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SCIENCE MEDICINES HEALTH

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Committee for Human medicinal products (CHMP)

Assessment report

Tacquell

common name: autologous melanoma-derived tumor infiltrating lymphocytes, ex vivo-expanded

Procedure No. EMEA/H/C/006563/0000

Note

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



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List of abbreviations

AJCC	American Joint Committee on Cancer
Bcl	B cell lymphoma
BMR	Batch manufacturing records
BTLA	B- and T-cell attenuator
CAT	Committee for Advanced Therapies
CCI	Container closure integrity
CCIT	National Center for Cancer Immune Therapy, Copenhagen
CCR7	C-C chemokine receptor type 7
CD	Cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CIM	Cell isolation medium
CM	Complete medium
CR	Complete response
CRR	complete response rate
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DGM	Density gradient medium
DP	Drug product
DS	Drug substance
E&L	Extractables and leachables
EM	Enzyme medium
EM	Effector memory
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
H23TIL	Hospital exemption program
HE	Hospital Exemption
HLA	Human leukocyte antigens
IFN γ	Interferon gamma
IL-2/IL2	interleukin-2
IM	Infusion medium
IMP	Investigational Medicinal Product
IPC	In process control
IPI	ipilimumab
irRC	immune-related response criteria
ITT	intention to treat
LAG-3	Lymphocyte activation gene 3
M14TIL	Confirmatory phase III trial
MA	Microarray
MEK	mitogen-activated extracellular signal-regulated kinase
MoA	Mechanism of action
ND	not determined
NE	could not be evaluated
NIVO	nivolumab
NKI	Het Nederlands Kanker Instituut
NOR	Normal operating range
NR	Non-responder
ns	Not significant
ORR	objective response rate
OS	overall survival
PAR	Proven acceptable range
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PD	Progressive disease
PD-1	Programmed cell death protein-1
PDE	Periodic daily exposure
PFS	progression-free survival

PK	Pharmacokinetics
PPS	per protocol analysis set
PR	Partial response
PRAC	Pharmacovigilance Risk Assessment Committee
R	Responder
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Rapid expansion phase
REPM	Rapid expansion phase medium
RMP	Risk management plan
RNA	Ribonucleic acid
RT	Release test
SD	Stable disease
SmPC	Summary of product characteristics
TCR	T cell receptor
TIL	Tumor infiltrating lymphocytes
TIL-IMP	Tumor infiltrating lymphocyte-investigational medicinal product used in M14TIL trial
TIM-3	T-cell immunoglobulin domain and mucin domain 3
TM	Transport medium
TM001	Tacquell (Drug product TM001 cell dispersion for infusion)
TM001DS	TM001 drug substance
TNF α	Tumor necrosis factor-alpha
WM	Wash medium

1. Administrative/regulatory information and recommendations on the procedure

1.1. Scientific advice

The applicant did not seek Scientific advice from the CAT/CHMP.

1.2. Eligibility to the centralised procedure

The applicant Netherlands Cancer Institute submitted on 7 March 2025 an application for marketing authorisation to the European Medicines Agency (EMA) for Tacquell (Autologous melanoma-derived tumor infiltrating lymphocytes, ex vivo-expanded), through the centralised procedure falling within the Article 3(1) and point 1a of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Tacquell is indicated for the treatment of adult patients with unresectable stage IIIC to IV melanoma following prior anti-Programmed Death-1 (PD-1)-based checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease or given as (neo)adjuvant therapy.

1.3. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, and non-clinical and clinical data based on applicant's own tests and studies and bibliographic literature substituting/supporting certain test(s) or study(ies).

1.4. Information on paediatrics

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA decision(s) P/0201/2024 on the granting of a product-specific waiver.

1.5. Information on orphan market exclusivity

1.5.1. Similarity with authorised 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 from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.6. Applicant's request(s) for consideration

1.6.1. New active substance status

The applicant requested the active substance *autologous melanoma-derived tumor infiltrating lymphocytes, ex vivo-expanded* 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.

1.6.1.1. CAT/CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CAT considers that *autologous-melanoma-derived-tumor-infiltrating-lymphocyte-ex-vivo-expanded* 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.

Refer to the Appendix on new active substance status claim assessment report.

The CHMP endorses the CAT conclusion on new active substance as described above.

1.7. Steps taken for the assessment of the product

The rapporteur and Co-rapporteur appointed by the CHMP were:

rapporteur:	Violaine Closso Carella
Co-rapporteur:	Rune Kjeklen

The application was received by the EMA on	7 March 2025
The procedure started on	27 March 2025
The CAT rapporteur's first assessment report was received on	16 June 2025
The CAT Co-rapporteur's first assessment report was added to the rapporteur's report on	18 June 2025
The PRAC rapporteur's first assessment report was added to the rapporteurs' report and circulated to all PRAC, CAT and CHMP members on	30 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 July 2025
The Biologics working party agreed on the Assessment Overview during their meeting on	15 July 2025
The CAT agreed on the consolidated list of questions (LoQ) to be sent to the applicant during the meeting on	18 July 2025
The applicant submitted the responses to the CAT consolidated List of Questions on	16 January 2026
The CAT rapporteur circulated the CAT and PRAC rapporteurs' joint assessment report on the applicant's responses to the list of questions (LoQ) to all CAT, CHMP and PRAC members on	24 February 2026
The PRAC agreed on the PRAC Assessment Overview and Advice to CAT/CHMP during the meeting on	12 March 2026
The CAT agreed on a list of outstanding issues (LoOI) to be sent to the applicant on	20 March 2026
The applicant submitted the responses to the CHMP list of outstanding issues on	10 April 2026
The CAT rapporteur circulated the CAT and PRAC rapporteurs' Joint assessment report on the applicant's responses to the list of outstanding issues to all CAT, CHMP and PRAC members on	30 April 2026
The outstanding issues were addressed by the applicant during an oral explanation before the CAT during the meeting on	12 May 2026
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Tacquell on	19 June 2026
The CHMP, in the light of the overall data submitted and the scientific	25 June 2026

discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Tacquell on	
Furthermore, the CAT/CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see appendix on NAS; note: this appendix will not be published)	CAT 19 June 2026 CHMP 25 June 2026

1.8. CHMP outcome

1.8.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5 of this report.

1.8.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6 of this report.

1.8.3. Opinion

Based on the CAT review of data on quality, safety and efficacy for Tacquell in the *treatment of adult patients with unresectable stage IIIC to IV melanoma following prior anti-Programmed Death-1 (PD-1)-based checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease, or given as (neo)adjuvant therapy*, the CAT considers by consensus that the quality, safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and, therefore, recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product.

The CAT considers that:

- The comparability between the clinical batches from the manufacturing sites , and between the M14TIL clinical trial batches and the commercial batches is not established.
- EU GMP compliance, including manufacturing authorisations and GMP certificates, for all the sites responsible for manufacture and quality control of the commercial active substance and finished product, is incompletely documented.
- The control strategy lacks the necessary robustness to ensure consistent quality, safety, and efficacy of the commercial medicinal product.
- The control strategy regarding the non-proliferation of feeder cells is inadequate, and aseptic process validation does not encompass the full feeder cell manufacturing process.
- The GCP inspection identified critical GCP compliance concerns in the pivotal clinical trial which impact the reliability, integrity, traceability, and re-constructability of the clinical data package.
- Multiple methodological and statistical concerns limit the interpretability of the pivotal study. These include inadequate original pre-specification of censoring rules and the handling of intercurrent events, the lack of an appropriate mitigation strategy for investigator-assessed PFS in an open-label study and key modifications to the primary endpoint framework and analysis strategy,
- The *post-hoc* restriction of the randomized comparison and the exclusion of a substantial proportion of patients from the primary analysis deviate from the ITT principle, reducing the robustness and generalisability of the retained dataset, particularly in the context of an MAA based on a single pivotal randomized trial.

- A comprehensive safety assessment is restricted by how the safety profile was characterized, in particular by limited safety data collection and follow-up, potential misclassifications of SAEs as AEs, and lack of detailed death narratives.

In the context of a potential future application, the applicant should consider the post-approval efficacy and safety follow-up according to Article 14 of Regulation on advanced therapy medicinal products (EC Regulation 1394/2007).

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following the review of the available data in the context of the applicant's claim of new active substance status, the CAT/CHMP position at the time of this report is reflected in appendix 1.

Based on the draft CHMP opinion review of data on quality, safety and efficacy for Tacquell in the *treatment of adult patients with unresectable stage IIIC to IV melanoma following prior anti-Programmed Death-1 (PD-1)-based checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease, or given as (neo)adjuvant therapy*, adopted by the CAT the CHMP considers by consensus that the quality, safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and, therefore, recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product based on the same grounds for refusal as adopted by the CAT.

2. Introduction

2.1. Therapeutic context

Cutaneous melanoma is a cancer type that derives from melanocytes.

Disease staging is based on a four-tiered staging system defined by the American Joint Committee on Cancer (AJCC) depending on tumor thickness, presence of mitosis and ulceration in the primary stages and regions of metastases in the later ones. Once the melanoma is locally advanced and has spread to the lymph nodes (stage III) or is spread to organs or other parts of the body (stage IV), it is called advanced stage disease. Patient prognosis is related to the disease stage.

Cutaneous melanoma is one of the most common malignancies, accounting for 1.7% of global cancer diagnoses according to GLOBOCAN. The risk of developing melanoma increases with age, possibly related to a greater cumulative exposure to UV radiation. However, melanoma can also develop on areas of the skin that are not UV-exposed.

Melanoma has an estimated yearly increasing incidence of >150.000 newly diagnosed cases per year in Europe (Dyba et al., 2021). The global age-standardized incidence rate is 3.8/100,000 for males and 3.0/100,000 for females. In Europe, the incidence rate is 10 – 25 new melanoma cases per 100,000 inhabitants, with a dramatic increase seen in the last years in many parts of Europe for all age groups. Most diagnoses are made prior to the development of lymph node or distant metastases (stage III to IV, advanced disease). The risk of developing melanoma increases with age, possibly related to a greater cumulative exposure to ultraviolet (UV) radiation. However, melanoma can also develop on areas of the skin that are not UV-exposed (Dennis et al., 2008; Rozeman et al., 2018; Ting et al., 2007).

Surgical resection is the preferred first line of therapy for patients with localized melanoma (stages I to III). However, despite resection of the primary tumor, the disease metastasizes in about 14% of patients. Previously, patients with stage IIIC to IV melanoma had a poor prognosis, with a 10-year

survival of less than 5%, due to the very limited effect of traditional first-line therapies like radiation and chemotherapy (Balch et al., 2009; Bhatia & Thompson, 2012).

In the past years, different immune checkpoint inhibitors, such as anti-programmed cell death protein 1 (PD-1) or anti-T-cell coinhibitory receptor CTLA-4 antibodies, have been developed with the aim of reactivating pre-existing anti-tumor T-cell reactivity. Moreover, targeted therapies directed against aberrant molecules or pathways that drive uncontrolled growth of tumor cells (e.g. BRAF gene mutation) have been developed to inhibit tumor cell growth. These developments have significantly improved the prognosis of patients with unresectable stage IIIC to IV melanoma.

The anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody ipilimumab (IPI) was the first immune checkpoint inhibitor to achieve a significant improvement in survival of advanced stage melanoma and was approved as a Standard of Care (SoC) for the management of those patients in Europe in 2011. A switch in clinical practice occurred with the approval of molecules targeting PD-1 as first-line therapy in 2015 and as adjuvant therapy for patients with unresectable stage IIIC to IV melanoma in 2018. The current European Society's for Medical Oncology (ESMO) clinical practice guideline (Amaral et al, 2024) for the management of cutaneous melanoma indicates "*current first-line SoC treatment options for unresectable stage III/IV melanoma are PD-1 blockade (nivolumab, pembrolizumab), PD-1 blockade combined with CTLA-4 blockade (nivolumab-ipilimumab), PD-1 blockade combined with lymphocyte activation gene-3 (LAG-3) blockade (nivolumab-relatlimab)*".

After failure of first-line treatment with anti-PD-1 antibodies, second-line treatment with other immune checkpoint inhibitors or targeted therapy leads to objective response rates (ORR) of 28% to more than 50%, however of relatively short duration. Due to this limited clinical benefit of second-line treatment with the currently available immune checkpoint inhibitors and targeted therapies, there is a clear unmet medical need for novel treatment modalities for relapsed/refractory patients with advanced stage melanoma.

2.2. Aspects of development

Table 1 provides an overview of the Tacquell (TM001) clinical development program.

Table 1. Tacquell (TM001) clinical development program

Study ID Title	Number of Study Centers Location(s)	Study Period, No. of Patients Enrolled / Completed Treatment	Study Design and Type of Control	Study & Comparator Dose, Route & Regimen	Study Objective	Primary Endpoint(s)
Feasibility studies with developmental TIL products – not included in TM001 efficacy and safety evaluation						
<i>EudraCT nr.: 2008-008141-20</i> <i>ClinicalTrials.gov nr.: NCT00937625</i>	Department of Oncology and CCIT, Copenhagen University Hospital, Herlev, Denmark	<i>Studied Period:</i> 2008-2014 <i>Patients treated:</i> 25	Phase I/II Open label study	<i>Study Product:</i> Development TIL (Herlev) <i>Dose:</i> Single dose of 1E9 – 1E10 viable cells <i>Mode of Adm.:</i> single IV infusion	TIL therapy in progressive metastatic or locally advanced melanoma patients	
<i>EudraCT nr.: 2010-021885-31</i>	NKI-AVL, Amsterdam, The Netherlands	<i>Studied Period:</i> 2010-2014 <i>Patients enrolled:</i> 10	Phase I/II Feasibility study	<i>Study Product:</i> Development TIL (NKI) <i>Dose:</i> Single dose of 5E9 – 2E11 viable cells <i>Mode of Adm.:</i> single IV infusion	TIL therapy in metastatic (stage IV) melanoma patients refractory to chemotherapy, immunotherapy and/or targeted therapy	

Confirmatory Phase III trial – NKI data pivotal efficacy and safety data (CCIT data were included in the full analysis for Clinical Study Report as per protocol yet not included in TM001 efficacy and safety evaluation)						
M14TIL <i>EudraCT nr.: 2013-005406-54</i>	- NKI-AVL, Amsterdam, The Netherlands - Department of Oncology and CCIT, Copenhagen	<i>Studied Period:</i> SEP2014 to DEC2023	Phase III, multicenter, open-label, randomized, controlled trial	<i>Study Product:</i> TIL-IMP / TM001 <i>Dose:</i> Single dose of 5E9 – 2E11 viable cells	<i>Primary objective:</i> To compare PFS (according to RECIST 1.1) between patients treated with IPI as compared to patients	PFS (according to RECIST 1.1); defined as the time from randomization to first disease progression (either
<i>ClinicalTrials.gov nr.: NCT02278887</i> <i>Title:</i> Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma.	University Hospital, Herlev, Denmark	<i>Patients enrolled</i> total: 168 NKI: 132 CCIT: 36 <i>Patients completed</i> total: 162 NKI: 128 CCIT: 34		<i>Mode of Adm.:</i> single IV infusion <i>Regimen:</i> TIL-IMP / TM001 infusion preceded by preparative non-myeloablative lymphocyte depleting chemotherapy and followed by supportive administration of interleukin-2 (IL-2) <i>Comparator:</i> Ipilimumab (IPI) <i>Dose:</i> 3 mg/kg every 3 wks, for a max. of 4 doses <i>Mode of Adm.:</i> IV infusion	receiving TIL-IMP therapy. <i>Secondary objectives:</i> - PFS at 6 months according to RECIST 1.1 and PFS according to irRC; objective response rate (ORR) according to RECIST 1.1; complete response rate (CRR); overall survival (OS), and safety (according to CTCAE v 4.0). - Constructive technology assessment (CTA) including evaluation of health related Quality of Life (QoL).	radiologic progression or subsequent anticancer therapy, including systemic therapy, radiotherapy, or surgery) or death
Study ID Title	Number of Study Centers Location(s)	Study Period, No. of Patients Enrolled / Completed Treatment	Study Design and Type of Control	Study & Comparator Dose, Route & Regimen	Study Objective	Primary Endpoint(s)
TM001 Supportive Efficacy and Safety Data						
M14TIL Side Study <i>Title:</i> Side study of confirmatory phase III trial for patients with unresectable Stage IIIC to IV melanoma receiving TM001 therapy in the period between the confirmatory phase III trial and the start of the hospital exemption	NKI-AVL, Amsterdam, The Netherlands	<i>Studied Period:</i> JUN2022 to DEC2023 4 patients treated	Side study to M14TIL Open label, no randomization, no control treatment	<i>Study Product:</i> TM001 <i>Dose:</i> Single dose of 5E9 – 2E11 viable cells <i>Mode of Adm.:</i> single IV infusion <i>Regimen:</i> TM001 infusion preceded by preparative non-myeloablative lymphocyte depleting chemotherapy and followed by supportive administration of IL-2	To bridge the period between the confirmatory phase III trial and the start of the hospital exemption program.	Best Overall Response (according to RECIST 1.1)
H23TIL Hospital exemption for patients with unresectable Stage IIIC to IV melanoma receiving TM001 therapy	NKI-AVL, Amsterdam, The Netherlands	<i>Studied Period:</i> JAN2023 – ongoing (data lock point for interim report: 06NOV2024) <i># Patients at data lock point:</i> 50	Hospital Exemption program	<i>Study Product:</i> TM001 <i>Dose:</i> Single dose of 5E9 – 2E11 viable cells <i>Mode of Adm.:</i> single IV infusion <i>Regimen:</i> TM001 infusion preceded by preparative non-myeloablative lymphocyte depleting chemotherapy and followed by supportive administration of IL-2	To treat patients with unresectable stage IIIC to IV melanoma with TM001 therapy.	Clinical parameters used for evaluation - PFS (RECIST 1.1) in patients receiving TM001 therapy. - PFS at 6 months (RECIST 1.1) - Best overall response (RECIST 1.1) - Overall survival - Safety (CTCAE v5)

The clinical sites involved in the confirmatory phase III trial also performed phase I/II feasibility trials (discussed in Andersen et al, 2016 and in van den Berg et al, 2020) with developmental TIL products that contributed to the design and final manufacturing process applied in the confirmatory phase III trial.

