days) post AMTAGVI or up to the start of a new anti-cancer therapy, whichever occurs first).

TEAEs during the Treatment-emergent Period defined by the interval from the day of lifileucel infusion to Day 30, consisted of persistent toxicities of the preparatory regimen, AEs related to lifileucel only and to IL-2 (Aldesleukin).

TEAE were reported as related to lifileucel only in proportion of 36.5%. Totally, 5.1% of patients experienced a Grade 3 or 4 TEAE that was related to lifileucel only. 1 (0.6%) patient experienced a related fatal TEAE of intra-abdominal haemorrhage reported as related to lifileucel as well as the NMA-LD and IL-2.

Overall, the most common TEAEs (ie, incidence of ≥ 30%) reported during the Treatment-emergent period were thrombocytopenia (82.7%), chills (75.0%), anaemia (62.2%), pyrexia (51.9%), neutropenia (42.3%), febrile neutropenia (41.7%), hypophosphataemia (37.2%), hypotension (33.3%), leukopenia (34.6%), fatigue (32.7%), lymphopenia (31.4%), and diarrhoea (30.8%). 94.9%

of patients in Pooled Cohorts 2 and 4 experienced at least 1 Grade 3 or 4 TEAE and 4 (2.6%) experienced a TEAE that resulted in death.

The applicant has listed hypersensitivity, uveitis, and vitiligo as ADRs to lifileucel. Hypersensitivity reaction is a broad term. Cytokine release syndrome (CRS) is commonly seen with infusion of cell therapies. Furthermore, capillary leak syndrome is a potentially life-threatening AE considered related to IL-2, and these risks and their treatment are described in the SmPC, and CSR and capillary leak syndrome have been included in the Summary of safety concerns as Important known risks (see OCs).

Deaths

In the clinical trial, the treatment-related mortality rate was 9.6% (15/156), including 2 deaths during the lymphodepleting period, 4 deaths within 30 days, 6 deaths 30 to 180 days and 3 deaths beyond 180 days following lifileucel administration. The adverse events associated with these deaths included severe infections (sepsis, pneumonia and encephalitis), internal organ haemorrhage (abdominal haemorrhage and intracranial haemorrhage), acute renal failure, acute respiratory failure, cardiac arrythmia, extensive ascites, liver injury, and bone marrow failure. No trend for a specific AE leading to death in the 30 days interval following lifileucel infusion was noted. In a single case the causality considered related to lifileucel and IL-2 by Investigator. In this case, the fatal TEAE reported was bone marrow hypoplasia Day 35 after the infusion of first dose IL-2.

Bone marrow failure, febrile neutropenia, serious infection and acute kidney injury are recognized ADR for the lifileucel included in the 4.8 ADR table.

The fatal TEAEs are described in the section 4.8 of the AMTAGVI PI under the corresponding AESI considered relevant for inclusion in the section Description of selected adverse reactions in 4.8.

In the treatment-emergent period (D0-D30) 54 patients (34.6%) experienced at least one **SAE**. The most frequent preferred terms/grouped terms were observed in the SOCs Blood and lymphatic system disorders (10.9%; cytopenias, febrile neutropenia), Respiratory, thoracic and mediastinal disorders (8.3%; hypoxia, oedema, dyspnoea, pulmonary oedema, acute respiratory failure, pleural effusion), Infections and infestations (6.4%; pneumonia, sepsis), Nervous system disorders (5.1%; encephalopathy), and Vascular disorders (5.1%: hypotension, capillary leak syndrome).

The SAEs reported per time-interval were as follows:

In the NMA-LD period, there were 15 patients (9.4% of SAF) reported with at least 1 SAE, 2 of which with Grade 5 SAE.

In the TE interval, a total of 8 patients (5.1%) experienced at least one SAE reported as related to lifileucel (2 cases of anaphylactic reaction and 1 case each of infection, intra-abdominal haemorrhage, alanine aminotransferase increased, aspartate aminotransferase increased, brain oedema, chills, pyrexia, sepsis, and uveitis). The contribution of all components of the lifileucel regimen including the preparative cyclo-fludara to the serious toxicity may be suspected, and all these events are more or less labelled as ADRs.

In the Post-TE period (i.e. beyond 30 days after lifileucel infusion up to 6 months or until start of NAT) there were 29 patients (18.6% of SAF) with SAE reported.

The SAEs are adequately described in the SmPC as a general information in the introduction in section 4.8 and under the relevant heading in 4.4 and 4.8. T

AESI

In details, the following AESI were identified and classified as ADR based on the biological plausibility and the temporal association with AMTAGVI regimen:

Hypersensitivity reactions

Hypersensitivity reactions are identified risks for lifileucel with onset strictly related to the lifileucel infusion. So far, there have been 9 cases (5.8%) of infusion related reaction, 2 cases (1.3%) of anaphylactic reaction, and 1 case (0.6%) of hypersensitivity under the TE period. A warning on Hypersensitivity reactions is included in section 4.4 and anaphylactic reaction and Hypersensitivity are labelled ADRs.