2.3. Description of the product

Tacquell cell dispersion for infusion is an autologous cell-based immunotherapy product that contains viable autologous CD45+CD3+ T-cells, isolated and expanded ex vivo from a melanoma metastasis with the goal of generating immune reactions against the patient's own tumor.

The mechanism of action of the autologous tumor infiltrating lymphocytes relies on anti-tumor reactivity mediated by CD45+CD3+ T cells. Anti-tumor reactivity is mediated by CD45+CD3+ T cells and by both CD4+ and CD8+ subpopulations, and that there is long-term persistence of tumor-reactive T cells in peripheral blood of patients after product infusion. In addition, it was shown that the anti-tumor reactivity is directed against both patient-specific neoantigens and tumor-associated antigens.

Tacquell is intended for autologous use and should only be administered as a single dose via intravenous infusion. The proposed recommended dose of Tacquell is $10 \times 10^9 - 1 \times 10^{11}$ viable CD45+CD3+ viable cells dispersion for infusion.

Tacquell must be administered in a qualified treatment centre by a physician with experience in adoptive cellular therapy and trained for administration and management of patients treated with Tacquell.

2.4. Inspection issues

2.4.1. Good manufacturing practice (GMP) inspection(s)

The GMP inspections for Tacquell were and should have been performed according to the following list:

- inspection at the 1st Dutch manufacturing site for the commercial activities.
- inspection at the 2nd Dutch manufacturing site for the commercial activities.

no outcomes have been received due to no completion of the inspections.

2.4.2. Good laboratory practice (GLP) inspection(s)

No inspection required

2.4.3. Good clinical practice (GCP) inspection(s)

A routine GCP inspection was performed by NL and NO for the following clinical study M14TIL. The inspections took place from August 18 to 22, 2025, at the investigator site, and from September 8 to 12, 2025, at the sponsor site. The Integrated Inspection Report (IIR) for the European Medicines Agency (EMA), reference number EMA/IN/0000276203, concerning the medicinal product Tacquell (Autologous melanoma-derived tumor infiltrating lymphocytes, ex vivo-expanded) has been provided, and the outcome of this inspection was submitted; the GCP inspection is an integral part of this procedure.

A total of 4 critical, 13 major, and 6 minor findings were identified across both sites. Some findings were attributed to both the sponsor and the principal investigator (PI), indicating shared responsibility:

The Critical Findings are summarized below:

-Serious shortcomings in trial management by the sponsor, including lack of documented governance and insufficient separation of sponsor and investigator site roles.

-Lack of control over key computerized systems used in the trial, including the electronic case report form (eCRF), safety database, and statistical analysis software.

-Significant shortcomings in data management processes, making it impossible to confirm data integrity.

-Shortcomings in the statistical analysis process, including the inability to reconstruct the course of events for tables, listings, figures, and statistical outcomes.

The Major Findings are below:

- Inadequate process for investigator review and sign-off of data.
- Issues with eCRF design causing discrepancies.
- Trial conduct aspects not compliant with ICH-GCP and the trial protocol.
- Inadequate quality management system (QMS) at the sponsor.
- Inadequate safety reporting and evaluation of serious adverse events (SAEs).
- Discrepancies between source data and eCRF.
- Inadequate management of investigational medicinal products (IMPs).
- Inadequate facilities and trial master file (TMF)/investigator site file (ISF) management.

Based on the above, the inspection team concludes that from the GCP perspective, the trial results could be used in an MAA-procedure only with major reservations, since multiple significant findings constituting (often significant) non-compliance with ICH-GCP E6 R2, have been raised in the two inspections. The inspectors were unable to establish integrity of the data reported in the CSR, in fact showing on multiple occasions that the data in the CSR were incorrect or incomplete. The quality of the data therefore cannot be concluded to be acceptable. It should be noted that the inspection report did not indicate that trial participant rights, dignity or well-being had been compromised, nor that a significant impact on participant safety had materialised.

3. Quality aspects

3.1. Introduction

Tacquell, also referred to as TM001, is an autologous cell therapy medicinal product containing T-cells isolated and expanded *ex vivo* from a melanoma metastasis.

The finished product is presented as a dispersion for infusion containing as active substance a proposed amount of $\geq 10 \times 10^9$ autologous CD45+CD3+ viable T-cells. Other ingredients include sodium chloride human serum albumin (HSA).

The product was proposed in an infusion bag with a spike connector containing 200 mL of dispersion for infusion.

3.2. Active substance

3.2.1. General information

TM001 active substance consists of autologous viable CD45+CD3+ T-cells isolated and expanded from a tumour lesion.

TM001 cell dispersion for infusion is a patient-specific cell product aimed at generating immune reactions against the patient's own tumour. The TM001 mechanism of action (MoA) relies on anti-tumour reactivity mediated by the CD45+CD3+ T-cells in TM001.

The Applicant stated that the MoA of TM001 active substance involves anti-tumour reactivity mediated by CD45+CD3+ T-cells isolated and expanded *ex vivo* from a melanoma metastasis, targeting neoantigens and tumour-associated antigens. Studies from a phase III trial confirmed long-term

persistence of this reactivity. However, the product was not sufficiently characterised to support the claimed MoA since the cytotoxic activity was not demonstrated.

3.2.2. Manufacture, characterisation, and process controls

Description of manufacturing process and process controls

The intended commercial active substance is manufactured at manufacturing sites in the Netherlands.

In relation to this marketing authorisation application (MAA), the sites were subject to pre-authorisation GMP inspections. **EU GMP compliance for the manufacture of the commercial active substance was not demonstrated and valid manufacturing authorisations and GMP certificates were not provided. This constitutes a ground for refusal.**

The description of the manufacturing process includes a flow chart, a brief narrative and in-process controls (IPCs). Critical process parameters (CPPs) are described. Briefly, TM001 active substance is manufactured in a continuous process that begins with the receipt of the resected tumour (Step 1), cell isolation (Step 2), cells proliferation (Step 3a), optional cryopreservation (Step 3b), first rapid expansion (REP) in static phase (Step 4) and rapid expansion in dynamic phase into closed bioreactor (REP2) (Step 5). Then the cells are harvested in infusion bags and washed (Step 6).

The duration of each step of the manufacturing process is included in the dossier.

The total viable cell count available at the start of proliferation step is dependent on tumour size. The Applicant proposed a minimum tumour size and a maximum fragmented volume with justification of the size thresholds.

Antibiotics used during the manufacturing process from Step 1 to Step 5 (REP 2). The Applicant justifies its use on the basis of the non-sterile nature of the starting material, as well as the long process duration and the multiple aseptic handlings required during the REP phase. Nonetheless, the use of antibiotics at later stages of the process should be avoided as per the Ph. Eur. 5.32 general chapter. To this end, the Applicant committed, in case a marketing authorisation for Tacquell had been granted, to submit a post-approval variation regarding the antibiotic removal beyond Step 3a.

Batch definition and numbering system are provided. TM001 is an autologous product: excised tumour starting material from a single patient is manufactured into one TM001 batch for infusion into the same patient. Patient traceability is maintained throughout the manufacturing process using unique numbered patient labels, dedicated operators, and batch dedicated equipment. Excised tumour starting material from a single patient is manufactured into one TM001 batch for infusion into the same patient.

Reprocessing is not described in the dossier.

Control of materials

An overview of the media and raw materials used for TM001 manufacturing is provided.

The Applicant provided the qualitative compositions of the base media.

The resection of the tumour and transport of the autologous tumour material to the manufacturing site is described.

The raw materials should be sterile or there should be a sterilisation step before they are introduced in the manufacturing process. The Applicant proposed to implement the indicated tests post-authorisation if a marketing authorisation for Tacquell had been granted. This was not acceptable since these tests should have been implemented before authorisation.

Feeder cells

Feeder cells used during the manufacturing process of TM001 are irradiated allogenic human peripheral blood-derived mononuclear cells (PBMCs). They are extracted from healthy donor fresh buffy coats. Fresh buffy coats can be pooled and the final pooled donor number per batch will not exceed 16 donors. Donors and donations are screened and tested in accordance with Directive 2004/33/EC. Briefly, the manufacturing process of feeder cells consists of collection of fresh buffy coats, feeder cell isolation, cryopreservation, thaw and wash and irradiation. Release specifications proposed by the Applicant for feeder cells are provided.

The current control strategy should be demonstrated to ensure control of number of viable irradiated PBMCs introduced into the manufacturing process.

In addition, the aseptic process validation should include step thaw and wash of the feeder cell manufacturing process and onwards.

The inadequate control strategy regarding the non-proliferation of feeder cells, and the aseptic process validation not encompassing the full feeder cell manufacturing process, constitute a ground for refusal.

Other issues regarding feeder cells remained unresolved, such as:

- Demonstrating how feeder cell performance is ensured;
- Suboptimal control strategy;
- Viral safety.

Control of critical steps and intermediates

The Applicant has implemented IPCs for controlling the TM001 manufacturing process. While, action limits are established for the IPCs, the Applicant stated that the action limits will be updated towards acceptance criteria, as requested during the procedure, to ensure the reproducibility of the process and the consistency of the finished product.

Action limits had been established based on confirmatory phase III M14TIL clinical data.

Process validation and/or evaluation

The manufacturing process of TM001 is a continuous process.

Manufacturing process development

Process development history was provided and mentions phase I/II feasibility studies, confirmatory phase III trial (M14TIL) and supportive clinical data (including M14TIL side study and hospital exemption program). However, since the manufacturing process of the TIL products used in the phase I/II studies is not comparable to TM001, their clinical results are not included in the efficacy, safety and benefit-risk evaluation of TM001.

Control strategy elements, TM001 manufacturing process and analytical development history are presented.

Although, a quality target product profile (QTPP) was presented, its role in guiding the definition of CQAs and process controls during development appeared to be negligible.

The Applicant stated that based on phase III manufacturing experience, and on comparability and critical quality attribute/critical process parameter (CQA/CPP) analyses, the process was standardised for the MAA.

The Applicant provided additional comparability studies for the TIL investigational medicinal product (TIL-IMP) manufactured at the sites for the confirmatory phase III trial (M14TIL), hospital exemption program (H23TIL) and hospital exemption program (commercial process).

A) Comparability

The Applicant failed to demonstrate comparability between the clinical batches from the manufacturing sites, and between the M14TIL clinical trial batches and the commercial batches. This constitutes a ground for refusal (points 1 and 2 below). Unresolved comparability issues are described below.

1. Comparability between the sites (M14TIL clinical trial)

The data provided during the procedure were insufficient to demonstrate comparability between batches manufactured at the manufacturing sites, which is critical for pooling clinical trial data and establishing a unified efficacy/safety profile. In particular, there were significant process and control strategy differences and several missing comparability data.

The Applicant stated that clinical performance was consistent between sites even though this was not addressed in Module 3. The comparability should have been further justified and demonstrated in a clear and precise manner, for example by comparing the number of responders and non-responders (and/or any other relevant clinical data) between the different processes as well as individual CQAs.

In order to inform the comparability evaluations and conclusions further, equivalence testing should have been part of the comparability exercise. The Applicant stated that, owing to the intrinsic variability of patient-specific starting material, direct one-to-one equivalence testing of each individual difference was not feasible. However, the Applicant was expected to provide quantitative evidence supporting these assertions.

Therefore, due to these gaps, no clear conclusion could be drawn regarding the comparability between batches.

2. Comparability between clinical M14TIL and commercial batches

During the procedure, the Applicant addressed some of the concerns raised regarding comparability between clinical M14TIL and commercial batches. However, concerns remained.

3. Comparability between M14TIL clinical trial and H23TIL hospital exemption

The data provided were considered supportive. During the procedure, the Applicant addressed some of the concerns raised. However, concerns remained unresolved.

B) CPP analysis

The Applicant stated that none of the process parameters (PPs) are considered critical, that none of them impacts the CQAs, and no IPCs with acceptance criteria are defined for TM001 active substance and TM001 manufacturing steps. This was not endorsed.

The Applicant should have established and justified a robust commercial control strategy that ensures consistent product quality, safety and efficacy, in accordance with ICH Q8, Q9, and Q11.

A control strategy lacking the necessary robustness to ensure consistent quality, safety, and efficacy of the commercial medicinal product constitutes a ground for refusal.

Characterisation

TM001 active substance consists of autologous, viable CD45+CD3+ T-cells isolated and expanded from melanoma metastasis, which have been cultured and expanded.

The Applicant completed the S.3.1 Characterisation section with a description of the characterisation attributes investigated for defining product identity and purity. Batch analysis results regarding subpopulations and different status of T-cells were provided for M14TIL and H23TIL batches.

3.2.3. Specification

Specifications

Given that there is no hold step between the active substance manufacturing and finished product final formulation and filling, all release tests are described in the finished product part.

Analytical procedures and validation

All analytical procedures are described in the finished product part.

Batch analyses

The manufacturing process is continuous and there is no active substance batch.

Reference standards or materials

There is no reference standard for TM001 active substance.

Container closure system

Not applicable.

3.2.4. Stability

Reference is made to the stability section in the finished product part.

3.3. Finished medicinal product

3.3.1. Description of the product and pharmaceutical development

Description of the product

TM001 cell dispersion for infusion containing $\geq 10 \times 10^9$ autologous viable CD45+CD3+ cells is composed of 200 mL in an infusion bag: containing sodium chloride and HSA.

The finished product is intended for intravenous infusion and requires no diluents nor vehicles for clinical administration. The composition of the finished product is presented in.

No overages are used in the manufacture of TM001.

Pharmaceutical development

Formulation development

TM001 active substance is an amplified version of the tumor-infiltrating lymphocytes (TIL) present in a patient's own tumor formulated as a cell suspension.

All the used excipients and their function have been described. No novel excipients are used.

TM001 finished product is formulated with HSA. The finished product is maintained until infusion. The Applicant stated that the container is a standard sterile infusion bag with spike connector, selected as suitable for the intended use.

Manufacturing process development

Manufacturing process development is discussed in the active substance part.

Microbiological attributes

The infusion bags comply to EN ISO 3826-1:2019. The impermeability testing is performed by the supplier during the design verification phase of the infusion bag.

Excipients used in TM001 are sterile.

Sterility testing during manufacturing is designed to ensure microbiological safety. A retrospective analysis of aseptic process simulation (APS) performance was conducted to provide information of container closure integrity.

3.3.2. Manufacture of the product and process controls

Manufacture

The commercial finished product is manufactured at manufacturing sites in the Netherlands. Quality control testing is performed at these sites and an external site.

In relation to this MAA for the manufacture and quality control testing of the commercial finished product valid manufacturing authorisations and GMP certificates were not provided. This constitutes a ground for refusal.

Description of manufacturing process and process controls

TM001 active substance is formulated, filled, tested and released to obtain TM001 for administration to the patient. A flow diagram of the TM001 manufacturing process is provided. TM001 manufacturing occurs in a closed system. TM001 can be stored in the primary packaging until administration.

Reprocessing is not described in the dossier.

TM001 cell dispersion for infusion is an autologous product: one patient's tumour material is manufactured into one batch for infusion into the same patient.

Control of critical steps and intermediates

The Applicant stated that there are no critical steps and intermediates to be controlled by IPC during the finished manufacturing process.

Process validation

The process validation strategy of TM001 included the following elements:

- Retrospective process validation of all TM001 batches manufactured during the confirmatory phase III trial (M14TIL).
- Retrospective process validation of all TM001 batches manufactured under hospital exemption.
- Concurrent process validation of TM001 batches consecutively manufactured under routine conditions/according to the process described in Module 3, section S.2.2.
- Additional supportive data – H23TIL batches manufactured according to the commercial process (ongoing at the time of CAT/CHMP Opinion).

During the manufacturing process, optional steps can be applied. The corresponding intermediates are validated in PPQ batches.

Retrospectively defining successful clinical batches as validation batches is not considered appropriate. It is normally expected that the prospective consecutive process validation batches are presented to demonstrate process validation to support approval. As for the concurrent validation approach, it is only foreseen for exceptional circumstances. While concurrent validation could be used alongside or instead of traditional process validation, this only applies to processes that are highly controlled, well-understood, and have a low risk of variation where continuous monitoring ensures consistent quality. This is not the case for Tacquell.

Control of excipients

TM001 is formulated in sodium chloride and HSA All excipients are authorised medicinal products and their quality is confirmed.

3.3.3. Product specification

Specifications

The specification acceptance criteria are based on the analysis of the TM001 batches data manufactured for the confirmatory phase III (M14TIL).

The release specification for TM001 finished product is provided.

The Applicant acknowledged that any finished product batch failing release criteria must be rejected, claiming robust OOS procedures are in place to ensure proper investigation and necessary actions.

Analytical procedures

An overview of analytical procedures used to control TM001 was provided. The analytical test methods used for product release testing are identified by the corresponding method number. It is stated that each manufacturing site in the manufacturing framework is responsible for complete manufacturing and product control testing. Thus, it was not considered necessary to indicate the testing site for each method. This was considered acceptable.

Validation of analytical procedures

The analytical procedures used for release and stability testing are validated.

Batch analysis

Batch release results were provided from:

- TM001 batches used for the confirmatory phase III trial (M14TIL)
- M14TIL side study batches
- Hospital exemption program (H23TIL) batches
- Hospital exemption program (H23TIL- commercial process) including the process performance qualification (PPQ) batches.

Reference standard

There is no reference standard for TM001.

Characterisation of impurities

The Applicant provided an overview of the evaluation of cellular impurities.

A nitrosamine risk evaluation was performed, screening all materials contacting the active substance and finished product. The Applicant concluded that no nitrosamine risks exist for Tacquell. This is deemed acceptable.

An extractables & leachable (E&L) assessment reviewed material quality documentation, accepting untested materials with certificates (e.g., USP Class VI) or Ph. Eur. compliance. No E&L risks are identified for active substance and finished product materials.

Container closure

TM001 is stored in infusion bags. Justification for the use of container configurations was provided. A benefit/risk assessment (performed by the supplier of the container closure system) for phthalate (DEHP) was provided. The suitability of the container closure system for the intended use is demonstrated.

Tacquell was intended to be transported within the administration facility in closed, break-proof, leak-proof containers.

3.3.4. Stability of the product

TM001 can be stored in its labelled packaging until administration. Stability has been assessed under real-world conditions, including in-use and shipment studies.

In-use stability study has been performed. The Applicant committed to providing post-approval stability studies using commercial batches. This would have been acceptable in case of positive CAT/CHMP Opinion for the MAA.

Shipment study was performed mimicking the shipment conditions.

3.3.5. Adventitious agents

The active substance is composed of T-cell isolated from autologous tumour starting material and expanded *ex vivo* using frozen human feeders. Due to the cellular nature of the product, there is no possibility to introduce viral removal steps in the manufacturing process. Therefore, precautions are taken to prevent and/or detect the introduction of adventitious agents throughout the control of raw materials.

Overall, at the time of CAT/CHMP Opinion, available data to support adventitious agents safety of Tacquell could not be considered satisfactory.

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

The current dossier, in many parts, cannot be considered of acceptable quality according to EU standards. Therefore, the MAA for Tacquell is not considered approvable from a quality point of view. The quality grounds for refusal for the granting of a marketing authorisation, as described above, are:

- The comparability between the clinical batches from the manufacturing sites, and between the M14TIL clinical trial batches and the commercial batches is not established.
- EU GMP compliance, including manufacturing authorisations and GMP certificates, for all the sites responsible for manufacture and quality control of the commercial active substance and finished product, is incompletely documented.
- The control strategy lacks the necessary robustness to ensure consistent quality, safety, and efficacy of the commercial medicinal product.
- The control strategy regarding the non-proliferation of feeder cells is inadequate, and aseptic process validation does not encompass the full feeder cell manufacturing process.

The CHMP endorses the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

3.5. Recommendation(s) for future quality development

Not applicable.

4. Non-clinical aspects

4.1. Introduction

The Tacquell (TM001) therapy consists of TM001 infusion, preceded by a preparative regimen of non-myeloablative lymphocyte depleting chemotherapy and followed by supportive administration of interleukin-2 (IL2) post TM001 infusion. TM001 is made of autologous viable CD45+CD3+ T cells, isolated and expanded from a melanoma metastasis. It is an autologous somatic cell therapy products and consequently no animal models are suitable to evaluate its efficacy. Autologous mouse models are not appropriate since they do not replicate the same mechanisms of recognition and cytotoxicity activity. For this reason, no pivotal GLP studies were presented in this dossier, and the non-clinical package is based mainly on literature references.

Pharmacology studies for in vitro and ex vivo analyses used cryopreserved materials from patients participating in the confirmatory phase III trial.

4.2. Analytical methods

No preclinical GLP studies have been evaluated and therefore there are no validated analytical methods to present in this section.

4.3. Pharmacology

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Tacquell (TM001) is an autologous, patient-specific T cell product composed of viable CD45+CD3+ T cells expanded ex vivo from tumor lesions. The product aims to induce broad immune responses against tumor-specific antigens, including neoantigens and tumor-associated antigens.

Due to limited availability of autologous tumor material, nonclinical pharmacology studies rely on ex vivo analyses of patient-derived samples from clinical trials and literature data. These studies have demonstrated that TM001 TILs recognize tumor antigens, as shown by CD137 expression and IFN γ production when co-cultured with autologous tumour cell lines. Both CD4+ and CD8+ T cells contribute to this tumor reactivity, with CD8+ T cells being predominant.

The T cell subpopulations in TM001 batches of the confirmatory phase III trial were described but the characterization of these TILs IMP is not detailed.

Following infusion, tumor-reactive T cells, initially absent in patients' peripheral blood, expanded markedly and persisted, indicating sustained immune activation.

Mapping of CD8+ T cells recognizing neoepitopes in TIL infusion products and blood samples from treated patients led to identification of 106 neoepitopes within the TIL infusion products (Kristensen et al, 2022). The investigators have addressed the specificity for neoantigens and tumor-associated antigens in a selection of TIL-IMP batches from the confirmatory phase III trial. They found that the mechanism of action of TM001 relies on the presence of anti-tumor-reactivity of CD45+CD3+ T cells, reactive against neoantigens or tumor-associated antigens.

Published literature supports these findings (Alfei F et al. 2021, Sun J, Zhang J, Hu H, et al. 2021, Dhodapkar MV, Dhodapkar KM. Et a. 2020). Studies have reported response rates around 50%, including durable complete responses, with persistent neoantigen-specific T cells and manageable safety profiles,

particularly in patients resistant to anti-PD-1 therapy (Verdegaal EME et al. 2020). Other reports confirm long-term persistence of tumor-reactive T cells and show correlations between neoantigen-reactive T cell diversity and improved progression-free and overall survival (Kristensen et al. 2022)

4.3.1.2. Secondary pharmacodynamics

No provided studies.

4.3.1.3. Safety pharmacology

No provided studies.

4.3.1.4. Pharmacodynamic drug interactions

No provided studies.

4.3.2. Pharmacokinetics

No biodistribution study has been performed.

4.4. Toxicology

4.4.1. Single-dose toxicity

No single dose toxicity studies have been performed.

4.4.2. Repeat-dose toxicity

Not applicable.

4.4.3. Genotoxicity

Not applicable.

4.4.4. Carcinogenicity

No carcinogenicity studies have been performed.

4.4.5. Developmental and reproductive toxicity

No studies have been performed with TM001.

4.4.6. Toxicokinetics and exposure margins

No provided studies.

4.4.7. Local tolerance

Not applicable.

4.4.8. Other toxicity studies

No other safety/toxicity studies were performed with TM001.

4.4.9. Ecotoxicity/environmental risk assessment

TM001 consist of autologous, viable CD45+CD3+ T-cell isolated and expanded from a tumour lesion of the patient under treatment. It is considered a medicinal product comprised of naturally occurring substance and is manufactured and administered under controlled close system. TM001 is not genetically modified. It consists of living cells that have a limited survival ability outside the temperature-controlled manufacturing and shipping environment. Manipulation and precaution of the product is to be carried out in accordance with local guidelines on handling of human-derived material.

In conclusion, 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, TM001 is not expected to represent a risk to the environment.

4.5. Overall discussion and conclusions on non-clinical aspects

4.5.1. Discussion

The non-clinical package is mainly based on literature references with the aim to demonstrate that TM001 presents with the key characteristics of an active TIL preparation. This approach is acceptable taking into account the nature of the product and the low relevance of in vivo models for highly patient specific products as well as the availability of published results studying TILs in general.

The mechanism of TM001 was investigated through ex vivo analyses of tumor-reactive T cells in samples from patients participating in the confirmatory phase III trial (M14TIL). The T cells expressed activation markers and immune checkpoint molecules. This may reflect both activation and exhaustion in the tumor microenvironment. Variations in T-cell populations were observed between patients who responded well to the treatment and those who did not. However, no direct correlation between these variations and clinical response was demonstrated.

It was confirmed that TIL-IMP contains tumor-reactive T cells, but the proportion of such cells varies between patients, and the specific roles of different TIL subpopulations are not fully defined.

From a non-clinical perspective, and in line with the guidelines, the absence of PK and biodistribution studies is considered acceptable. Considering that T cells are naturally trafficking cells, their ability to circulate and migrate throughout the body as part of their immune function is well established. Moreover, given that TILs are fully differentiated cells, the risk of ectopic implantation is low. Overall, the justification provided is considered appropriate and consistent with regulatory expectations for this type of product.

Given the nature of the product and the absence of a suitable animal model, to assess safety the applicant has relied on clinical data and literature. Evidence from earlier studies (Muul et al, 1987); Topalian et al, 1987) supports the absence of tumor cells in expanded TIL preparations and their selective cytotoxicity toward tumor cells only.

As TM001 is a single-dose treatment for adults with advanced melanoma, repeated-dose and juvenile toxicity studies are not required. The absence of developmental and reproductive toxicity studies is considered acceptable given both the therapeutic indication, and the autologous, patient-specific nature of the product challenging the relevance of conventional experimental models (EMA/CHMP/410869/2006; ICH S9//2018). In addition, treatment with Tacquell is preceded by a conditioning regimen with cyclophosphamide (2 days) followed by fludarabine (5 days). Both substances were shown to induce embryo-foetal lethality and malformations in animal studies. Adverse reproductive outcomes were reported in humans with cyclophosphamide (incl. malformations, foetotoxicity, intrauterine death) which is contraindicated in pregnant women and in women of

reproductive potential not using contraception, while it is generally reported that fludarabine should not be used during pregnancy unless clearly necessary. Contraception is also requested during treatment with IL-2 which is recommended for 5 days following Tacquell infusion. Therefore, it is expected that measures will be already in place to avoid foetal exposure for any woman of childbearing potential treated with Tacquell, strengthened further with a recommendation to verify the pregnancy status for females of childbearing potential prior Tacquell therapy.

Given the nature of the infused T cells, carcinogenicity studies are not considered necessary as the tumorigenic potential of T cells is low (EMA/CHMP/410869/2006). Furthermore, it was previously demonstrated that culture-expanded human TILs able to perform autologous tumor cell killing were free from tumor cells (Muul et al, 1987; Topalian et al, 1987), therefore not causing any potential carcinogenic risk. The absence of tumor cells and B cells is confirmed for each TM001 batch. Lastly, the available clinical data for autologous TILs do not indicate any carcinogenicity issues (Chesney et al, 2022).

Due to the nature of the product, additional studies on genotoxicity, environmental risk or other toxicity are not warranted (EMA/CHMP/410869/2006). Moreover, no safety/toxicity studies were performed for the other products used in the TM001 therapy (namely preparative non-myeloablative lymphocyte depleting chemotherapy and supportive IL-2) because these products are approved/used as previously described in the literature and in accordance to their use in the clinical setting (Dafni et al, 2019; Warner et al, 2023). Nonclinical pharmacodynamic drug interactions studies have not been performed due to lack of relevant animal models.

The CHMP endorses the CAT discussion on the non-clinical aspects as described above.

4.5.2. Conclusions

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

The CHMP endorses the CAT conclusions on the non-clinical aspects as described above.

5. Clinical aspects

5.1. Introduction

5.1.1. Good Clinical Practice (GCP) aspects

The Clinical trials were claimed by the applicant to have been performed in accordance with the ethical principles of Good Clinical Practice (GCP), according to the ICH Harmonized Tripartite Guideline.

A routine GCP inspection was performed by NL and NO for the clinical trial M14TIL. Description of the relevant concerning critical findings are provided in section 3.4.3.

Based on the review of clinical data and the above-mentioned reports, including its outcomes, the CAT and the CHMP did not identify the need for a further GCP inspection of the clinical trials included in this dossier as sufficient elements have been provided in section 2.4.3.

5.1.2. Tabular overview of clinical trials

Table 2. Clinical studies

Study ID	Enrolment status Start date	Design Control type	Study & control drugs	Population Main inclusion/ exclusion criteria
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	Total enrolment/ enrolment goal		Dose, route of administration and duration Regimen	
EudraCT nr.: 2008-008141-20 ClinicalTrials.gov nr.: NCT00937625	Completed (N=25 treated subjects) Studied Period: 2008-2014 Last enrolment date: 20AUG2014	Phase I/II Open label study	Study Product: Development TIL (Herlev) Dose: Single dose of 1E9 – 1E10 viable cells Mode of Adm.: single IV infusion Follow-up to disease progression or death	Adult patients with AJCC stage IV or unresectable stage III metastatic melanoma, good clinical performance, and a life expectancy of at least 3 months were eligible for the study. Main exclusion criteria: uveal melanoma, symptomatic brain metastases, severe comorbidities, active autoimmune disease, and chronic infections
EudraCT nr.: 2010-021885-31	(Completed N=10) Studied Period: 2010-2014 Last enrolment date: 01APR2014	Phase I/II Feasability study	Study Product: Development TIL (NKI) Dose: Single dose of 5E9 – 2E11 viable cells Mode of Adm.: single IV infusion, Follow-up at least 6 weeks	Adult patients with metastatic (stage IV) melanoma patients refractory to chemotherapy, immunotherapy and/or targeted therapy Main exclusion criteria : patients with autoimmune disease, requirement of corticosteroids, two or more CNS metastases, symptomatic CNS metastasis and inability to receive HD IL-2
2013-005406- 54/NCT02278887 - M14TIL study	Completed N=168 subjects randomized to	Phase III multicenter, open label,	Arm A: TM001 / TIL-IMP Arm B: ipilimumab	Adult patients with unresectable stage IIIC or IV

	either TM001/TIL-IMP (N=84) or ipilimumab (N=84) Last enrolment date: 28APR2022	randomized, controlled trial	Dose: 5E9 – 2E11 viable cells, single IV infusion Follow-up to disease progression or death	melanoma (86% of patients had disease refractory to anti-PD-1 treatment) Life expectancy of less than three months. Main exclusion criteria: metastatic ocular/ mucosal or other non-cutaneous melanoma; more than two CNS metastases; any CNS lesion that is symptomatic, greater than 1 cm in diameter or show significant surrounding edema on MRI scan
NCT02278887 – M14TIL side study	Completed (N=4) Enrolment between June and December 2022	Open-label Side study of phase III M14TIL trial	TM001 Dose: 5E9 – 2E11 viable cells, single IV infusion Follow-up to disease progression or until formal end-of-study (31DEC2023), whatever came first.	Adult patients with unresectable stage IIIC or IV melanoma Similar to study M14TIL
H23TIL	Ongoing Start on 15 January 2023 Interim data cut-off 06NOV2024 (N = 50) Interim data cut-off 08OCT2025 (N=91)	Open-label Hospital exemption in NL)	TM001 $\geq 10E9$ viable CD45+CD3+ T cells viable cells, single IV infusion Follow-up to disease progression or death or until 5 years after TM001 treatment, whatever comes first.	Adult patients with unresectable stage IIIC to IV melanoma Similar to study M14TIL

5.2. Clinical pharmacology

No biopharmaceutics studies nor specific clinical pharmacokinetic studies were performed for TM001. The formulation used has not been changed during the development of TM001.

Pharmacodynamics, including a description of the mechanism of action of TM001, is presented in the non-clinical part of the dossier and includes ex vivo evaluation of tumor reactive T cells in batches and peripheral blood samples of a limited set of patients from the confirmatory phase III trial (M14TIL) to assess anti-tumor reactivity, the persistence of anti-tumor reactivity, and the anti-tumor reactivity against patient-specific neoantigens and tumour-associated antigens. All *in vitro* data are included in the non-clinical section (see section 4.3).

5.2.1. Pharmacokinetics

Not applicable.

5.2.2. Pharmacodynamics

5.2.2.1. Mechanism of action

The mechanism of action of Tacquell relies on anti-tumour reactivity mediated by CD45+CD3+ T cells isolated and expanded ex vivo from a melanoma metastasis.

5.2.2.2. Primary and secondary pharmacology

See the non-clinical section 4.3

5.2.3. Pharmacokinetics/pharmacodynamics (PK/PD)

Not applicable

5.2.4. Dose selection and therapeutic window

TIL-IMP therapy

The dose of TIL-IMP administered in this study was within the standard dosage range of TIL products that have been used in previous phase I/II studies (Andersen et al, 2016, van den Berg et al, 2020).

The number of cells reached with the TIL expansion protocol varies between patients and the dose administered to patients was therefore not set on a fixed number of cells. The cells manufactured are formulated to the TIL-IMP product and should contain between $5E^9$ to $2E^{11}$ viable cells. In the confirmatory phase III trial, TM001 was dosed based on the total number of viable cells within a preset range of $5E^9$ and $2E^{11}$ cells. This dose was established following phase I/II feasibility studies (Andersen et al, 2016, van den Berg et al, 2020). Based on the results from the batches in the confirmatory phase III trial (M14TIL), the dose has been set on $\geq 10E^9$ viable CD45+CD3+ T cells, the active moiety in TM001.

Dose/response data of infused Tacquell viable CD45+CD3+ cell dose versus Best Overall Response (BOR) have also been provided concerning patients treated in the pivotal study M14TIL. (See section 5.3.1 below)

A categorical analysis has also been performed by the applicant. This evaluated the relationship between viable CD45+CD3+ cell dose and clinical outcomes, including ORR, PFS, and OS, in study M14TIL. (See section 5.3.1 below).

Preparative chemotherapy consisted of a non-myeloablative lymphodepletion (NMA-LD) regimen of cyclophosphamide (60 mg/kg/day x 2 days IV) and fludarabine (25 mg/m²/day x 5 days IV).

After TIL-IMP infusion, in-vivo outgrowth of T-cells from the TIL-IMP was supported by high dose IL-2 IV (600,000 IU/kg/dose every 8 hours) for a maximum of 5 times.

5.2.5. Overall discussion and conclusions on clinical pharmacology

5.2.5.1. Discussion

Tacquell consists of autologous viable CD45+CD3+ T cells, isolated and expanded ex vivo from a melanoma metastasis, also referred to as tumor infiltrating lymphocytes (TILs).

No biopharmaceutics studies have been performed for TM001, as this class of autologous somatic cell therapy products administered intravenously does not require bioavailability studies (EMA/CHMP/410869/2006).