Uveitis

Uveitis appears to be an identified risk for the AMTAGVI regimen with 6 cases reported during TE period and additional 2 cases during post-TE period. Most of the events of uveitis were nonserious (87.5%, 7/8), with 1 serious event of uveitis (12.5%). The median time to onset following the lifileucel infusion was 16 days (min, max: 5, 119), with most occurring within 3 weeks of the lifileucel infusion (75%, 6/8). There was variability in the duration of the events, with a median duration of 122 days (min, max: 2, 400). Uveitis is labelled as ADR in the AMTAGVI PI 4.8 and described adequately in section 4.4 and 4.8 as Selected adverse reaction due to its specificity for this regimen. A

Vitiligo

Totally 13 cases of vitiligo were reported mainly during TE period (n=9) and post-TE period (n=4). Vitiligo was typically reported within 2 weeks to a month of the lifileucel infusion and was Grade 1 or 2 in severity. The patients who experienced vitiligo in Study C 144 01 received prior ICI with a median time from the start of the patients' latest ICI therapy to the onset of vitiligo was 8.84 months (min, max: 2.2, 23.9). Vitiligo is included in the AMTAGVI PI 4.8 as ADR with frequency common.

Cytokine Release Syndrome

CRS was reported in 3.2% (5/156) of the patients with time to onset following the lifileucel infusion was 0 to 9 days. Grade 3 CRS was reported in 1.3 % (n=2 / 156) of patients, with no reports of Grade 4 or 5 CRS. Serious CRS was reported in 0.6 % (n=1 / 156) of patients. Treatment of CRS was required in 3 of the cases including tocilizumab and IV dexamethasone in one case. In 2 of the 5 patients, CRS resolved with no treatment. All 5 CRS cases recovered.

CRS was labelled as ADR in 4.8 Table 1 and description of the risk of CRS based on data from Study C-144-01 was included under description of selected adverse reactions in section 4.8

Tocilizumab intervention was required in a single case, according to the applicant. In this case the patient developed both ICANS and CRS requiring intervention with IV dexamethasone and 500 mg of tocilizumab for a day. This suggest that the immune-mediated ADRs specific for CARTs may be also expected for Amtagvi although with lower incidence and severity grades. Hence, a 4.4 warning on the risk of CRS including the management recommendation based on the study data is considered justified.

According to the applicant the single event of cytokine release syndrome for which Tocilizumab was required was Grade 2, considered nonserious, and resolved within 3 days.

It is therefore agreed that the recommendation on Tocilizumab availability prior lifileucel infusion is not necessary to be included in the 4.2 section. Instead, considering the short time to the event oftill CRS after lifileucel infusion, the CRS should be added to the risks recommended for monitoring during hospitalization in the section 4.2 Monitoring recommendation.

Cytopenias

Cytopenia is an identified risk associated with AMTAGVI regimen, mainly associated with the cyclo-fludara regimen of which fludarabine is given in myeloablative doses.

During the TE period there were 88.5% (138/156) of the patients that had a treatment-emergent cytopenia of which 5.8% (9/156) had SAEs, none of them related to lifileucel. None of the cytopenia events irrespective grade or seriousness was considered related to lifileucel only.

In addition, there were 35 patients (22.4%) who experienced post-treatment emergent cytopenia. In the pivotal studies leading to indications labelling for Proleukin, IL-2 was reported leading to anemia, thrombocytopenia or leukopenia in therapeutic doses. All 35 patients (22.4%) who experienced post-treatment emergent cytopenia had the events begin during the NMA-LD or TE period (30 days following lifileucel), 4 of which had prolonged cytopenia beyond 30 days. Totally, in Study C-144-01, 1.9 % of the patients who experienced a Grade 3 or 4 decrease in neutrophils, 3.4 % of the patients who experienced a Grade 3 or 4 decrease in platelet count, and 3.5 % of the patients who experienced a Grade 3 or 4 decrease in haemoglobin following the administration of the AMTAGVI regimen had not resolved to Grade 2 or lower by 30 days following the AMTAGVI infusion. The risk for Prolonged cytopenia is adequately described under the Selected adverse reactions in section 4.8 and in section 4.4 of the SmPC.

Cardiac Arrhythmias

Cardiac arrythmias were commonly reported TEAEs, in 47.4% of patients. Majority were low grade events and grade 3 and 4 only in 11 patients (7.1%). SAEs were reported in 2 pats (1.3%), one of which was the fatal case likely related to cyclo by the INV and the other case reported as atrial fibrillation likely related to IL-2. In 4 patients the events of arrhythmia were reported as related only to lifileucel occurring during infusion or within 1 day after infusion together with other concomitant events suggesting symptoms of hypersensitivity related to lifileucel infusion. Arrythmia, bradycardia and palpitations are labelled as ADRs in the Table of 4.8 section of the PI. This is agreed.

The risk for arrhythmias is described in 4.8 Description of selected adverse reactions and in 4.4 together with the recommended monitoring and risk minimization measures.

Vascular Hypotensive Disorders and Capillary leak Syndrome (CLS)

During TE period totally 16 (10.3%) patients had vascular hypotensive events that were reported as related to lifileucel, of which 3 were reported as related only to lifileucel, none of them considered serious. The events occurred on the same day as or within 1 day of lifileucel administration and were concurrent with events that suggest that the hypotension may have been part of an infusion-related reaction to either lifileucel or IL-2. The median time to onset following the lifileucel infusion of any events within vascular hypotensive disorders was 3.0 days. Vascular hypotensive disorders area labelled as ADR presented in Table 1 in section 4.8 of the PI. This is agreed and considered sufficient. Capillary leak syndrome was appropriately described in both 4.4 warning and under 4.8 Description of selected adverse reactions sections.

Non-infectious Encephalopathy/Delirium

Non-infectious encephalopathy/delirium was reported in 32.1% (50/156) of the patients during the TE period with 9.0% (14/156) of the patients having a Grade 3 or 4 event and 3.2% reporting SAEs none of which fatal. TTO was 5 days after infusion of lifileucel. In 14 pats with Non-infectious encephalopathy/delirium the outcome was reported as not yet recovered by the time the patients exited the study.