No specific clinical pharmacokinetic studies were performed for TM001 (EMA/CHMP/410869/2006). Pharmacodynamics, including a description of the mechanism of action of TM001, is presented in the non-clinical section 4.3. As regards the TIL dose, no justification was provided for the dose selected for the marketing authorisation. The applicant proposed a minimum dose of 10E9 viable CD45+CD3+ cells. Compared to the cell doses administered to patients in studies M14TIL and H23TIL, 10E9 viable CD45+CD3+ cells is outside of the 1.5 IQR. Considering the lack of a clear correlation between cell dose and clinical response in combination with the lowest viable CD45+CD3+ cell dose administered to patients that had an objective response, the minimum dose of 10E9 viable CD45+CD3+ cells is insufficiently justified.

No upper dose was proposed by the applicant under the clinical aspects, which is not in line with the data provided. The highest cell dose administered to patients in the target population of the claimed indication is 46E9 in study M14TIL and 86E9 in the H23TIL HE program. An appropriate choice of a maximal dose should be based on clinical outcome in the target population.

Since IL-2 high dose may be associated with increased toxicity further, clarification has been provided regarding the administration scheme and the number of doses received by the patients in the clinical trial with an objective response (CR or PR) after Tacquell therapy. The dosing regimen for NMA-LD and IL-2 are in line with those used in previous phase I/II TIL studies and in line with their registered dosing schedule.

5.2.5.2. Conclusions

As regards the TIL dose, the Applicant proposed a dose range of $\geq 10 \times 10^9$ to 1×10^{11} viable CD3+CD45+ cells/ which is considered too wide for the reasons provided in the discussion above. The posology is therefore not acceptable at this stage.

The CHMP endorses the CAT assessment regarding the conclusions on the clinical pharmacology as described above.

5.3. Clinical efficacy

5.3.1. Dose response study

Preparative Chemotherapy Administration

One week prior to the TM001 infusion, patients were admitted to the hospital for administration of preparative non-myeloablative lymphodepleting chemotherapy, comprised of (cyclophosphamide at a dose of 60 mg per kilogram of body weight per day for 2 days intravenously, followed by fludarabine at a dose of 25 mg per square meter of body-surface area per day for 5 days intravenously).

A post hoc analysis of the administration procedure identified that in the confirmatory phase III trial (M14TIL), the treating physicians commonly proceeded with TM001 infusion with a median of approximately 37 hrs after the last fludarabine administration. Taking into account both recommendations by protocol (administration within 24-36h) as well as practical execution, infusion 24-42 hours after the last fludarabine administration can be justified.

Supportive IL-2 Administration

TM001 infusion was followed by supportive i.v. administration of IL-2 (600,000 IU per kilogram of body weight every 8 hrs). Based on clinical experience collected during the course of the confirmatory phase III trial (M14TIL), up to 5 doses IL-2 i.v could be tolerated.

The administration procedure for supportive IL-2 described in the prescribing information has been aligned with these findings.

TM001 Dose Recommendation summary efficacy

In the confirmatory phase III trial, TM001 was dosed based on the total number of viable cells within a preset range of $5E9$ and $2E11$ cells. This dose was established following phase I/II feasibility studies (Andersen et al, 2016, van den Berg et al, 2020). Based on the results from the batches in the confirmatory phase III trial (M14TIL), the dose has been set on $\geq 10E9$ viable CD45+CD3+ T cells, the active moiety in TM001.

It has been evaluated if a relationship between dose and response could be established. Within the Per Protocol Analysis Set (PPS which consisted of all patients that received treatment) of anti-PD-1 pretreated patients who received TM001 therapy at the NKI site.

The Odds Ratio (OR) is reported as just above 1 for the analyses on the M14TIL and H23TIL. Significant p value of <0.05 is only observed for the analysis on the H23TIL cohort whereas no significant p-value is provided for the analysis of the M14TIL Tacquell target population.

To further assess the relation between the Tacquell viable CD45+CD3+ cell dose range and efficacy data for the primary and selected efficacy endpoints (ORR, PFS and OS) for the Tacquell target population within M14TIL, a categorical analysis was performed by dividing patients into high versus low dose groups based on the cohort median of infused Tacquell viable CD45+CD3+ dose. In addition, a continuous analysis was performed using Cox proportional hazards models in which the Tacquell viable CD45+CD3+ cell dose was modelled per 10-unit increase to capture linear dose-outcome relationships across the full dosing range. Relation with objective response rate (ORR) was assessed using logistic regression for objective response (CR/PR) versus no objective response (SD/PD) in a categorical analysis for Tacquell dose ($>$ median vs $\leq$ median), whereas relation with progression-free survival (PFS) and overall survival (OS) was analysed using Kaplan-Meier estimates and Cox regression with right-censoring incorporated via event indicators for progression and death.

In the categorical analysis, patients receiving a Tacquell viable CD45+CD3+ cell dose above the median demonstrated a significantly higher ORR compared with those receiving a dose equal to or lower than median. The effect of the Tacquell dose on PFS and OS did not reach statistical significance with p values >0.05 . The continuous-dose analyses did not reach statistical significance.

In addition, a logistic regression analysis of viable CD45+CD3+ cells Tacquell dose administered versus best overall response (CR, PR) was performed for patients in the Tacquell target population in the

confirmatory phase III trial (M14TIL). The response probability increases with increasing dose. The logistic regression model suggests that for doses under 20E9 viable CD45+CD3+ cells, there may still be a probability of response. In view of this response potential and taken into consideration the manufacturing consistency of the phase III trial batch data, a minimal dose has been defined with an acceptance criterium set at $\geq 10E9$ viable CD45+CD3+ cells.

The applicant proposes maintaining the minimum dose of 10E9 viable CD45+CD3+ cells and proposes monitoring dosages (batch sizes) as part of the continuous process validation (CPV). The applicant proposes to re-evaluate the specifications once a statistically significant number of batches have been manufactured using the commercial process.

5.3.2. Main study

5.3.2.1. Study M14TIL

5.3.2.1.1. Study title

Randomized phase III study comparing a non-myeloablative lymphocyte depleting regimen of chemotherapy followed by infusion of tumor infiltrating lymphocytes and interleukin-2 to standard ipilimumab treatment in metastatic melanoma

5.3.2.1.2. Study design

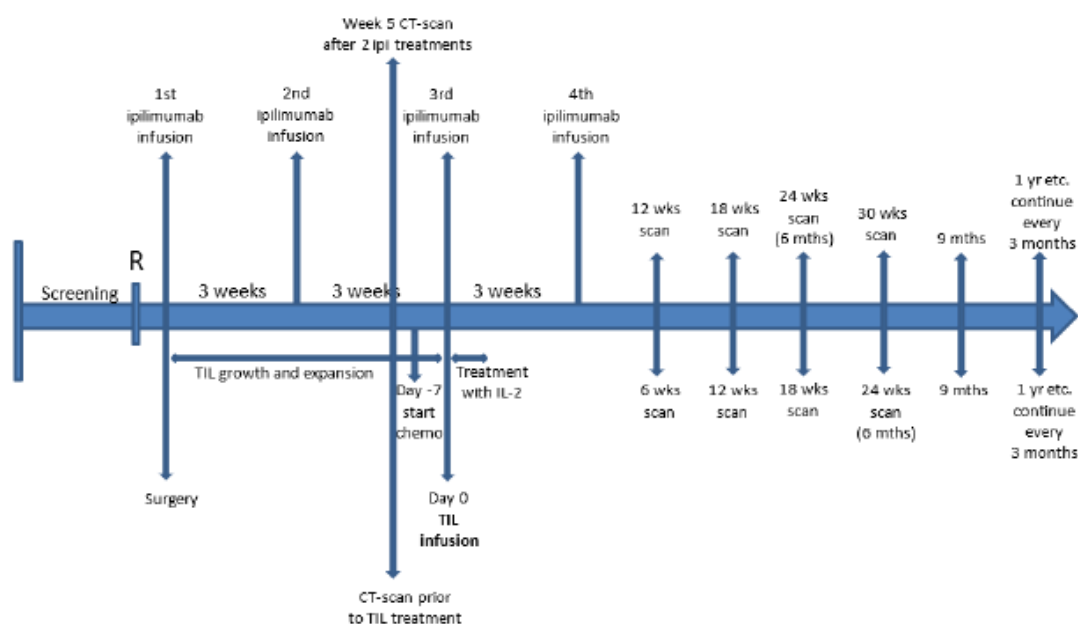
This was a Phase III multicenter, open-label, randomized trial to evaluate TIL-IMP therapy or anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) therapy (ipilimumab) administered intravenously in patients with unresectable stage IIIC to IV melanoma. A total of 168 patients were randomized in a 1:1 ratio to receive either ipilimumab or TIL-IMP therapy. The study design is illustrated in **Figure 1**.

For patients in the TIL-IMP therapy group, follow-up assessments were scheduled at 6 weeks after TIL-IMP infusion and then at 12, 18 and 24 weeks. Thereafter, every 3 months for 2 years, every 4 months the subsequent one year, every 6 months in the further subsequent 2 years, and yearly thereafter until disease progression, start of subsequent line of therapy or formal end of study.

For patients in the ipilimumab group, follow-up assessments were scheduled at 12 weeks after first ipilimumab infusion and then at 18 and 24 weeks. Thereafter, every 3 months for 2 years, one year every 4 months, 2 years every 6 months, and yearly thereafter until disease progression, start of subsequent line of therapy or formal end of study.

Figure 1. Schematic of the confirmatory phase III trial design

Arm A: Ipilimumab treatment and tumor assessments



Arm B: TIL treatment and tumor assessments

The phase III trial (M14TIL) was conducted at Het Nederlands Kanker Instituut – Antoni van Leeuwenhoek Ziekenhuis Stichting (NKI, Amsterdam, The Netherlands) and the National Center for Cancer Immune Therapy (CCIT, Copenhagen University Hospital, Herlev, Denmark).

End of Study (EOS) was defined as being 5 years after study treatment of last randomized patient or when sufficient events were available for the evaluation of OS (i.e. when >50% of patients died and median OS could be defined), whatever came first. The formal end of study was set to 31DEC2023 based on an event-driven decision (>50% patients died).

Treatment

Tumor/TIL harvest

Patients who were randomized for TIL treatment, underwent resection of a metastatic lesion to be used for growing TIL. The minimal period between surgery and TIL infusion was 4-6 weeks. This could have been longer, in case of surgery related complications. In that situation, intermediate TIL product (before rapid expansion), has been frozen. These specimens have been studied for HLA expression and melanoma antigens.

Additionally, bridging therapy was allowed between surgery and lymphodepletion for disease control, depending on the patient's clinical status.

In the TIL arm, the median time from randomisation to first metastasectomy was 10.31 days (Q1, Q3: 7.40, 14.42). The minimum time to metastasectomy was -14.52 days.

TIL-IMP therapy

The treatment schedule was according to the following scheme, comprising a course of therapy from day -7 through day 5:

NMA-LD chemotherapy regimen

- Days -7 and -6

Cyclophosphamide: 60 mg/kg/day in 500 mL 0.9% NaCl infused in one hour. Mesna, 300 mg/m² in 50 mL 0.9% NaCl was given according to the local standard for patients treated with high-dose cyclophosphamide.

- Day -5 to Day-1

Fludarabine: daily, 25 mg/m²/day (with a maximum of 50 mg/m²/day) in 50 mL 0.9% NaCl infused over 15-30 min. TIL-IMP infusion was given 24-36 hours after the last fludarabine administration.

TIL-IMP treatment

- Day 0

TIL-IMP: a dose of minimum 5E9 up to a maximum of 2E11 viable cells administered IV over 20 to 30 min.

IL-2

- Day 0 to Day 5

IL-2: 600,000 IU/kg IV over 15 min every 8 hours started within 24 hours of TIL-IMP infusion and continued for up to 5 days (maximum 5 doses). Actual body weight was used in calculating the dose of IL-2.

Re-treatment with TIL-IMP was not allowed in this study. Patients that did not respond to TIL-IMP therapy were allowed to receive IPI if indicated.

The median time between randomisation and TIL infusion was 48.59 days (Q1, Q3: 42.54, 53.69), with a minimum of 27.48 days and a maximum of 356.43 days. The applicant specified that of the 80 patients receiving TIL-IMP in the M14TIL trial, 3 patients had an interval longer than 100 days and the reasons for this have been provided (delayed response to prior therapy, which was then continued before proceeding to TIL therapy; in another patient, unsuccessful manufacture and further delay due to patient infection; and in a third patient failed manufacture followed by apparently stable disease, before new metastasectomy, manufacture and infusion of TIL product).

Patients generally remained in the hospital for 2-3 weeks. This duration was determined according to the clinical ward's specific admission and discharge procedures, as outlined in their work instructions.

IPI dose regimen

Patients randomized for IPI received IPI IV 3 mg/kg once every 3 weeks, maximal 4 times as described in the SmPC of Yervoy. Treatment modifications were made based on specified safety criteria.

Ipilimumab was delayed (up to 60 days) or discontinued if patients experienced at least one AE, following their prior dose of ipilimumab. However, no dose reductions were allowed. Retreatment with IPI upon response or durable disease stabilization $\geq$ 6 months was dependent on local reimbursement policies.

Concomitant medications

The use of systemic corticosteroids may interfere with the activity of Tacquell. The use of systemic corticosteroids was therefore not recommended in combination with Tacquell". It was therefore avoided to give systemic corticoids for the treatment of AEs after Tacquell infusion, unless absolutely required from a safety perspective. Antibiotics were allowed and used after Tacquell infusion.

Regarding the premedication, before initiation of IL-2, the use of anti-hypertensive drugs were to be discontinued. Anti-emetic treatment was planned according to local institutional guidelines.

Pneumocystis jirovecii pneumonia prophylaxis with trimethoprim/sulfamethoxazole (cotrimoxazole; 480 mg daily orally) is recommended to start at the day of Tacquell administration until 6 months after

lymphodepleting chemotherapy. It is recommended that premedication with paracetamol 6 times daily, and ranitidine 150 mg twice daily is started. Prophylactic filgrastim should be administered as of day 1 after Tacquell therapy according to standard institutional guidelines.

Randomisation

Randomization was performed via an online randomisation service.

Patients were randomized per site in a 1:1 ratio to receive either IPI or TIL-IMP therapy, with the following stratification factors: BRAF V600 mutation, line of treatment and treatment center.

Blinding

Not applicable as M14TILis an open label study.

Patient population

Main inclusion criteria:

- Histologically confirmed unresectable AJCC stage IIIC or stage IV melanoma.
- Patients had metastatic melanoma with at least one resectable metastatic lesion of sufficient size ($\geq$ 2-3 cm in total) and had to undergo such a resection for experimental purposes. Patients had received a maximum of one line of prior systemic therapy, excluding ipilimumab, for unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant melanoma therapy was permitted if it was completed at least six weeks prior to randomization, and all related adverse events (AEs) returned to baseline or stabilized.
- Patients (male and female) were $\geq$ 18 years and $\leq$ 75 years of age and had measurable disease by CT or MRI per RECIST 1.1 criteria next to the resected lesion.
- Patients had to have a clinical performance status of ECOG/WHO 0 or 1.
- Patients of both genders were willing to practice a highly effective method of birth control during treatment and for four months after receiving the preparative lymphodepleting chemotherapy regimen.
- Patients were able to understand and sign the Informed Consent Form.
- Laboratory Parameters (Note: patients might undergo resection with lab values outside of the parameters listed below if it was anticipated that the resection would correct the abnormality).
 - Hematology:
 - Absolute neutrophil count greater than $1.5 \times 10^9/L$ without support of filgrastim.
 - Platelet count greater than $100 \times 10^9/L$.
 - Hemoglobin greater than 5 mmol/L, or 80 g/L.
 - Chemistry:
 - Serum ALAT/ASAT less than 3 times the upper limit of normal, or less than 5 times ULN for patients with liver metastases.
 - Serum creatinine clearance 50 mL/min or higher.
 - Total bilirubin less than or equal to $20 \mu\text{mol/L}$, except in patients with Gilbert's Syndrome who had to have a total bilirubin less than $50 \mu\text{mol/L}$.

- LDH $\leq$ 2x ULN
- Serology:
 - Seronegative for anti-HIV antibodies (the experimental treatment evaluated in this protocol depended on an intact immune system. HIV seropositive patients could have decreased immune-competence and would thus be less responsive to the experimental treatment and more susceptible to its toxicities).
 - Seronegative for anti-hepatitis B antigen, and anti-hepatitis C antibodies. Seronegative for syphilis antibodies.
- HSV, EBV, and CMV (positivity for HSV, EBV, or CMV was not an exclusion criterion for participation, but prophylactic medication could be started when deemed necessary prior to chemotherapy treatment in case patients were randomized to the TIL-IMP treatment arm).

Main Exclusion criteria:

- Life expectancy of less than three months.
- Patients with metastatic ocular/ mucosal or other non-cutaneous melanoma.
- Adjuvant treatment with ipilimumab within 6 months prior to randomization.
- Requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressive drugs within the last 3 weeks prior to randomization.
- Patients who have more than two CNS metastases.
- Patients who have any CNS lesion that is symptomatic, greater than 1 cm in diameter or show significant surrounding edema on MRI scan will not be eligible until they have been treated and demonstrated no clinical or radiologic CNS progression for at least 2 months.
- Patients with the following factors were excluded because of inability to receive high dose interleukin-2:
 - History of coronary revascularization
 - Documented LVEF of less than 45% in patients with:
 - Clinically significant atrial and/or ventricular arrhythmias including but not limited to: atrial fibrillation, ventricular tachycardia, 2° or 3° heart block
 - Documented FEV1 less than or equal to 60% predicted for patients with:
 - A prolonged history of cigarette smoking (greater than 20 pack/year within the past 2 years)
 - Symptoms of respiratory distress
- Patients with toxicities from prior non-systemic treatment that had not recovered to grade 1 or less. Patients might have undergone minor surgical procedures or focal palliative radiotherapy (to non-target lesions) within the past 4 weeks, as long as all toxicities had recovered to grade 1 or less.
- Pregnant or breastfeeding women, because of the potentially dangerous effects of the preparative chemotherapy on the fetus or infant.
- Any active systemic infections, coagulation disorders or other active major medical illnesses.
- Any autoimmune disease: patients with a documented history of inflammatory bowel disease, including ulcerative colitis and Crohn's disease were excluded from this study, as were patients with a

history of symptomatic autoimmune disease including rheumatoid arthritis, autoimmune thyroiditis (e.g. Hashimoto's disease), autoimmune hepatitis, systemic progressive sclerosis (scleroderma), Systemic Lupus Erythematosus, and autoimmune vasculitis (e.g., Wegener's Granulomatosis). Subjects with motor neuropathy considered of autoimmune origin (e.g., Guillain-Barré Syndrome) were excluded from this study. Patients with vitiligo were eligible to enter the study.

5.3.2.1.3. Objectives and estimands

Primary objective

Primary objective

To compare progression-free survival (PFS) (according to RECIST 1.1) between patients treated with ipilimumab as compared to patients receiving TIL therapy.

Primary endpoint

PFS assessed by the investigator with the use of RECIST, version 1.1. PFS was defined as the time from randomization to first disease progression (either radiologic progression or subsequent anticancer therapy, including systemic therapy, radiotherapy, or surgery) or death.

Estimand for the primary objective

An estimands table was provided.

Table 3. Estimands table for the confirmatory phase III trial (M14TIL) in line with ICH E9 (R1) - primary objective

	POPULATION	TREATMENT	VARIABLE (ENDPOINT)	INTERCURRENT EVENTS	STRATEGY TO HANDLE IE'S	POPULATION-LEVEL SUMMARY	ESTIMAND AS RESEARCH QUESTION
PRIMARY ENDPOINT PFS – INTENTION-TO-TREAT EFFECT	Patients diagnosed with advanced melanoma. Full Analysis Set (FAS): all randomized patients; analyzed by intention-to-treat	TIL-IMP therapy versus ipilimumab	Progression-free-survival, defined as the time from randomization till progression or death from any cause		Treatment policy strategy, no censoring for when any intercurrent event occurred.	Hazard Ratio	What is the effect of TIL therapy compared to ipilimumab on progression-free-survival in adult patients diagnosed with advanced melanoma?
PRIMARY ENDPOINT PFS – LANDMARK ANALYSIS (PER PROTOCOL)	Patients diagnosed with advanced melanoma who would not progress within 5 weeks. Per-Protocol (PPS) landmark set: PFS starts at 5 weeks post-randomization; patients progressing within first 5 weeks are excluded	As above	As above	Progression within 5 weeks precluding start TIL therapy	Principal stratum estimand (landmark analysis)	As above	What would be the effect of TIL-IMP therapy compared to ipilimumab on PFS in the subpopulation of adult patients diagnosed with advanced melanoma who would not progress within 5 weeks.

Treatment discontinuation and initiation of new anticancer therapies were handled using a treatment policy strategy, with all patients analysed according to their randomised treatment group.

Statistical methods for estimation and sensitivity analysis on primary estimand<s>

The primary efficacy analysis was based on the Full Analysis Set (FAS), defined as all randomized patients analysed according to their allocated treatment. The primary estimand targeted the treatment effect on progression-free survival (PFS) from randomization to the earliest of disease progression or death, assessed per RECIST 1.1. Intercurrent events, including treatment discontinuation and initiation of new anti-cancer therapy, were handled using a treatment policy strategy. A formal estimand table was prespecified in the SAP.

The primary analysis used a stratified log-rank test and Cox proportional hazards model adjusted for stratification factors (BRAF mutation status, treatment line, and center). Additional methods included Fleming-Harrington weighted log-rank tests and Restricted Mean Survival Time (RMST) analysis, although key parameters (e.g. weight function, truncation time) were not prespecified.

No formal multiplicity adjustment was applied. Missing data were not imputed; a complete-case approach was used. No prespecified sensitivity analyses were conducted to explore the robustness of results under alternative estimand strategies or missing data assumptions. A supportive analysis was performed in the Per Protocol Set (PPS), excluding patients with early progression using a week-5 landmark approach.

Secondary objectives

Table 4. Secondary objectives and endpoints

Secondary objectives	Secondary endpoints
Progression free survival at 6 months according to RECIST 1.1	PFS at 6 months (according to RECIST 1.1)
Progression free survival according to irRC	PFS according to irRC
Overall response rate according to RECIST 1.1 and irRC	Overall response rate (ORR)
Complete response rate	Complete response rate (CRR)
Overall survival	Overall survival (OS)
Safety (according to CTCAE v 4.03).	
To evaluate the impact of TIL therapy on patient, organizational and economic consequences performed by a constructive technology assessment (CTA), including evaluation of health related Quality of Life (QoL) using a questionnaire, a semi-structured interview with patients receiving TIL therapy and with their partner or (family) caregiver, and an estimation of the incremental costs per Quality Adjusted Life Year (QALY) gained (cost-effectiveness).	

Estimands for the secondary objectives

A formal estimand table was provided for the secondary objectives (**Table 5**). The clinical questions of interest include whether TIL-IMP improves progression-free survival at 6 months (according to RECIST 1.1), progression-free survival according to irRC, overall response rate (ORR) according to RECIST 1.1 and irRC, and complete response rate (CRR) compared to ipilimumab. These endpoints were analysed in the Full Analysis Set using a treatment policy approach, i.e. patients were analysed according to their randomised treatment group, regardless of treatment discontinuation or subsequent therapies.

Table 5. Estimands table for the confirmatory phase III trial (M14TIL) in line with ICH E9 (R1) - secondary objectives

	POPULATION	TREATMENT	VARIABLE (ENDPOINT)	INTERCURRENT EVENTS	STRATEGY TO HANDLE IE'S	POPULATION-LEVEL SUMMARY	ESTIMAND AS RESEARCH QUESTION
SECONDARY ENDPOINT: PFS AT 6 MONTHS – INTENTION-TO-TREAT EFFECT	Patients diagnosed with advanced melanoma. FAS (ITT). PFS at 6m is a secondary endpoint in the protocol; analyzed on all randomized patients.	TIL-IMP therapy versus ipilimumab	Probability of being progression-free at 6 months (per RECIST 1.1)	—	Treatment-policy (analysed as randomized); no special handling beyond endpoint definition	Risk difference in P(PFS@6m) (supportive: risk ratio / odds ratio)	What is the effect of TIL-IMP therapy compared to ipilimumab on the probability of being progression-free at 6 months in adult patients diagnosed with advanced melanoma?
SECONDARY ENDPOINT: irRC PFS (PER irRC) – INTENTION-TO-TREAT EFFECT	Patients diagnosed with advanced melanoma. FAS (ITT). Endpoint specified in protocol; immune-related criteria in Appendix A	TIL-IMP therapy versus ipilimumab	Immune-related progression-free survival, per irRC	—	Treatment-policy (analysed as randomized)	Hazard Ratio	What is the effect of TIL-IMP therapy compared to ipilimumab on immune-related progression-free survival in adult patients diagnosed with advanced melanoma?

SECONDARY ENDPOINT: OVERALL SURVIVAL (OS) – INTENTION-TO-TREAT EFFECT	Patients diagnosed with advanced melanoma. FAS (ITT). OS listed as a secondary endpoint; analyzed on all randomized patients.	TIL-IMP therapy versus ipilimumab	Overall survival (time from randomization to death from any cause)	—	Treatment-policy strategy, no censoring for when any intercurrent event occurred.	Hazard Ratio	What is the effect of TIL-IMP therapy compared to ipilimumab on overall survival in adult patients diagnosed with advanced melanoma?
SECONDARY ENDPOINT: OBJECTIVE RESPONSE RATE (ORR) – INTENTION-TO-TREAT EFFECT	Patients diagnosed with advanced melanoma with measurable disease at baseline. Subset of FAS with measurable disease per RECIST/irRC definitions	TIL-IMP therapy versus ipilimumab	Best overall response CR/PR per RECIST 1.1 within the on-study response window	—	Treatment-policy (analysed as randomized)	Risk difference in response rate	What is the effect of TIL-IMP therapy compared to ipilimumab on the objective response rate in adult patients diagnosed with advanced melanoma?
SECONDARY ENDPOINT: COMPLETE RESPONSE RATE (CRR) – INTENTION-TO-TREAT EFFECT	Patients diagnosed with advanced melanoma with measurable disease at baseline. Subset of FAS with measurable disease per RECIST/irRC definitions (same operational rules as for ORR).	TIL-IMP therapy versus ipilimumab	Complete response (CR) per RECIST 1.1 within the on-study response window	—	Treatment-policy (analysed as randomized)	Risk difference in CR rate	What is the effect of TIL-IMP therapy compared to ipilimumab on the complete response rate in adult patients diagnosed with advanced melanoma?

	POPULATION	TREATMENT	VARIABLE (ENDPOINT)	INTERCURRENT EVENTS	STRATEGY TO HANDLE IE'S	POPULATION-LEVEL SUMMARY	ESTIMAND AS RESEARCH QUESTION
SAFETY ENDPOINT: TEAEs/SAEs – SAFETY SET	Safety Analysis Set (patients receiving ≥1 dose; in TIL arm, summaries pre- and post-infusion). Safety population (protocol v10): safety “evaluated from day of randomization”; in TIL-IMP arm pre- vs post-infusion reported separately.	As treated	Incidence and severity of TEAEs/SAEs (CTCAE v4.03)	—	Descriptive summaries within the safety set	Incidence / grade distribution	What is the incidence and severity of treatment-emergent adverse events for TIL-IMP therapy compared to ipilimumab?

FAS full analysis set; ITT intention to treat; PPS per protocol set; PFS progression free survival; OS overall survival; CR complete response; PR partial response; irRC immune-related response criteria

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Secondary analyses were conducted using standard statistical methods. PFS at 6 months, ORR, and CRR were analysed as binary endpoints using Fisher’s exact test. PFS according to irRC and OS were analysed using stratified log-rank tests and Cox proportional hazards models. All secondary endpoints were assessed in the Full Analysis Set. No formal multiplicity adjustment or hierarchical testing strategy was applied. Missing data were handled via a complete-case approach without imputation. No sensitivity or supplementary analyses were performed to assess the robustness of the secondary estimands.

5.3.2.1.4. Results

Participant flow and numbers analysed

Number analysed

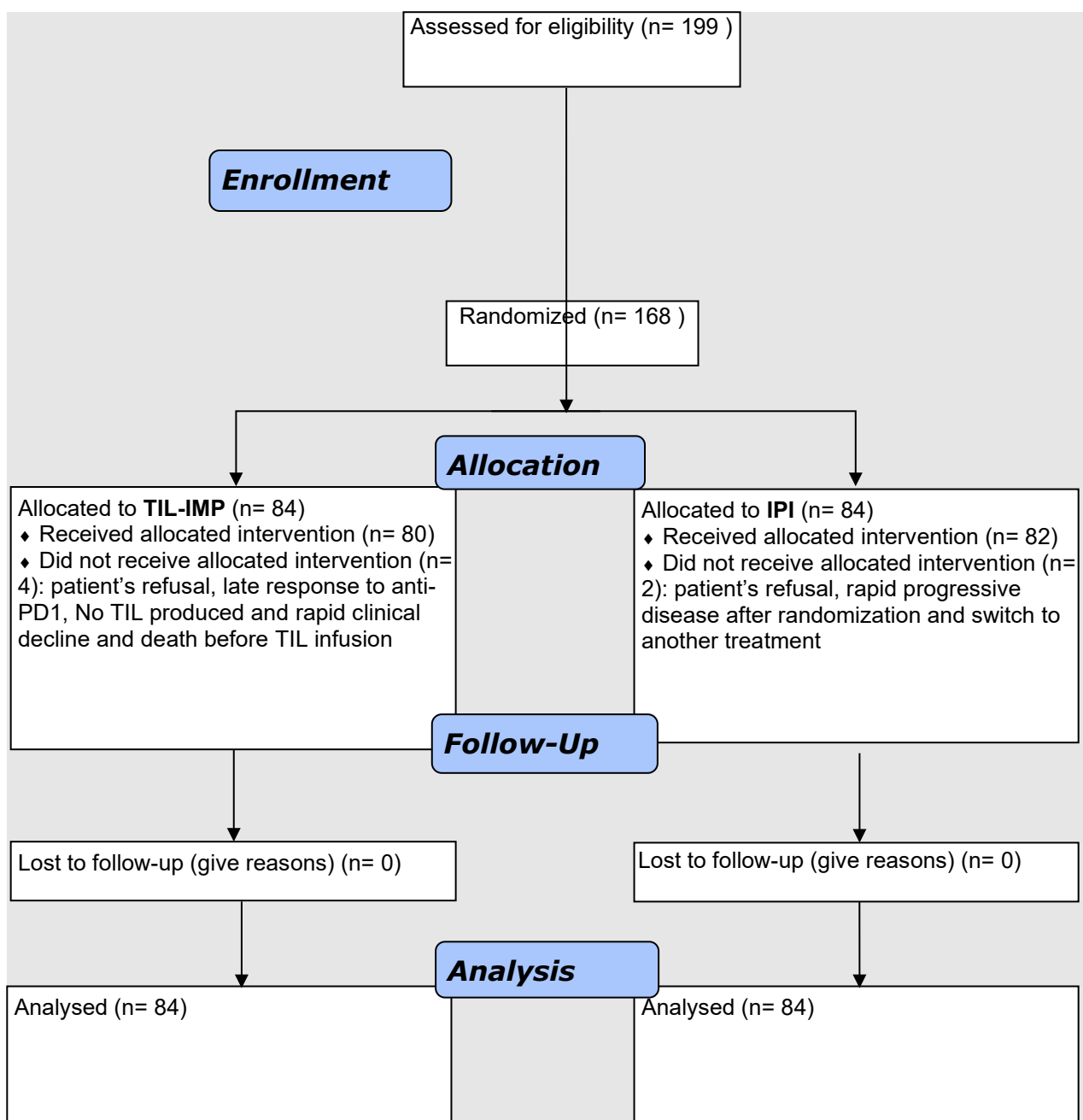
The study initiation date (First patient enrolled) is 23 September 2014

The study completion date (Last patient completed) is 31 December 2023

The initial analysis of the study results was event-driven and performed with data cut-off point June 9, 2022 (first evaluation point of last enrolled patient, 6 weeks after randomization)

The end-of-study analysis was performed with data cut-off at 31 December 2023 since at that time sufficient events were available for evaluation of OS (event-driven).

Figure 2. Participant flow



31 patients had screening failures most of which (n=17) were due to rapidly progressive disease or new CNS metastases, 6 patients presented with non-resectable lesion of sufficient size or of difficult collection and 8 patients due to other reason including remission of tumour, cardiac risk, decreased pulmonary function etc.

In the TIL-IMP arm 80 patients received TIL-IMP infusion and in the IPI arm 82 patients received at least one IPI treatment.

Four patients in the TIL-IMP arm did not receive TIL-IMP therapy, 1 patient refused the TIL-IMP therapy (patient decision), 1 patient showed a late response to prior anti-PD-1 treatment, for 1 patient no TIL-IMP could be produced and 1 patient showed rapid clinical decline and died before start of TIL-IMP therapy. These patients were part of the total of 84 patients included in the ITT analysis (FAS population). All dosed patients in the TIL-IMP arm completed TIL-IMP therapy.

Two patients in the IPI arm did not receive IPI, 1 patient refused the IPI treatment (patient decision) and 1 patient showed rapid progressive disease after randomization and was switched to another treatment. These patients were part of the total of 84 patients included in the ITT analysis (FAS population). 44 patients randomised to the IPI arm did not complete the full IPI treatment schedule. Only 47.62% of patients completed all four cycles of ipilimumab treatment according to protocol.

An overview of the reasons for which patients discontinued IPI treatment (FAS population) is given in Table 6.

Table 6. Reason for end of IPI treatment – total group IPI arm (FAS population)

	IPI (N=84)
Reason end of treatment	N (%)
According to protocol	40 (47.62%)
Disease progression	15 (17.86%)
Toxicity	26 (30.95%)
Patients refusal	2 (2.38%)
Other	1 (1.19%)

Data: Table 9 M14TIL final report NL DK – adjusted based on review of safety data

An overview of the reasons for which patients at the NKI discontinued IPI treatment (modified FAS population) is given in Table 7.

Table 7. Reason for end of IPI treatment –IPI arm NKI site (modified FAS population)

	IPI (N=66)
Reason end of treatment	N (%)
According to protocol	30 (45.45%)
Disease progression	10 (15.15%)
Toxicity	23 (34.85%)
Patients refusal	2 (3.03%)
Other	1 (1.52%)

Data: Table 9 M14TIL_final_report_NL – adjusted based on review safety data

In the confirmatory phase III trial (M14TIL), TIL-IMP was manufactured at two Dutch sites and one Danish site. A post-trial product quality comparability analysis showed that the manufacturing process between the Dutch manufacturing sites and the Danish manufacturing site revealed differences on a product quality level, leading to the conclusion that the manufacturing processes between the three sites differ, and only the 2 Dutch sites are considered comparable by the Applicant. For this reason, a distinction has been made between TIL-IMP (any TIL product administered in the confirmatory phase III trial) and TM001 (the TIL-IMP product manufactured by the Dutch sites being the subject of this marketing authorization application).

An overview of patient numbers in the confirmatory phase III trial in relation to treatment received, clinical site of trial, and prior anti-PD-1 treatment is provided in Table 8.

The subset to evaluate the efficacy pertinent to the proposed indication and the to-be-marketed product (TM001) is referred as the *TM001 Efficacy Analysis Set*. This set (mITT) is the primary focus for the analysis and includes the patients randomized to (FAS, N=59) and treated with (PPS, N=57) TM001 at the NKI clinical site that received prior anti-PD-1 treatment.