Encephalopathy is labelled ADR with frequency very common in Table 1 of the PI. In addition, several other neurological and psychiatric events are also labelled ADR although no discussion of neurotoxicity, or CNS toxicity was submitted. Generally, fludarabine in therapeutic doses and long-term treatment intervals in acute or chronic leukemia has been associated with serious neurotoxicity including CNS neurotoxicity (Leukoencephalopathy, Reversible posterior leukoencephalopathy syndrome) with TTO 21

to 60 days from the last dose. A single case of Grade 3 ICANS that occurred concurrently with a Grade 2 event of CRS 2 days after administration of lifileucel, and 2 days after receiving the first of 6 doses of IL-2 has been reported as such. Taking into account the time to onset and the response to the specific intervention with dexamethasone IV and Tocilizumab, the reported events are assumed to be CRS and ICANS and considered ADRs for lifileucel. Hence, it is considered that update of the ADR table 1 in 4.8 with ICANS as new ADR under SOC Nervous system disorders is warranted. The ICANS case should be included in the paragraph on Neurological adverse reactions under the Description of selected adverse reactions. Considering the seriousness of neurological adverse reactions reported, a 4.4 warning on neurological toxicities, including ICANS is considered warranted.

Immune-mediated/Autoimmune Disorders

Treatment-emergent immune-mediated/autoimmune disorders were reported in 6.4% (10/156) of the patients. Only 2 TEAEs within the Immune-mediated/autoimmune disorders were reported: vitiligo (n=9) and cutaneous vasculitis (n=1). None of them was serious or severe.

The median time to onset following the lifileucel infusion of any immune-mediated/autoimmune disorder event was 19.5 days (min, max: 6 to 88).

Laboratory findings

The hematological findings showing anemia, leukopenia, neutropenia, lymphopenia and thrombocytopenia are corroborating with the myelosuppressive effect of the cyclo-fludara regimen were fludarabin was given in myeloablative doses. The majority of the patients experienced leukopenia, neutropenia, anemia, thrombocytopenia and lymphopenia from the start of the NMA-LD preparative regimen (Day -7 to Day -4) with a mean nadir value was observed on Day -1 to Day 3 and recovery to the baseline values by Day 14 reached for the majority of the patients with any form of cytopenia.

A small proportion of these patients were not recovering by the Day 30 of follow-up according to the Company.

Decreased albumin levels, increased alkaline phosphatase, decrease in phosphate and decrease in sodium levels were reported during the different parts of the AMTAGVI regimen, potentially correlated with some of the components for which these are recognized ADRs. Although also reported as Grade 3 and 4, these laboratory abnormalities were reported as recovered within days. The laboratory changes of hypoalbuminemia, hypophosphatemia, increased alkaline phosphatase and decreased sodium levels are labelled as ADRs with appropriate frequency in the Table 1.

Discontinuations were reported only to the level of administration of lifileucel only. The events leading to discontinuation consisted of interruption of lifileucel infusion due to anaphylactic reactions and occurred only in 2 (1.3%) of patients.

With regards to **age subgroups**, particularly encephalopathy-related AEs were seen more frequently in the ≥ 65 compared to the <65 years of age with asthenia (27.0% vs 10.1%), encephalopathy (13.5% vs 3.4%), and hallucination (8.1% vs 0.8%) clearly more frequent as well as hypertension (32.4% vs 11.8%).

Additional safety data needed in the context of a conditional MA

The dossier is lacking in a general description and discussion of adverse events related to the entire treatment regimen.

Final efficacy and safety results from the confirmatory phase 3 study TILVANCE-301, which investigates the efficacy and safety of Amtagvi plus pembrolizumab versus pembrolizumab

monotherapy in the first line setting of recurrent or metastatic melanoma. The data should be provided as a specific obligation for the CMA, please refer also to section 7.2: Proposed list of post-authorisation measures.

Based on the responses to the LoQ specific safety concerns may be raised.

3.3.9. Conclusions on clinical safety

Safety for the lifileucel treatment regimen is considered challenging with at least 12 treatment-related deaths. Particularly the conditioning regimen (cyclophosphamide with mesna and fludarabine), which is mandatory for the treatment, led to several deaths and SAEs. Of particular concern are encephalopathy, CRS, cytopenias including severe infections and haemorrhage, respiratory failure, acute kidney injury, capillary leak syndrome, and arrhythmia.

Overall, due to particularity of the AMTGAVI regimen there is a need for adequate information in the 4.4 and 4.8 section Description of selected adverse reactions of the AMTGAVI PI to adequately inform the prescribers on the specific risks identified. (refer to LoQ)

With a median follow up of 48.1 months for the Pooled Cohort 2+4, the long-term safety is considered sufficiently characterized. Several safety risks that require further characterization are proposed to be included in the RMP. (refer to LoQ) The Confirmatory Phase 3 study would provide additional data to support characterization of the safety profile of AMTAGVI, although the combination with pembrolizumab might complicate the background safety of the regimen, in particular the immune-related adverse events.

The following measures are necessary to address the missing safety data in the context of a conditional MA:

Safety results from the confirmatory phase 3 study TILVANCE-301, which investigates the efficacy and safety of Amtagvi plus pembrolizumab versus pembrolizumab monotherapy in the first line setting of recurrent or metastatic melanoma.