Table 8. Patient numbers in the confirmatory phase III trial M14TIL

	NKI site	CCIT site	TOTAL
Nr of patients included (FAS/ITT)	132 TM001 : 66 IPI : 66	36 TIL-IMP : 18 IPI : 18	168 TM001/TIL-IMP : 84 IPI : 84
Nr of patients treated (PPS)	128 TM001 : 64 IPI : 64	34 TIL-IMP : 16 IPI : 18	162 TM001/TIL-IMP : 80 IPI : 82
Nr of patients with prior anti-PD-1 treatment included (FAS)	117 TM001 : 59 IPI : 58	28 TIL-IMP : 14 IPI : 14	145 TM001/TIL-IMP : 73 IPI : 72
Nr of patients with prior anti-PD-1 treatment treated (PPS)	114 TM001 : 57 IPI : 57	26 TIL-IMP : 12 IPI : 14	140 TM001/TIL-IMP : 69 IPI : 71

FAS: full analysis set; ITT: intention to treat; PPS: per protocol analysis set

For patients treated at both NKI and CCIT sites: at time of data cutoff on 31 December 2023, the overall median follow-up time for all 168 patients (FAS) was 52.42 months (95% Confidence Interval [CI] = 46.14 - 58.56), being 55.80 months (95% CI, 45.52 - 70.92) and 49.95 months (95% CI, 42.37 to 58.56) in the TIL-IMP and IPI arm, respectively.

For the patients from the NKI site, previously treated with anti-PD-1, at time of data cut-off, the overall median follow-up time was 45.52 months (95% CI = 38.62 - 54.82), being 45.52 months (95% CI, 38.98 - 60.37) and 42.37 months (85% CI, 37.20 - 57.64) in the TM001 and IPI arm, respectively.

Deviations from study plan

As regards the protocol deviations, 12 patients were listed in this submitted data without specifying which treatments were received. Three important deviations were reported related to SAE reporting at multiples dates, efficacy assessment and tumor measurement assessment. The others were classified as minors. In the IPI arm, there were 2 male patients older than 75 years. According to the investigator these patients were physically able to undergo treatment.

Baseline data

Table 9. Baseline characteristics of the patients (FAS) – NKI and CCIT sites

	A= standard ipilimumab (N=84)	B= TIL (N=84)	Total (N=168)
Gender			
Male	53 (63.10%)	47 (55.95%)	100 (59.52%)
Female	31 (36.90%)	37 (44.05%)	68 (40.48%)
Age in years			
Median	58.50	59.00	59.00
Min - Max	30.00 - 77.00	26.00 - 74.00	26.00 - 77.00
BRAF V600 mutation			
no	48 (57.14%)	47 (55.95%)	95 (56.55%)
yes	36 (42.86%)	37 (44.05%)	73 (43.45%)
Who status			
0	70 (83.33%)	69 (82.14%)	139 (82.74%)
1	14 (16.67%)	15 (17.86%)	29 (17.26%)
Stage at study entry			
IV	82 (97.62%)	82 (97.62%)	164 (97.62%)
Irresectable IIIc	2 (2.38%)	2 (2.38%)	4 (2.38%)
LDH screening <ULN			
0= no	14 (16.67%)	17 (20.24%)	31 (18.45%)
1= yes	70 (83.33%)	67 (79.76%)	137 (81.55%)
LDH screening 1-2x ULN			
0= no	70 (83.33%)	67 (79.76%)	137 (81.55%)
1= yes	14 (16.67%)	17 (20.24%)	31 (18.45%)
Smoking status			
No	49 (58.33%)	46 (54.76%)	95 (56.55%)
yes, smoker	11 (13.10%)	9 (10.71%)	20 (11.90%)
yes, ex-smoker	24 (28.57%)	29 (34.52%)	53 (31.55%)
Prior systemic therapies			
None	10 (11.90%)	9 (10.71%)	19 (11.31%)
Adjuvant PD-1	23 (27.38%)	17 (20.24%)	40 (23.81%)
Firstline anti-PD-1	49 (58.33%)	56 (66.67%)	105 (62.50%)
Other	2 (2.38%)	2 (2.38%)	4 (2.38%)

Due to the non-comparability of TIL-IMP manufactured for the NKI and CCIT site and considering that the proposed indication for TM001 will be second-line treatment after anti-PD-1 either as first-line or (neo)adjuvant treatment, results are also presented for the patients at the NKI site that had received prior anti-PD-1 treatment before TM001 or IPI treatment.

Table 10. Baseline characteristics anti-PD-1 pretreated patients - NKI site

	A= standard ipilimumab (N=58)	B= TM001 (N=59)	Total (N=117)
Gender			
Male	38 (65.52%)	34 (57.63%)	72 (61.54%)
Female	20 (34.48%)	25 (42.37%)	45 (38.46%)
Age in years			
Mean (SD)	58.26 (11.13)	59.80 (9.45)	59.03 (10.30)
Median	58.50	61.00	61.00
	A= standard ipilimumab (N=58)	B= TM001 (N=59)	Total (N=117)
Q1,Q3	52.00, 67.00	54.00, 67.50	53.00, 67.00
Min - Max	36.00 - 77.00	29.00 - 74.00	29.00 - 77.00
First line of treatment			
no	55 (94.83%)	56 (94.92%)	111 (94.87%)
yes	3 (5.17%)	3 (5.08%)	6 (5.13%)
First line of treatment - corrected			
no	58 (100.00%)	59 (100.00%)	117 (100.00%)
yes	0 (0.00%)	0 (0.00%)	0 (0.00%)
BRAF V600 mutation			
no	35 (60.34%)	32 (54.24%)	67 (57.26%)
yes	23 (39.66%)	27 (45.76%)	50 (42.74%)
Who status			
0	47 (81.03%)	47 (79.66%)	94 (80.34%)
1	11 (18.97%)	12 (20.34%)	23 (19.66%)
Stage at study entry			
IV	58 (100.00%)	58 (98.31%)	116 (99.15%)
Irresectable IIIc	0 (0.00%)	1 (1.69%)	1 (0.85%)

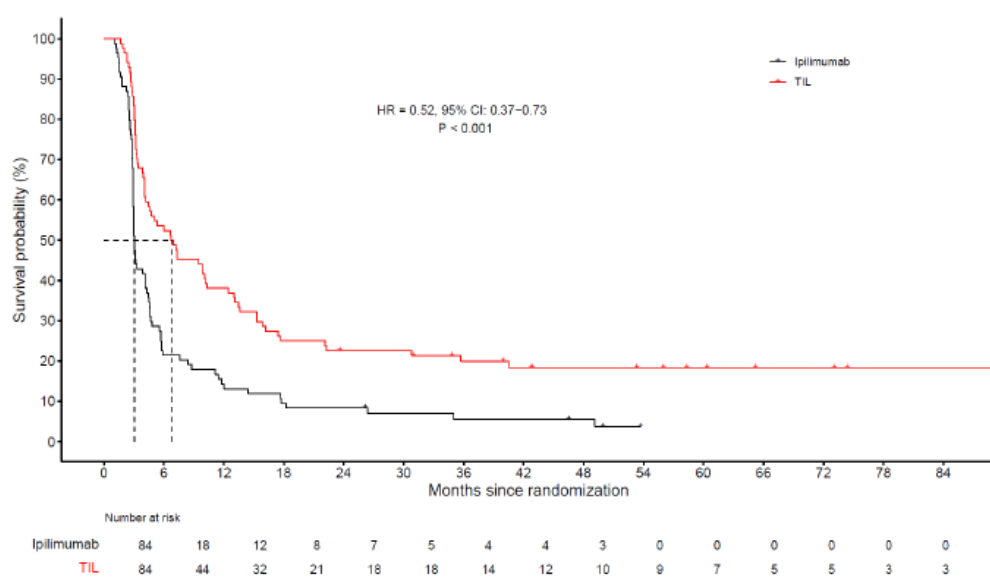
LDH screening <ULN			
0= no	9 (15.52%)	13 (22.03%)	22 (18.80%)
1= yes	49 (84.48%)	46 (77.97%)	95 (81.20%)
LDH screening 1-2x ULN			
0= no	49 (84.48%)	46 (77.97%)	95 (81.20%)
1= yes	9 (15.52%)	13 (22.03%)	22 (18.80%)
Smoking status			
No	33 (56.90%)	28 (47.46%)	61 (52.14%)
yes, smoker	8 (13.79%)	7 (11.86%)	15 (12.82%)
yes, ex-smoker	17 (29.31%)	24 (40.68%)	41 (35.04%)
Prior systemic therapies			
None	0 (0.00%)	0 (0.00%)	0 (0.00%)
Adjuvant PD1	17 (29.31%)	14 (23.73%)	31 (26.50%)
Firstline antiPD1	41 (70.69%)	45 (76.27%)	86 (73.50%)
Other	0 (0.00%)	0 (0.00%)	0 (0.00%)

Outcomes and estimation

Primary Endpoint - Progression free survival (PFS)

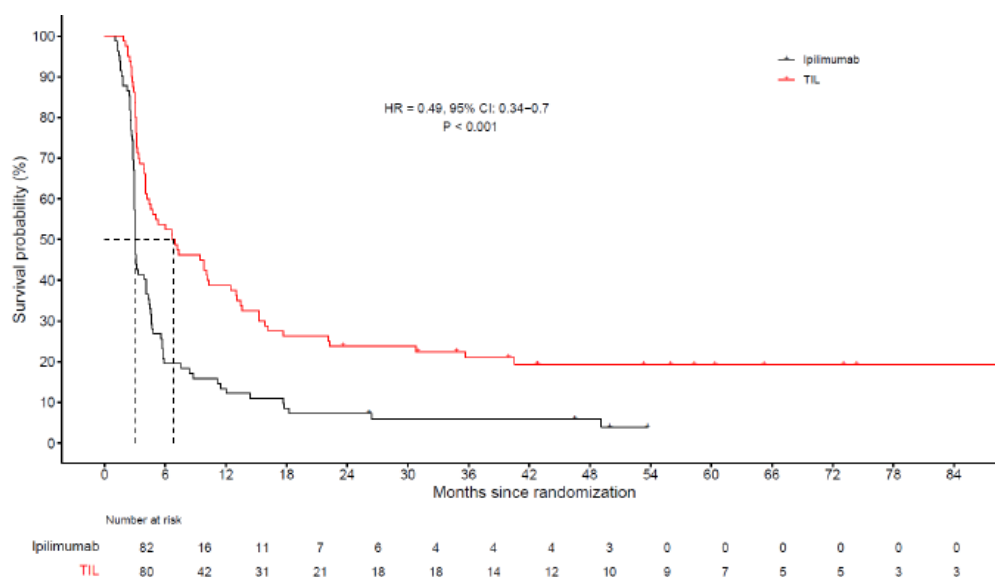
In the FAS (ITT population (N=168)) the median PFS assessed according to RECIST was 6.81 months (95% CI, 4.19 - 12.47) in the TIL-IMP arm, compared to 3.06 (95% CI, 2.97 - 4.32) months in the IPI arm. The complete PFS curves are shown in **Figure 3**.

Figure 3. PFS – FAS population total group (NKI and CCIT site)



The complete PFS curves for the PPS population are shown in **Figure 4** below.

Figure 4. Progression free survival – PPS population total group (NKI and CCIT site)



A significant difference in PFS between ipilimumab and TIL in favor of TIL ($\chi^2 = 8.69$, $p = 0.003$) was observed when using the Fleming-Harrington weighted log rank test. In the RMST analysis, the restricted mean survival time for the ipilimumab arm was 7.9 months and for the TIL arm was 16.7 ($p = 3.96 \times 10^{-4}$).

Results for the primary endpoint progression free survival (PFS) in the modified ITT and/or modified FAS (patients who were treated at NKI site and who received prior anti-PD1) are summarized in Table 11 and the PFS curves are shown in Figure 5.

Figure 5. Progression Free Survival – modified ITT - Phase III trial (M14TIL)

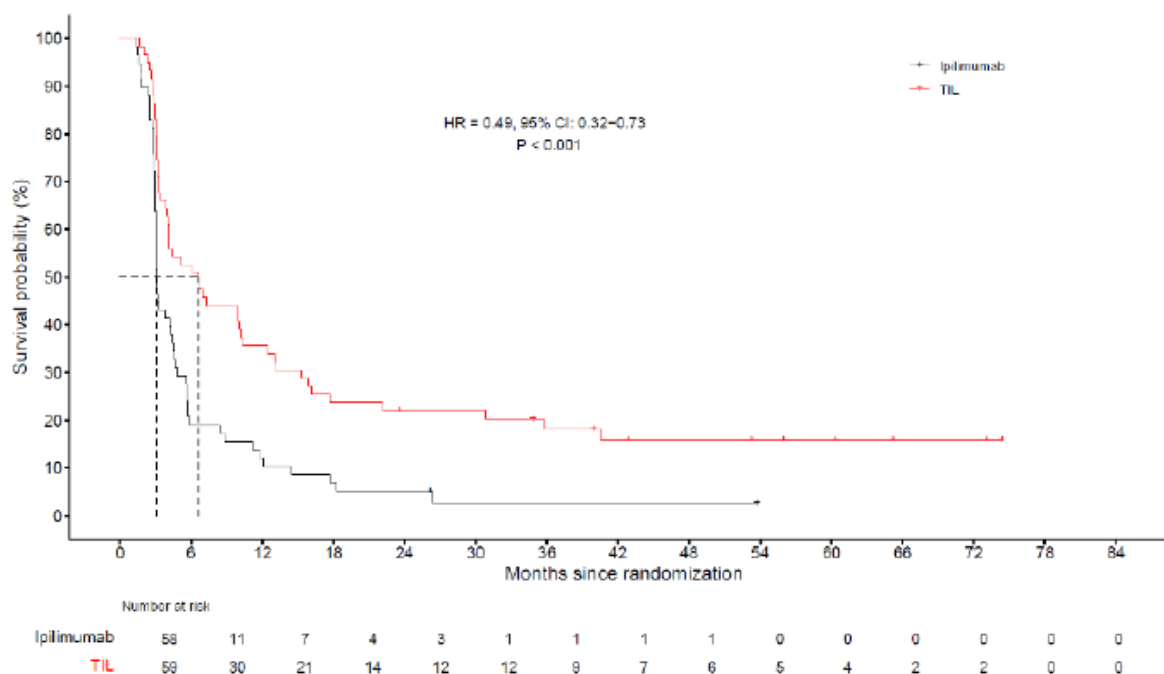
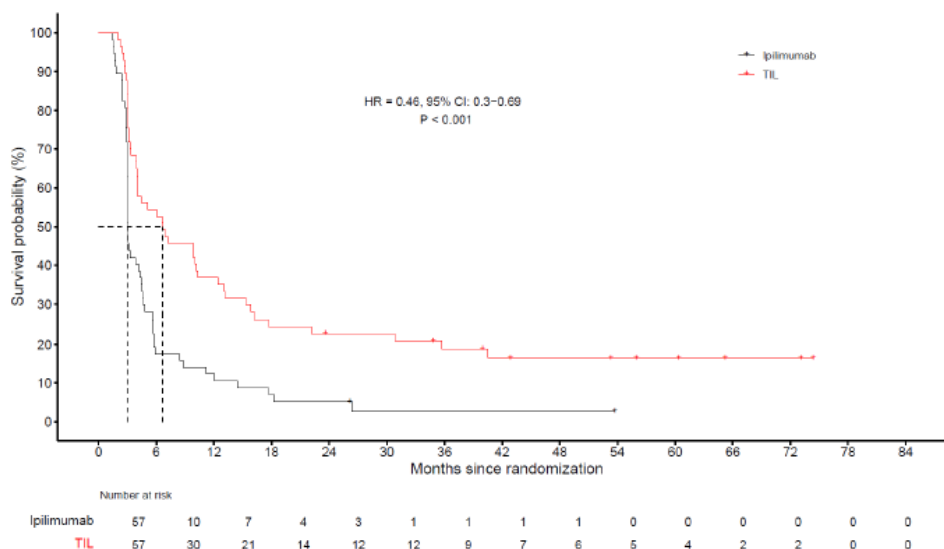


Table 11. Progression Free Survival – modified ITT - Phase III trial (M14TIL)

	TM001	IPI
RECIST 1.1		
Median PFS (months)	6.65	3.08
Confidence interval	4.06 – 12.47	3.01 – 4.48

For the PPS the median PFS assessed according to RECIST was 6.68 months (95% CI, 4.09 - 12.47) in the TM001 arm, compared to 3.07 (95% CI, 3.01 - 4.42) months in the IPI group. The complete PFS curves for the PPS population are shown in Figure 6.

Figure 6. PFS – PPS population anti-PD-1 pretreated patients – NKI site

Secondary endpoint: PFS at six months and PFS according to irRC

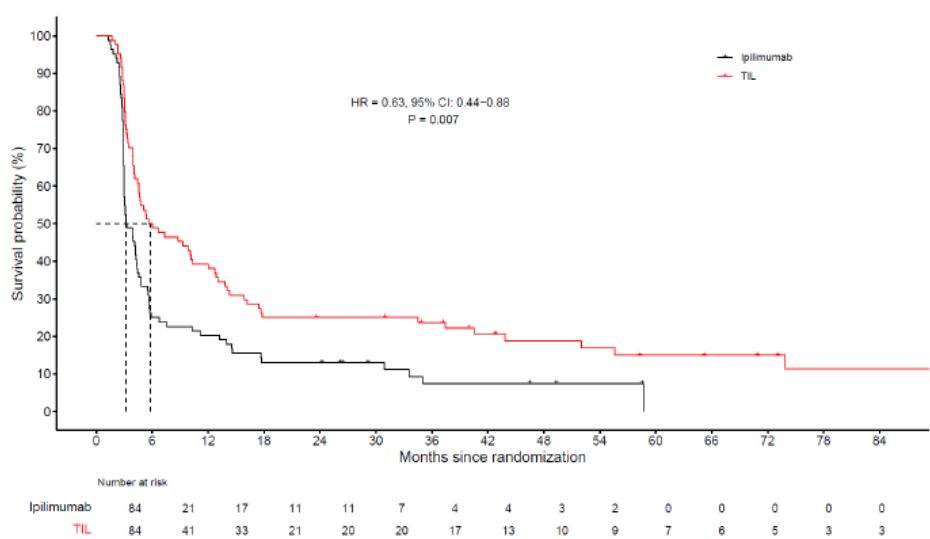
In the FAS/ITT, the 6-month PFS event-free rate was 21.4% (95%CI: 14.23-32.27) in the ipilimumab arm and 52.4% (95%CI: 42.72-64.23) in the TIL arm. PFS at six months for the PPS population was 52.5% (95% CI, 42.62 - 64.67) in the TIL-IMP arm and 19.5% (95% CI, 12.57 - 30.28) in the IPI arm. PFS according to irRC was similar to PFS per RECIST

The median (in months) as well as the PFS at 6 months (in %) according to irRC for the TIL-IMP and the IPI arm is shown in **Table 12** below.