3.4. Risk management plan

3.4.1. Safety specification

Summary of safety concerns

The applicant updated the summary of safety concerns in the RMP (version 0.2):

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Capillary leak syndrome Neurologic toxicity Serious infections and sepsis Serious haemorrhage
Important potential risks	Prolonged severe cytopenia Embryo-fetal toxicity and the risk with breast-feeding
Missing information	None

3.4.1.1. Discussion on safety specification

The Summary of safety concerns was amended to include Capillary leak syndrome, Neurologic toxicity, Serious infections and sepsis, Serious haemorrhage, Prolonged severe cytopenia and Embryo-fetal toxicity and the risk **with** breast-feeding (corrected from the risk of breast-feeding). This is endorsed.

The following safety concerns, not agreed by the applicant, are however requested to be included in the RMP:

1.The CRS risk with lifileucel is warranted to be classified as Important Identified Risk and included in the list of safety concerns in the RMP. This risk requires further characterization of seriousness, frequency and of the required management.

2. The Immune-mediated disorders should be further monitored in postmarketing as Important Potential risk and included in the list of safety concerns in the RMP.

The PRAC Rapp still would propose to amend the Summary of safety concerns should be further amended as follows: Missing information should not be "none", instead "long-term safety" should be added, Neurologic toxicity should be rephrased to "Neurologic toxicity including ICANS" and CRS should be included separately.

3.4.1.2. Conclusions on the safety specification

Having considered the data in the safety specification it is considered that the following issues should be addressed:

The CRS risk with lifileucel is warranted to be classified as Important Identified Risk and included in the list of safety concerns in the RMP.

The Immune-mediated disorders should be further monitored in postmarketing as Important Potential risk and included in the list of safety concerns in the RMP.; please refer to the LoOI.

3.4.2. Pharmacovigilance plan

The applicant states that there are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

The pharmacovigilance plan has been updated by the applicant. The updated PhV is acceptable, however may need again to be revised following further amendments in the list of safety concerns. The applicant is asked to revise its list of safety concerns and to address them through appropriate pharmacovigilance activities.

Updated Table Part III-2: On-Going and Planned Additional Pharmacovigilance Activities

Study/ Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

IOV MEL 401: A Prospective, Non-Interventional Post- Authorisation Safety Study of Patients treated with Lifileucel for Unresectable or Metastatic Melanoma in the Real-World Setting Planned	To characterize the long-term safety profile of lifileucel in adult patients with unresectable or metastatic melanoma treated in a real-world setting in the approved indication. To assess the safety concerns in terms of incidence, seriousness, severity, time to onset, and management or resolution.	Capillary leak syndrome Neurologic toxicity Serious infections and sepsis Serious haemorrhage Prolonged severe cytopenia Embryo-fetal toxicity and risk of breast-feeding	Final Protocol submission (EMA)	2 months post EC decision
			Date of Protocol approval, start of data collection	TBD, TBD
			Safety updates	Aligned with the reporting period of the PSUR.
			Interim report (planned)	TBD
			Final report (planned)	TBD

The pharmacovigilance plan has been updated by the applicant to include the non-interventional post-authorisation safety study IOV-MEL-401. Following plenary discussion, the PRAC considered the proposed PASS IOV-MEL-401 not required. Although the proposed PAES IOV-MEL-301 uses Amtagvi in a different line of treatment and setting when compared with the currently sought indication, the PRAC concluded that the safety follow-up from this study is also relevant to and sufficient for this indication.

This PASS is currently included in Annex IIE of the SmPC and should be removed, since this study is not part of the specific obligation.

Overall conclusion on the pharmacovigilance plan:

There are still outstanding issues regarding the RMP but a preliminary view is that, in addition to the safety information, which is expected to be obtained from the proposed PAES IOV-MEL-301, routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.3. Risk minimisation measures

Table Part V.3: Updated summary table of pharmacovigilance activities and risk minimisationactivities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Capillary leak syndrome	Routine risk minimisation measures: SmPC Sections 4.4, 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
	PL Section 4	None
	Amtagvi must be administered in a qualified treatment centre by physicians experienced in the use of anticancer agents.	Additional pharmacovigilance activities: PASS (IOV MEL 401)
	Additional risk minimisation measures:	

	HCP education material PAC	
Neurologic toxicity	Routine risk minimisation measures: SmPC Sections 4.4, 4.7, 4.8 PL Sections 2, 4 Amtagvi must be administered in a qualified treatment centre by physicians experienced in the use of anticancer agents. Additional risk minimisation measures: HCP education material PAC	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS (IOV MEL 401)
Serious infections and sepsis	Routine risk minimisation measures: SmPC Sections 4.4, 4.8 PL Section 4 Amtagvi must be administered in a qualified treatment centre by physicians experienced in the use of anticancer agents. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS (IOV MEL 401)
Serious haemorrhage	Routine risk minimisation measures: SmPC Section 4.8 PL Section 4 Amtagvi must be administered in a qualified treatment centre by physicians experienced in the use of anticancer agents. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS (IOV MEL 401)
Prolonged severe cytopenia	Routine risk minimisation measures: SmPC Sections 4.4, 4.8 PL Section 4 Amtagvi must be administered in a qualified treatment centre by physicians experienced in the use of anticancer agents. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS (IOV MEL 401)

Embryo-fetal toxicity and the risk of breast- feeding	Routine risk minimisation measures: SmPC section 4.6 PL section 2 Amtagvi must be administered in a qualified treatment centre by physicians experienced in the use of anticancer agents. Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PASS (IOV MEL 401)

The proposed routine risk minimisation measures are considered acceptable. In the updated RMP version 0.2, the applicant included educational tools (HCP educational program and patient card) which address the important identified risks of capillary leak syndrome and neurologic toxicity. This is endorsed.

However, amendments to the list of safety concerns may require further revisions of the risk minimisation measures. If added to the list of safety concerns, the key messages of the HCP educational program and the patient card should also reflect the safety concerns of cytokine release syndrome and ICANS. Key elements should include the provision of all relevant information on these risks to HCPs and patients, as well as some guidance for HCPs on monitoring of these risks.

The applicant proposes a site training which includes specific modules for the administration of the lymphodepleting treatment and IL-2 and reviews the safety of all components of the lifileucel treatment regimen. Such a training is considered a controlled distribution program which should be included in the RMP. In line with the terminology in the updated version of GVP XVI – Risk minimisation measures (Rev 3) – this programme should be included as a risk minimisation control tool and should be included in Annex IID of the SmPC. Also, the patient alert card should be renamed to patient card.

The applicant provided an updated Table Part V.2 aligning the safety concerns mentioned in Part II SVIII.

Table Part V.2: Updated Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

HCP Educational Program	
Objectives	To inform HCPs on how to monitor and manage symptoms associated with CLS and neurologic adverse reactions and provide guidance on reporting these adverse reactions associated with the lifileucel regimen.
Rationale for the additional risk minimisation activity	The HCP educational tool is designed to minimise the risk of CLS and Neurologic toxicity and provide information on the management of the risks and the necessary steps to prevent serious CLS and/or Neurologic toxicity.
Target audience and planned distribution path	The target audience is HCPs who are expected to prescribe and/or administer lifileucel.

Plans to evaluate the effectiveness of the interventions and criteria for success	PSUR as per EU guidance
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable
Patient Alert Card	
Objectives	To inform patients of the risks of CLS and neurologic toxicity associated with the lifileucel regimen and encourage them to share the information in the PAC with their HCPs.
Rationale for the additional risk minimisation activity	The PAC will provide convenient and immediate access to information regarding the most common signs and symptoms of CLS and neurotoxicity, and will encourage patients to seek early medical attention and treatment which will help mitigate the risks.
Target audience and planned distribution path	The target audience is the patient who will receive lifileucel. The PAC will be part of the HCP Educational Program and provided to the patient by the HCP who prescribes or administers lifileucel.
Plans to evaluate the effectiveness of the interventions and criteria for success	PSUR as per EU guidance
Rationale for proposing to remove additional risk minimization measure(s)	Not applicable

Overall conclusions on risk minimisation measures

There are still outstanding issues regarding the RMP but a preliminary view is that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication. Nevertheless, there is a need to revise this part of the RMP.

3.4.4. Elements for a public summary of the RMP

The elements for a public summary of the RMP require revision in line with the issues raised in other parts of the RMP.

3.4.5. Annexes

The annexes have not been updated appropriately. For recommended changes, please refer to the list of outstanding issues.

3.4.6. Conclusion on the RMP

The CHMP and PRAC consider that the risk management plan version 0.2 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report and in the list of outstanding issues

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Personal Data (PD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

3.4.7. PRAC outcome

Safety specification

PRAC supported the PRAC Rapporteur's proposal to rename the important identified risk of "Neurologic toxicity including ICANS" and add "Long-term safety" as a Missing Information; in addition, in the view of the indication, the kind of treatment, and the difficulty of capturing additional structured data post-marketing on this, the PRAC considers that the potential risk related to embryo-foetal toxicity and the risk with breast-feeding does not raise to the level of "important" and could be removed from the list of safety concerns.

Pharmacovigilance plan

Despite use of Amtagvi in a different line of treatment in the proposed PAES IOV-MEL-301 Phase 3 melanoma study than in the proposed indication, the PRAC concluded that the safety follow-up from this study is sufficient for the indication sought. In consequence, the PASS IOV MEL 401 is not considered required and should be deleted from the Pharmacovigilance Plan. The safety follow-up in study 301 should consider the safety profile of the product in the approved indication; the safety concerns listed in the RMP should be addressed when analysing and discussing data from this PAES.

Risk minimisation plan

PRAC supported the points raised by the Rapporteur without further additions.

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The IBD is 16 february 2024.

4. Benefit risk assessment

4.1. Therapeutic context

4.1.1. Disease or condition

The proposed indication for Amtagvi (lifileucel) is in 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.

The proposed treatment regimen lasts 11-12 days and consists of preconditioning non-myeloablative lymphocyte-depleting (NMA-LD) chemotherapy, a single dose infusion of Amtagvi, followed by IL-2 infusions (maximum of 6 doses). Lifileucel is a preparation of TIL derived from an individual patient's tumor for patient-directed immunotherapy. Lifileucel is provided as a single dose for infusion containing 1×10^9 to 150×10^9 viable cells suspended in a cryopreservation medium. However, the proposed indicated dose is $1{,}8 \times 10^9$ to 100×10^9 viable cells. Further justification should be provided for the proposed recommended dose range

The aim of therapy is to demonstrate treatment effect by inducing durable responses (ORR + DOR).

4.1.2. Available therapies and unmet medical need

Melanoma is the sixth most commonly diagnosed form of cancer in Europe after breast, colorectal, lung, prostate, and bladder cancers (Sung 2021). First-line therapy for metastatic disease includes anti-PD-1 monotherapy (nivolumab or pembrolizumab) or the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) or relatlimab (anti-LAG-3) as well as therapies targeting driver mutations in the BRAF pathway for tumours with these mutations (Keilholz 2020; Dummer 2015; Tawbi 2022). Limited treatment options are available for patients who have progressed on ICI and target therapies if BRAF mutated. Currently there are no therapies approved by the EMA specifically for the treatment of unresectable or metastatic melanoma that has progressed after treatment with ICIs/ targeted treatments. A recently published European consensus-based interdisciplinary guideline for melanoma indicates that patients who do not respond to PD-1-based immunotherapy have very limited therapeutic options available and recommends clinical trials as the best option in this setting (Garbe 2022). This guideline also states that chemotherapy should be considered as a last-line treatment. Overall, subsequent therapies have a low activity, therefore there is a clear unmet medical need in this clinical scenario.