Table 12. PFS according to irRC – FAS population total group (NKI and CCIT site)

	Median PFS (months)	95% Low	95% High	6 Month PFS (%)	95% Low	95% High
A = standard ipilimumab	3.22	3.01	4.42	25.00	17.26	36.21
B = TIL	5.82	4.58	12.73	48.81	39.21	60.76

Figure 7. PFS according to irRC - FAS population total group (NKI and CCIT site)

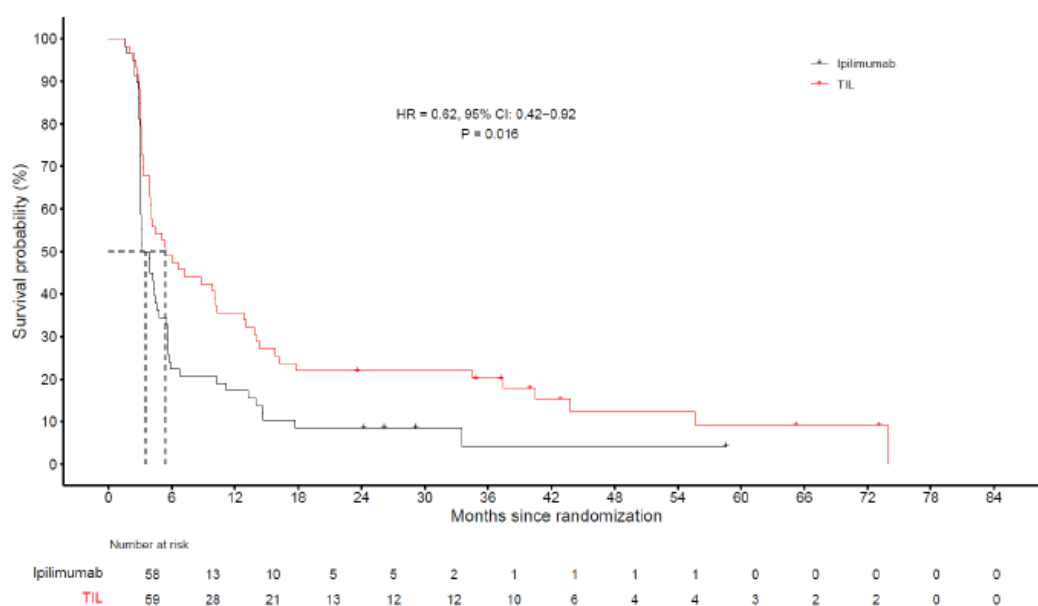


Results for the PFS secondary endpoints in the modified ITT Efficacy (patients treated at NKI site who received prior anti-PD1) are summarized in **Table 13**

Table 13. Progression Free Survival – modified ITT - Phase III trial (M14TIL)

	TM001	IPI
RECIST 1.1		
PFS at six months (%)	50.85	18.97
Confidence interval	39.57 – 65.35	11.14 – 32.28
irRC		
PFS (months)	5.40	3.55
Confidence interval	3.96 – 12.83	3.03 – 4.84
PFS at 6 months (%)	47.46	22.41
Confidence interval	36.28 – 62.07	13.89 – 36.18

The complete PFS curves for the modified ITT according to irRC are shown in Figure 8.

Figure 8. PFS according to irRC – modified ITT (NKI site)

Secondary Endpoint: Complete Response Rate and Objective Response Rate

Response was assessed according to RECIST version 1.1, according to the investigator review.

The results of the best overall response in the FAS population are presented in **Table 14**.

Table 14. Best OR and ORR FAS population total group (NKI and CCIT site)

Variable	IPI arm (N=84)	TIL-IMP arm (N=84)
Best overall response		
CR		
No. of patients	7	17
Percentage of patients (95% CI)	8.33% (3.4 - 16.4)	20.24% (12.3 - 30.4)
PR		
No. of patients	11	25
Percentage of patients (95% CI)	13.10% (6.7 - 22.2)	29.76% (20.3 - 40.7)
SD		
No. of patients	15	15
Percentage of patients (95% CI)	17.86% (10.4 - 27.7)	17.86% (10.4 - 27.7)
PD		
No. of patients	40	25
Percentage of patients (95% CI)	47.62% (36.6 - 58.8)	29.76% (20.3 - 40.7)
NE		
No. of patients	1	0
Percentage of patients (95% CI)	1.19% (0 - 6.5)	0.00% (0 - 4.3)
ND		
No. of patients	10	2
Percentage of patients (95% CI)	11.90% (5.9 - 20.8)	2.38% (0.3 - 8.3)
Objective response rate (CR+PR)		
No. of patients	18	42
Percentage of patients (95% CI)	21.43% (13.2 - 31.7)	50.00% (38.9 - 61.1)

Data: Table 26 1_M14TIL_final_report_NL_DK

Results for the best overall response (RECIST 1.1) and the secondary endpoints Complete Response Rate (CRR) and Objective Response Rate (ORR) in the modified ITT (patients who were treated at NKI site who received anti-PD1) are summarized in Table 15. The response duration is shown in Figure 9.

Table 15. Best Overall Response–modified ITT - Phase III trial (M14TIL)

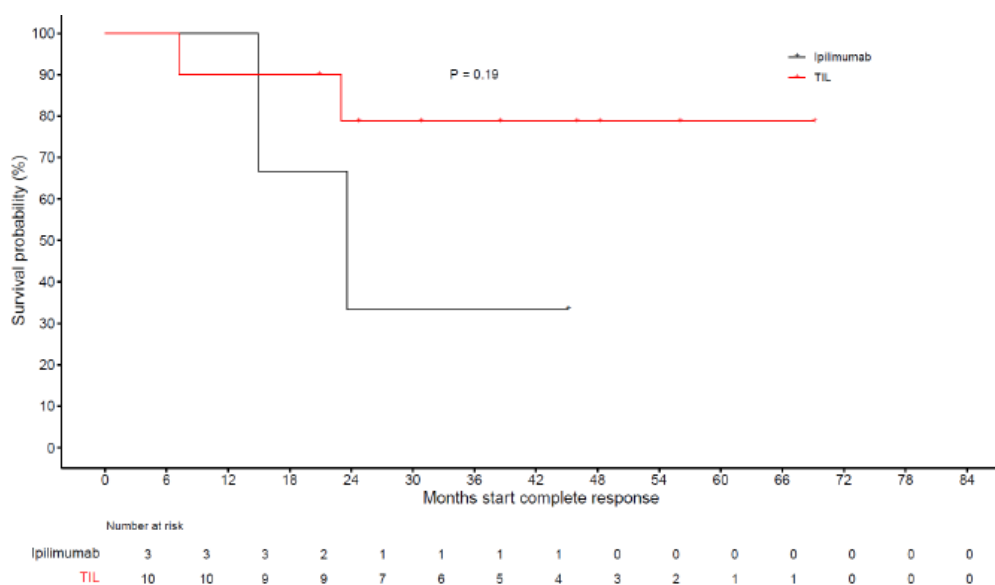
Variable	TM001 arm (N=59)	IPI arm (N=58)
Best Overall Response		
CR		
No. of patients	10	3
Percentage of patients (95% CI)	16.95% (8.4 to 29.0)	5.17% (1.1 to 14.4)
PR		
No. of patients	19	9
Percentage of patients (95% CI)	32.20% (20.6 to 45.6)	15.52% (7.3 to 27.4)
SD		
No. of patients	9	10
Percentage of patients (95% CI)	15.25% (7.2 to 27.0)	17.24% (8.6 to 29.4)
PD		
No. of patients	20	29
Percentage of patients (95% CI)	33.90% (22.1 to 47.4)	50.00% (36.6 to 63.4)
NE		
No. of patients	0	1
Percentage of patients (95% CI)	0.00% (0.0 to 6.1)	1.72% (0 to 9.2)
ND		
No. of patients	1	6
Percentage of patients (95% CI)	1.69% (0.0 to 9.1)	10.34% (3.9 to 21.2)
Objective Response		
ORR = CR and PR		
No. of patients	29	12
Percentage of patients (95% CI)	49.15% (35.9 to 62.5)	20.69% (11.2 to 33.4)
Clinical Benefit = CR, PR and SD		
No. of patients	38	22
Percentage of patients (95% CI)	64.41% (50.9 to 76.4)	37.93% (25.5 to 51.6)

Duration of response

Median DOR for FAS was 392.5 days (Q1, Q3: 202.75, 1221.75), i.e. approximately 13.1 months in the TIL-IMP arm and 359.5 days (Q1, Q3: 168.5, 900.25), i.e. approximately 12.0 months in the ipilimumab arm.

Median DOR in the modified ITT was 340 days (Q1, Q3: 127, 1049), i.e. approximately 11.3 months in the TIL-IMP arm and 243.5 days (Q1, Q3: 145.5, 517.75), i.e. approximately 8.10 months in the ipilimumab arm.

Figure 9. Response Duration until Progression or Death for Patients in the modified ITT with a Complete Response - Phase III trial (M14TIL)

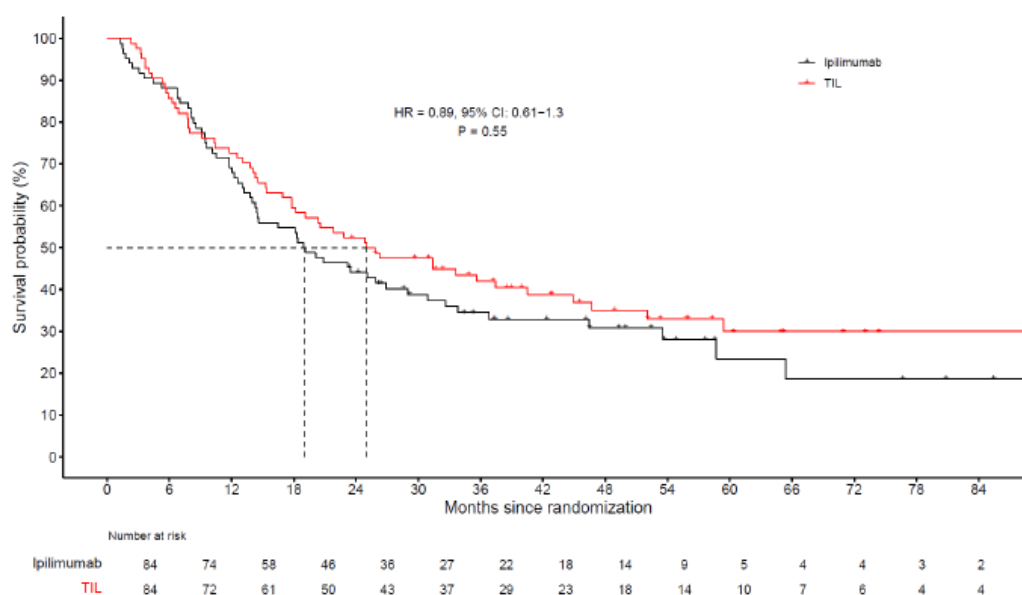


Secondary endpoint: Overall survival

Median overall survival (FAS/ITT population) was 25.04 months (95% CI, 17.82 - 44.93) in the TIL-IMP arm compared to 19.04 months (95% CI, 14.31 - 30.90) in the IPI arm.

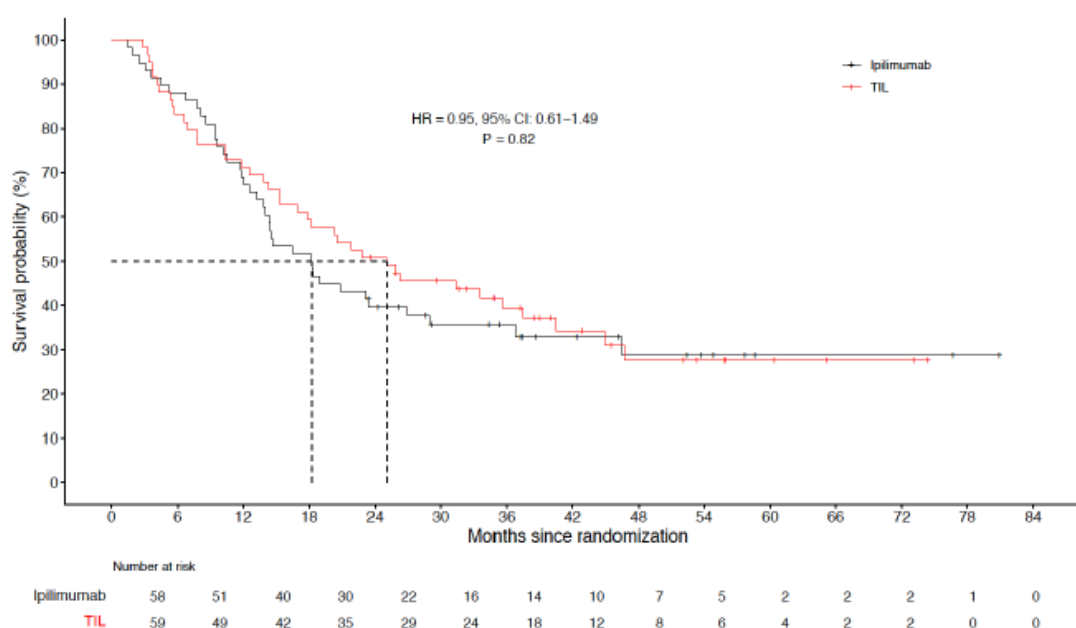
Complete overall survival curves are shown in **Figure 10**.

Figure 10. OS – FAS population total group (NKI and CCIT site)



The overall survival (OS) in the modified ITT (patients who were treated at NKI site who received prior anti-PD1) is 25.04 months (95% CI, 16.90 - 44.93) in the TIL-IMP arm, 18.22 months (95% CI, 13.98 - 36.81) in the ipilimumab arm and is shown in Figure 11.

Figure 11. Overall Survival – modified ITT – Phase III trial (M14TIL)



Clinical Study Report M14TIL Figure 12
TIL=TM001

Quality of Life (NKI and CCIT sites)

An additional analysis was performed to assess the health-related quality of life (HRQoL) in patients with metastatic melanoma treated with TIL-IMP or ipilimumab (IPI). HRQoL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care (EORTC QLQ-C15-PAL), EuroQol 5D-3L (EQ-5D), and the Impact of Event Scale (IES). Of 168 patients randomized 1:1, 143 responded to the baseline questionnaire (88% response rate). Of

these, 75 (89%) were in the TIL-IMP arm and 73 (87%) in the IPI arm. TIL-IMP-treated patients reported higher global health status scores at week 24 compared to ipilimumab-treated patients (78.2 vs 73.9; $p < 0.05$) and emotional functioning (85.9 vs 77.9; $p < 0.05$). Patients treated with TIL-IMP had significantly lower fatigue (25.0 vs 32.4; $p < 0.05$) and pain (13.7 vs 17.6; $p < 0.05$) scores at week 24, but marginal higher nausea & vomiting (7.5 vs 5.2; $p < 0.05$) symptom scores. EQ-5D scores were also higher in the TIL-IMP-group (0.89 vs. 0.83; $p < 0.05$). These statistically significant differences were not considered clinically meaningful. The hypothesized higher impact of the more intensive TIL-IMP-treatment compared to IPI was not observed, according to IES scores (11.8 vs. 17.4; $p < 0.05$ at 24 weeks).

Pre-defined and post-hoc subgroup analyses

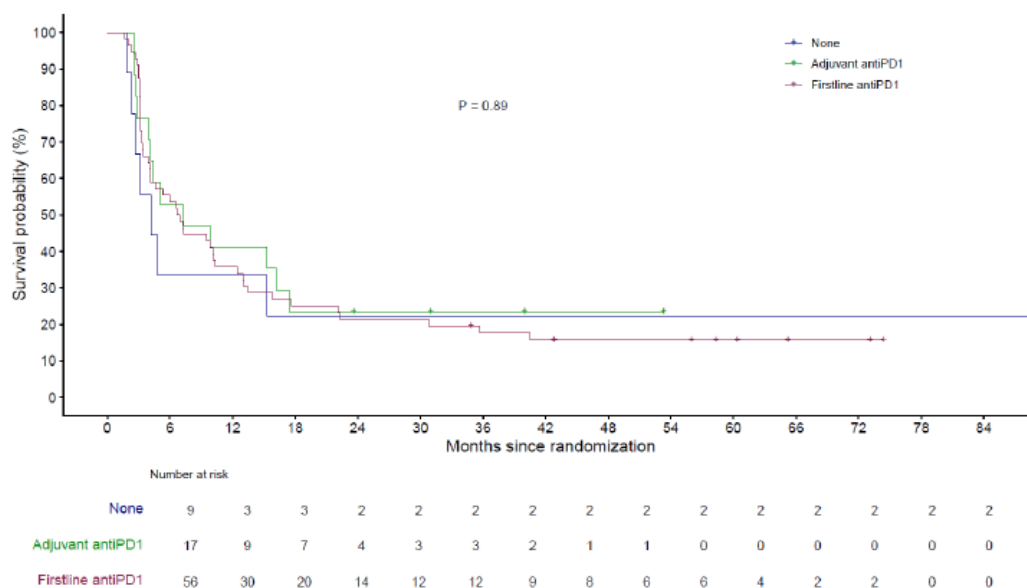
Use of an "Efficacy Subset" of Patients (NKI and CCIT sites)

An efficacy analysis of TIL-IMP therapy in treatment naive versus adjuvant/neoadjuvant anti-PD-1 pre-treated patients (patients treated at NKI and CCIT sites) was performed:

✓ PFS TIL-IMP patients (NKI and CCIT site) – by prior anti-PD-1 treatment

A subgroup analysis was performed on PFS according to RECIST 1.1 in patients (FAS, including patients at NKI or CCIT site) randomized for TIL-IMP based on no prior systemic therapy, adjuvant anti-PD-1 therapy or first-line anti-PD-1 as prior treatment (**Figure 12**).