4.1.3. Main clinical studies

The pivotal study for efficacy in this application is Study C-144-01, which is a single-arm, open-label study evaluating the anti-tumor activity of Lifileucel in adult patients with advanced or metastatic melanoma in the intended post-immunotherapy setting. Patients were enrolled in of 4 cohorts. Cohort 3 was the only re-treatment cohort, where patients from the other cohorts could be offered a second infusion with lifileucel. Cohorts 2 (n=78) and 4 (n=111) serve as the population for primary efficacy and safety for this CMA application. The applicant proposes pooling of data from cohort 2 and 4 based on similarity of included population, recipient of the cryopreserved TIL, treatment regimen and observed ORR results which are similar in both cohorts and are over 10%. Pooling of cohort 4 and cohort 2 is not agreed. Multiple amendments that were done during this study programme and only cohort 4 can potentially be considered to have a reasonable level of pre-definition in place before inclusion of patients. Furthermore, only cohort 4 have had an acceptable prespecified primary endpoint in the context of a SAT in oncology without sample size increases before initiation of patients.

The primary endpoint was confirmed ORR per RECIST v1.1 and evaluated by independent blinded review (ICR), while duration of response (DOR) was a secondary endpoint.

At the DCO (30 Jun 2023), pooled Cohorts 2 and 4 had a median of 12.0 months of follow-up for survival in the tumour harvested set (previously 27.6 months in the primary analysis) and a median follow-up of 13.8 months for responders in the safety analysis set (previously 21.5 months in the primary analysis). The Tumor Harvested Dataset from cohort 4 n=111 is considered as the primary population for efficacy with safety analysis dataset (cohort 4 n=89) viewed as the supportive.

4.2. Favourable effects

TH dataset (cohort 4 n=111)

- ORR by ICR:
    - 22.5% (95%CI: 15.1, 31.4) in cohort 4
        - 3.6% of patients achieved CR and 18.9% of patients achieved PR
- Median DOR (responders only, cohort 4 n=25) by ICR
    - 10.4 months (95%CI: 4.1, 26.2, min:1.4+, max: 45.8+) in cohort 4
    - Median DOR was 8.3 months in cohort 4 if the initiation of new anti-cancer therapy was used as event.

4.3. Uncertainties and limitations about favourable effects

- Non-comparative data based on SAT. Time to event endpoints are not fit for efficacy assessment since drug effects on these endpoints cannot be isolated.
- Based on the provided data, there is substantial uncertainty on the efficacy of Amtagvi at lower doses infused.
- The ORR is low (22.5%) and this activity level is not sufficient to conclude on clinical benefit in the absence of a randomised controlled trial to isolate treatment effects on PFS, OS or quality of life.

4.4. Unfavourable effects

At least 15 deaths were considered treatment-related of which two occurred after NMA-LD treatment and four deaths within 30 days of the lifileucel infusion. SAEs were seen in one third of patients.

The most concerning adverse events were:

- cytopenias (Grade 3-4 thrombocytopenia 78.8% and neutropenia 29.5%)
- infections (15.4% Grade 3-4)
- cardiac arrhythmias (grouped term; GT: 47.4% with 7.1% being grade 3-4 and at least 1 death occurring)
- encephalopathy (GT; 9 % grade 3-4 with a higher frequency in patients ≥ 65 y): Non-infectious encephalopathy/delirium was reported in 32.1% (50/156) of the patients during the TE period with 9.0% (14/156) of the patients having a Grade 3 or 4 event and 3.2% reporting SAEs none of which fatal. TTO was 5 days after infusion of lifileucel.

- hypersensitivity reactions (GT; 7.7% which includes IRR, CRS, and anaphylaxis). CRS was reported in 3.2% (5/156) of the patients with time to onset following the lifileucel infusion was 0 to 9 days. Treatment of CRS was required in 4 of the cases including tocilizumab and IV dexamethasone in 3 cases.
- vascular hypotensive disorders [(GT; 14.7% Grade 3-4. Capillary leak syndrome was seen in 12.8% (all grades)]

4.5. Uncertainties and limitations about unfavourable effects

Notably, some of the immune-related toxicities that have been associated with ICIs, or with CAR-T therapy, such as cytokine release syndrome (CRS) and neurotoxicity, were also identified with the lifileucel regimen, although with lower incidence. Tocilizumab intervention was required in a single case with concomitant CRS and ICANS. This raises the question whether additional risk minimisation measures would be required.

The single arm design and limited sample size adds uncertainty to the results. The randomised controlled phase 3 trial is important to alleviate some of these uncertainties.

4.6. Effects table

Effects table for Amtagvi for 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 (data cut-off: 30 Jun 2023).

	Effect	Short Description	Unit	Cohort		Uncertainties/ Strength of evidence/ Comments	References
Favourable Effects							
Tumor Harvested Dataset **Cohort 4 n=111**	cORR by IRC	Confirmed overall response rate by Independent Review Committee	% (95%CI)	Cohort 4: 22.5% (15.1, 31.4)		Open label, non-comparative	CSR
All datasets (responders only, cohort 4 n=25)	DOR by IRC	Median duration of response by Independent Review Committee	months (95%CI)	mDOR: 8.3 months			
Unfavourable Effects							
Safety analysis set **N=156**							
	Deaths due to AE		N (%)	4 (2.6)	First 30 days after infusion	2 AE-related deaths in the LD therapy period.	
	SAE	All	N (%)	54 (34.6)			

	Effect	Short Description	Unit	Cohort		Uncertainties/ Strength of evidence/ Comments	References
	Grade 3-4 AE		N (%)	151 (96.8)			
	Thrombocytopenia*	All Grade 3-4	N (%)	133 (85.3) 123 (78.8)		Bleeding related to thrombocytopenia?	
	Neutropenia*	All Grade 3-4	N (%)	68 (43.6) 46 (29.5)		Febrile neutropenia 32.6%	
	Infections (SOC)	All Grade 3-4	N (%)	54 (34.6) 24 (15.4)		At least 1 death due to pneumonia	
	Cardiac arrhythmias*	All Grade 3-4	N (%)	74 (47.4) 11 (7.1)		At least 1 death	
	Encephalopathy*	All Grade 3-4	N (%)	50 (32.1) 14 (9.0)		Higher in pts. ≥65 y.	
	Hypersensitivity reactions*	All	N (%)	12 (7.7)	Including infusion related reactions and anaphylaxis	IRR: 9 (5.8) Anaphylactic reaction: 2 (1.3) CRS: 5 (3.2)	
	Vascular hypotensive disorders*	All Grade 3-4	N (%)	64 (41.0) 23 (14.7)		Capillary leak syndrome (GT): 20 (12.8), Grade 3-4: 7 (4.5)	
	Uveitis	All	N (%)	6 (3.8)			

Abbreviations: CRS – cytokine release syndrome; CSR- clinical study report; FU- follow-up; IRR – infusion-related reaction; KM-Kaplan-Meier; LD therapy- lymphocyte-depleting therapy; m-median;
Notes: *Grouped term (GT)

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

There is an unmet need for patients with unresectable or metastatic melanoma who progressed on ICI and targeted therapies if BRAF mutation is present, as they are left with limited treatment options in the form of chemotherapy or ICI re-exposure. Such treatments exhibit overall low activity in this late treatment setting.

The applicant is seeking a conditional marketing authorisation and, in this context, it is acceptable that the activityof Amtagvi has been evaluated in a single arm study, which included 111 pre-treated (TH dataset) patients with unresectable or metastatic melanoma. The ORR is low. An ORR of 22.5% (95% CI 15.1, 31.4) based on the ITT population/TH set of cohort 4 of study C-144-01 is lower than usually accepted to infer clinical benefit based on single arm trials targeting solid tumours. The ORR of 22.5% is considered insufficient to conclude on clinical benefit in the absence of a RCT.

In relation to toxicity, the applicant conveys that the most common observed AEs during the tumor harvest were procedural pain, anaemia, GI AEs, fatigue and hyponatremia. No deaths related to the procedure were observed, however 20% of patients had at least one grade 3 or 4 AEs after the

procedure, still most patients recovered from the surgery without complications, which is reassuring. It is agreed with the applicant that the AEs related to lymphodepleting regimen and IL-2 are self-limiting occurring during the hospitalization and are usually reversible (~19% of patients had SAE beyond 30 days after Lifileucel infusion). The severity of AEs (87.5% of patients experienced grade 3 or higher AE) and risk of death due to AE (7.2% in the study C-144-01) are of a considerable magnitude.

The main uncertainties regarding the B/R assessment relate to study methodology, limited sample size and other limitations associated with the single-arm study design. Furthermore, there is also considerable uncertainty regarding the proposed dose of lifileucel. A different dose range compared to the studies is proposed. Very few patients in the study programme have received the higher doses. The lowest proposed dose must also be confirmed to be an effective dose. In the context of seeking a CMA for Amtagvi, a single-arm study is acceptable and the applicant has informed that confirmatory phase 3 study (TILAVNE-301) is being conducted. This study investigates the efficacy and safety of Amtagvi in combination with pembrolizumab in patients with unresectable or metastatic melanoma in the first line setting. The applicant provided a timeframe for the expected final analyses and included this study in the Annex II as SOB.

The majority of the toxicities associated with AMTAGVI regimen were related to the accompanying preparative myeloablative cyclophosphamide-fludarabine component and IL-2 therapy and manageable with standard supportive care. Among them, serious cytopenia and infections, as well as reports of cytopenia occurring during lymphodepleting regimen not resolving by 30 days following the lifileucel infusion is of concern, in particular since prophylactic measure and G-CSF were implemented during the study.

Furthermore, although the treatment-related mortality rate was 9.6% (15 /156), the onset of the fatal cases over time raises a question on the tolerability of this regimen. Although with low incidence, the reports of serious and fatal events in particular related to cytopenia and complications of cytopenia such as serious infections and haemorrhage are worrisome, especially if prolonged cytopenia is confirmed, requiring similar monitoring and interventions as in hematologic malignancies.

Cytokine release syndrome and neurotoxicity were identified as side effects of the lifileucel regimen. This is analogous to what is seen with CARTs, although with lower incidence and no Grade 5 reports identified so far.

Consequently, due to particularity of the AMTGAVI regimen, there is a need for amendments of the 4.4 and 4.8 section Description of selected adverse reactions of the AMTGAVI PI to adequately inform the prescribers on the specific risks identified.

In conclusion, the activity of 22.5% (95% CI 15.1, 31.4) for ORR is not sufficient to conclude on clinical benefit. In the absence of a randomised trial, it cannot be concluded that the benefits of Amtagvi outweigh the risks. Furthermore, the benefits to public health of the immediate availability of Amtagvi is not justified with the presented ORR of 22.5% which is not sufficient to conclude on clinical benefit. In the light of this level of antitumoral activity, the toxicity profile of Amtagvi is not acceptable. Since efficacy has not been demonstrated, B/R has not been shown to be positive.

In addition, a major objection is identified for the quality part of the dossier and confirmation of GMP compliance for both Iovance Biotherapeutics, LLC and WuXi Advanced Therapies, Inc is awaited on the basis of the requested pre-approval GMP inspections.

4.7.2. Balance of benefits and risks

It is currently not clear that the low ORR with potentially limited robustness due to issues with study methodology and uncertainties regarding posology outweigh the challenging, yet expected, toxicities

associated with treatment with the Amtagvi regimen. In addition, GMP certificates are still missing. The benefit/risk balance is negative.

4.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product Amtagvi are not available as discussed above, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease.

The targeted disease is melanoma in the advanced setting after first-line treatment has been given, and where only limited treatment options with low activity exist. Therefore, there is unmet medical need in the targeted setting.

The product needs to fulfil the requirements for a conditional marketing authorisation:

- The benefit-risk balance is to be defined as positive. Nevertheless, as the MOs listed in the LoQ need to be adequately addressed by the applicant, the benefit risk balance of the product is negative.
- It is likely that the applicant will be able to provide comprehensive data.

The proposed confirmatory study IOV-MEL-301 (referred now as TILVANCE-301) investigates the efficacy and safety of Amtagvi plus pembrolizumab over pembrolizumab monotherapy as first-line treatment in patients with previously untreated unresectable or metastatic melanoma. Since only limited treatment options for the targeted population in the 2L+ setting is available, it is considered acceptable to conduct the confirmatory study in the first-line setting, where the appropriate comparator is used. The justification on performing the confirmatory study in the earlier setting is accepted, as Lifileucel will be used in the same disease and there is a scientific rationale that it will be also effective in the earlier line setting as well. Moreover, it has been previously accepted by the CHMP that efficacy of new drug, used as monotherapy, established in the latter line allows for the assumption of its efficacy in prior lines, also as add-on treatment to SoC. The TILVANCE-301 study will condense the NMA-LD regiment to 5 days and initiate both agents simultaneously with the same doses as used in Study C-144-01. The IL-2 dose is maintained but administration will be restricted to max twice per day, max 6 doses and is not to be administrated after day 4 post lifileucel infusion. Lifileucel dose is 1.8-100x10^9 total viable cells. Pembrolizumab will be initiated after randomization and resection of tumour for lifileucel production. A dose for the lifileucel-arm will be given just before initiation of NMA-LD and then every 6 weeks until progression. The dosing schedule for pembrolizumab is the same for both treatment arms.

600 patients naïve for ICI are planned to be randomised 1:1 and an additional 70 non-ICI naïve patients are also planned to be randomised 1:1. Randomization is stratified by BRAF V600 mutation status (V600 mutation vs no V600 mutation); Disease stage at screening (Stage III/M1a or b vs M1c or d); Prior adjuvant/neoadjuvant ICI use (prior ICI use vs no prior ICI use); Region (North America vs Europe vs rest of world) as well as Lactate dehydrogenase (LDH) level at baseline (≤upper limit of normal [ULN] vs >ULN).

Primary endpoint in the EMA hierarchical testing strategy will be PFS by BICR in the ICI-naïve population. This will be followed by PFS in the overall population and OS in the ICI naïve and overall population respectively. Crossover will be allowed from pembrolizumab to lifileucel following

BICR and confirmed progression. Crossover will affect the interpretability of the OS results. A sensitivity analysis as a 2-stage method, or the inverse probability of censoring weighting (IPCW) method [Robins 2000] may be performed according to the protocol. The SAP appears not to have been finalized, however the main points of the statistical analysis plan is presented in the protocol.

The study is expected to be completed by 31 Mar 2030 and the final results will be submitted by 31 Mar 2031. TILVANCE-301 is ongoing. Overall, the proposed SOB is acceptable.

The confirmatory study is included in Annex II with a defined timeframe for the fulfilment of the SOB. Therefore, this criterion is considered to be fullfieled. However, considering the statistical plan's hierarchical testing, and likelihood of difficulties in interpreting the OS data due to crossover the applicant is asked to further specify the predicted OS maturity at the IA analysis and discuss the option of an earlier submission of the SOB.

Unmet medical needs/major therapeutic advantage will be addressed. Despite only limited treatment options exist for patients with unresectable or metastatic melanoma after progression on checkpoint inhibitors and, if applicable, BRAF and MEK inhibitors, the response rates to the subsequent therapies are low. From a clinical perspective, the results of study C-144-01 are not particularly impressive, but the mDOR is longer than expected for all authorized products in heavily pre-treated patients with malignant melanoma. Nevertheless, the severity of AEs (87.5% of patients experienced grade 3 or higher AE) and risk of death due to AE (7.2% in the study C-144-01) cannot be neglected and it cannot be concluded that the Amtagvi treatment regimen provides a major therapeutic advantage over existing therapeutic options in terms of improved safety.

An MTA for Lifileucel based on major contribution to patient care due to the single treatment cycle as compared to the other approved treatment options that are given repeatedly over a longer period of time is agreed.

However, B/R of Lifileucel is not positive and it is not obvious that the benefit to public health of the immediate availability on the market of Lifileucel outwights the risk inherent in the fact that additional data are still required.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Marketing authorisation under exceptional circumstances

Not applicable.

4.8. Conclusions

The overall benefit /risk balance of Amtagvi, subject to the conditions stated in the Recommendations' section, is negative.