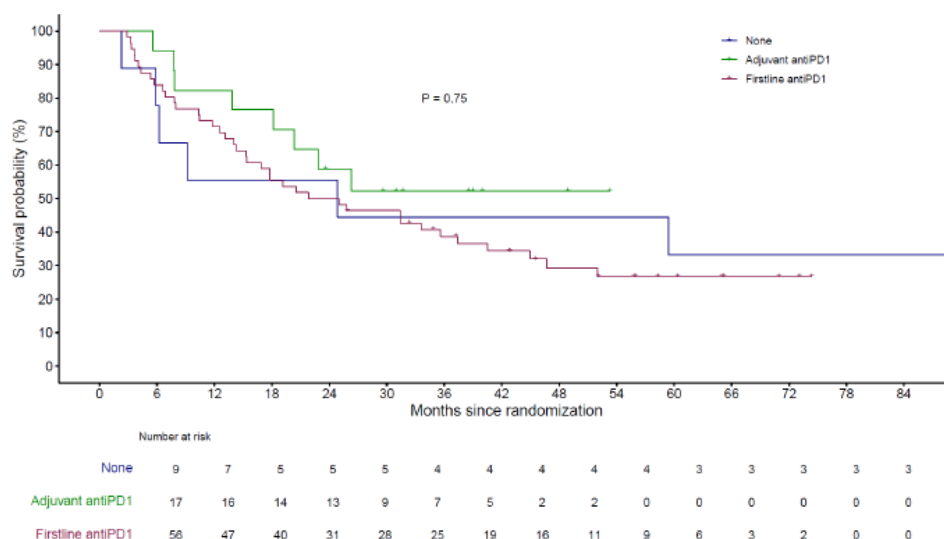
Figure 12. PFS TIL-IMP patients FAS population (NKI and CCIT site) – by prior anti-PD-1 treatment



✓ OS TIL-IMP patients (NKI and CCIT site) – by prior anti-PD-1 treatment

In addition, an analysis based on no prior systemic therapy, adjuvant anti-PD-1 therapy or first-line anti-PD-1 as prior treatment was performed on the OS in patients (total FAS including patients treated at the NKI or CCIT site) randomized for TIL-IMP (**Figure 13**).

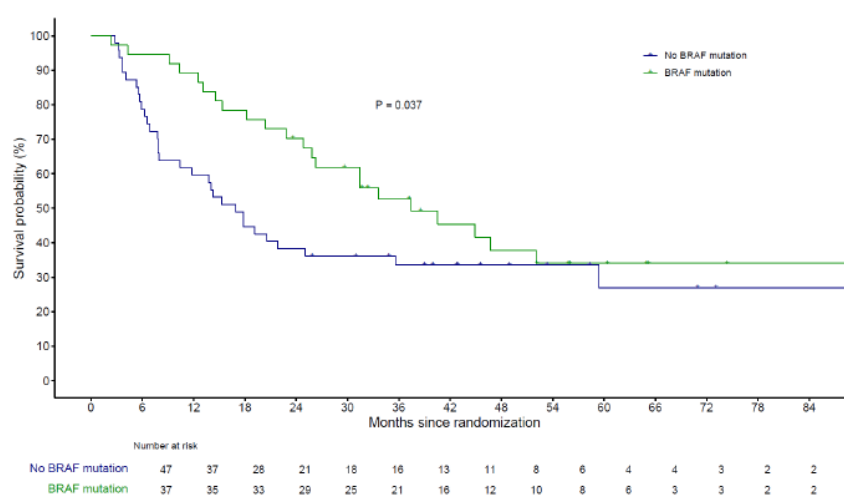
Figure 13. OS TIL-IMP patients FAS population (NKI and CCIT site) – by prior anti-PD-1 treatment



✓ OS TIL-IMP patients (NKI and CCIT site) – by BRAF mutation status

An OS sub-analysis was also performed on patients randomized for TIL-IMP with or without BRAF mutation (**Figure 14**).

Figure 14. OS TIL-IMP patients FAS population (NKI and CCIT site) – by BRAF mutation status



Pre-defined subgroup analyses

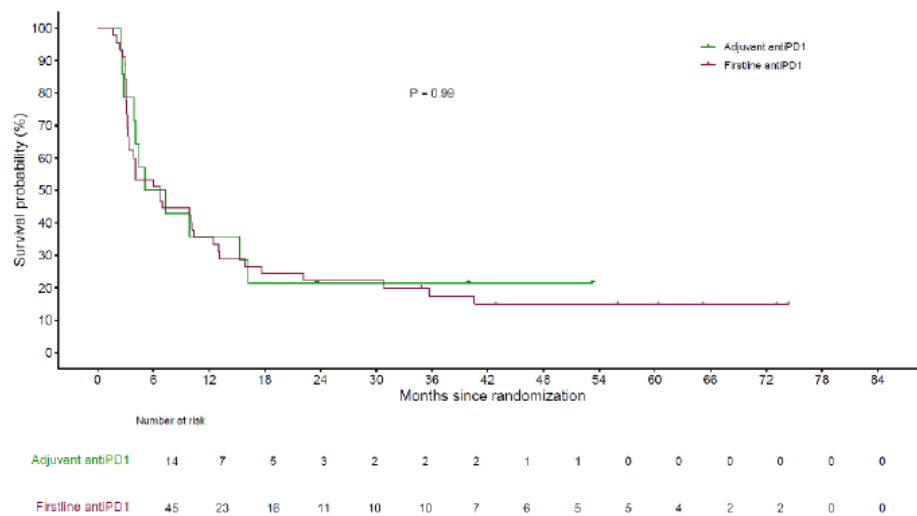
- Type of anti-PD-1 treatment (first-line or adjuvant)

✓ PFS TM001 patients (anti-PD-1 pretreated patients NKI site)

Nearly all patients treated with TM001 had received prior anti-PD-1 treatment except for 7 patients in the confirmatory phase III trial that were enrolled in the earlier phases of the trial when anti-PD-1 treatment was not standard of care.

The subgroup analysis on PFS according to RECIST 1.1, for anti-PD-1 pretreated patients at the NKI site in the TM001 arm, based on prior PD-1 therapy either as adjuvant or first-line treatment, is shown in Figure 15.

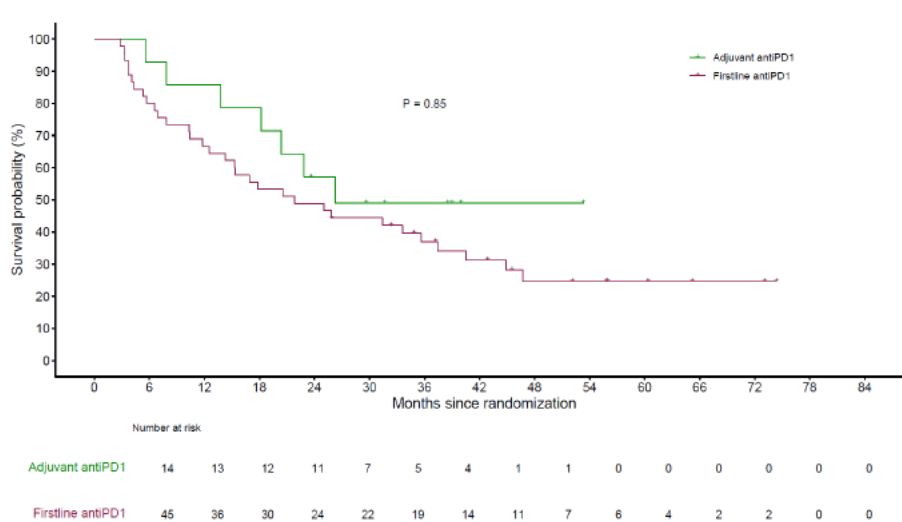
Figure 15. Progression Free Survival after TM001 therapy by prior anti-PD-1 treatment type (modified FAS/ITT) – Phase III trial M14TIL



✓ OS TM001 patients (anti-PD-1 pretreated patients NKI site)

The subgroup analysis on OS for anti-PD-1 pretreated patients at the NKI site in the TM001 arm, based on prior PD-1 therapy either as adjuvant or first-line treatment is shown in Figure 16.

Figure 16. OS TM001 patients FAS population (anti-PD-1 pretreated patients NKI site) - by type of prior anti-PD-1 treatment

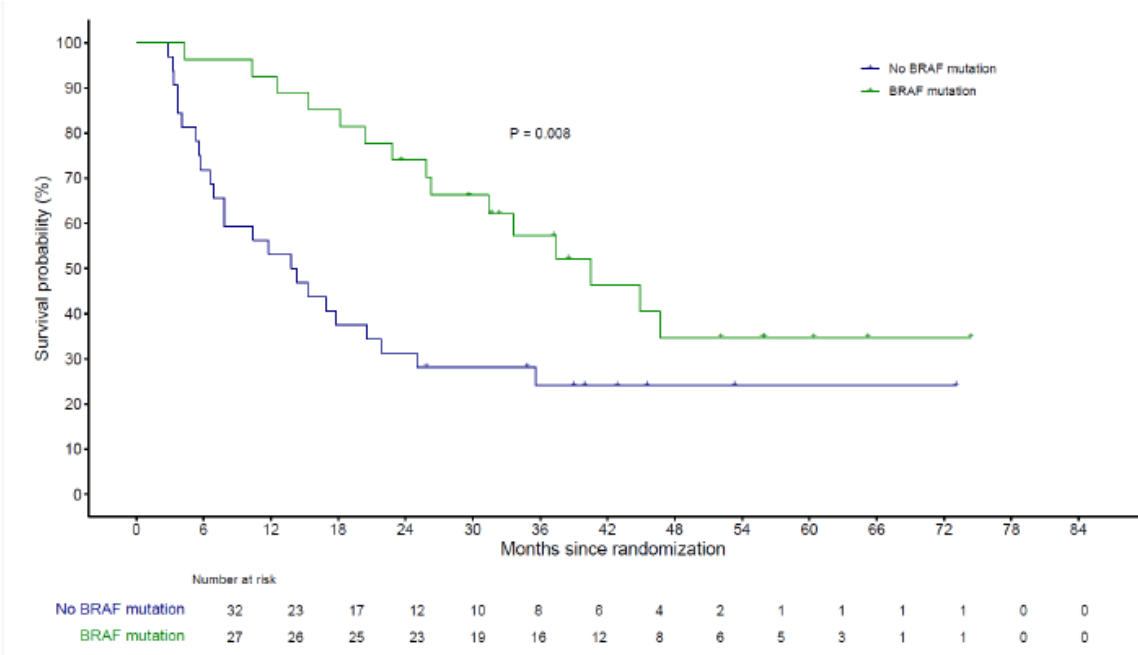


- BRAF mutation status

✓ OS TM001 patients (anti-PD-1 pretreated patients NKI site)

The subgroup analysis on OS for anti-PD-1 pretreated patients at the NKI site in the TM001 arm with or without a BRAF v600 mutation is shown in Figure 17. As a reminder, in the phase III trial (M14TIL) among the patients which where pre-treated with an anti-PD1 at the NKI site, in the TM001 arm, there were 32 (54.24%) patients without BRAF V600 mutation and 27 (45.76%) patients with BRAF v600 mutation.

Figure 17. OS TM001 patients FAS population (anti-PD-1 pretreated patients NKI site) – by BRAF mutation status



- Ad hoc analyses in the modified ITT (patients from NKI site who received prior anti-PD1)

OS responding and non-responding patients

Figure 18. Overall survival responder vs. non-responder IPI arm

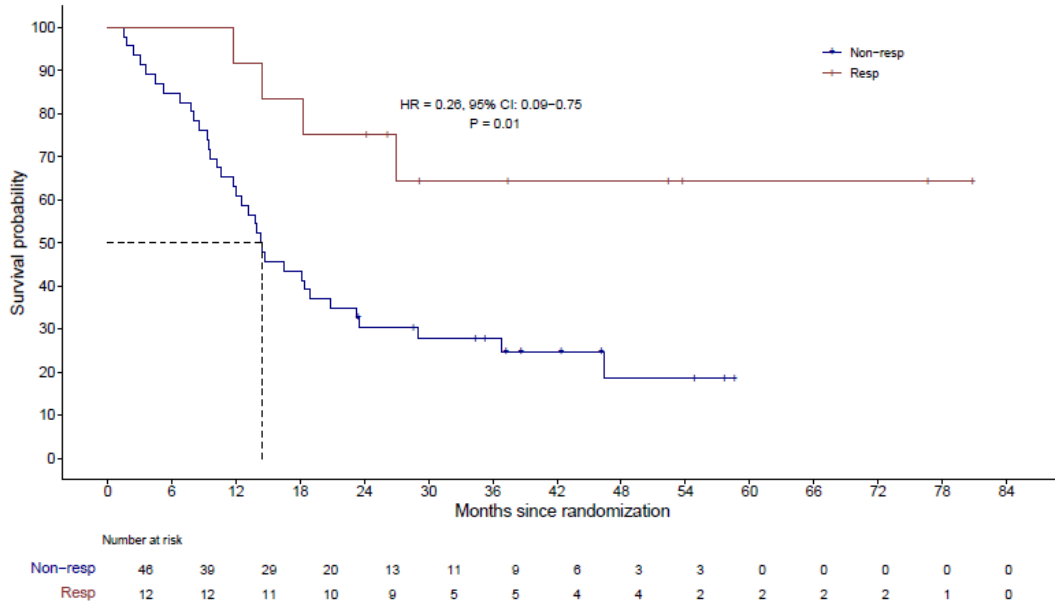


Figure 19. Overall survival responder vs. non-responder TIL arm

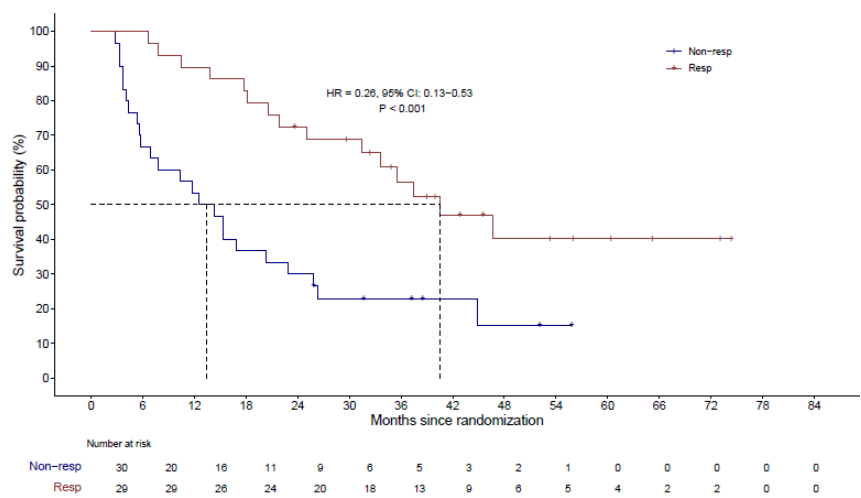


Figure 20. Overall survival by Best Overall Response - TIL arm

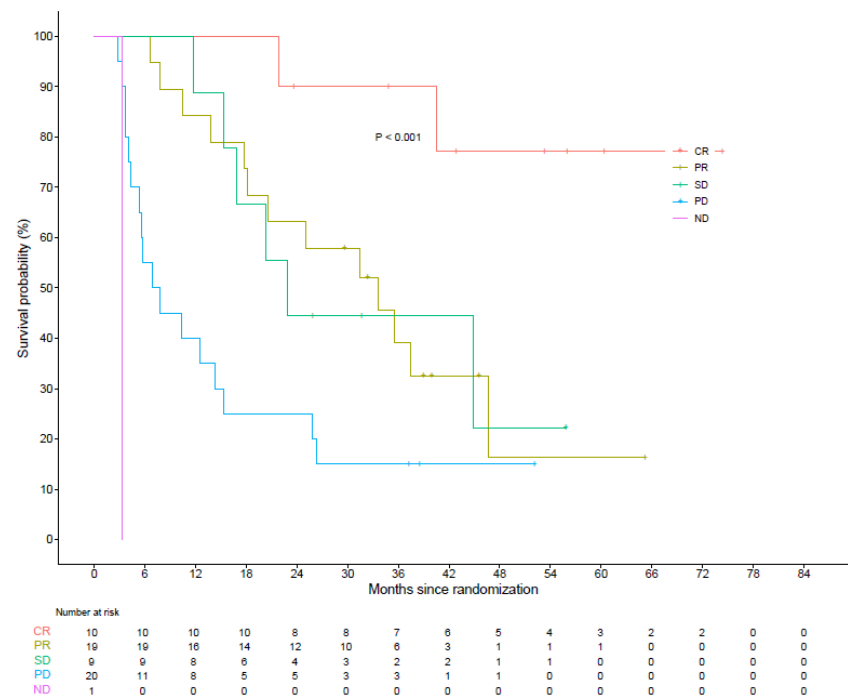


Figure 21. Forest plot progression free survival

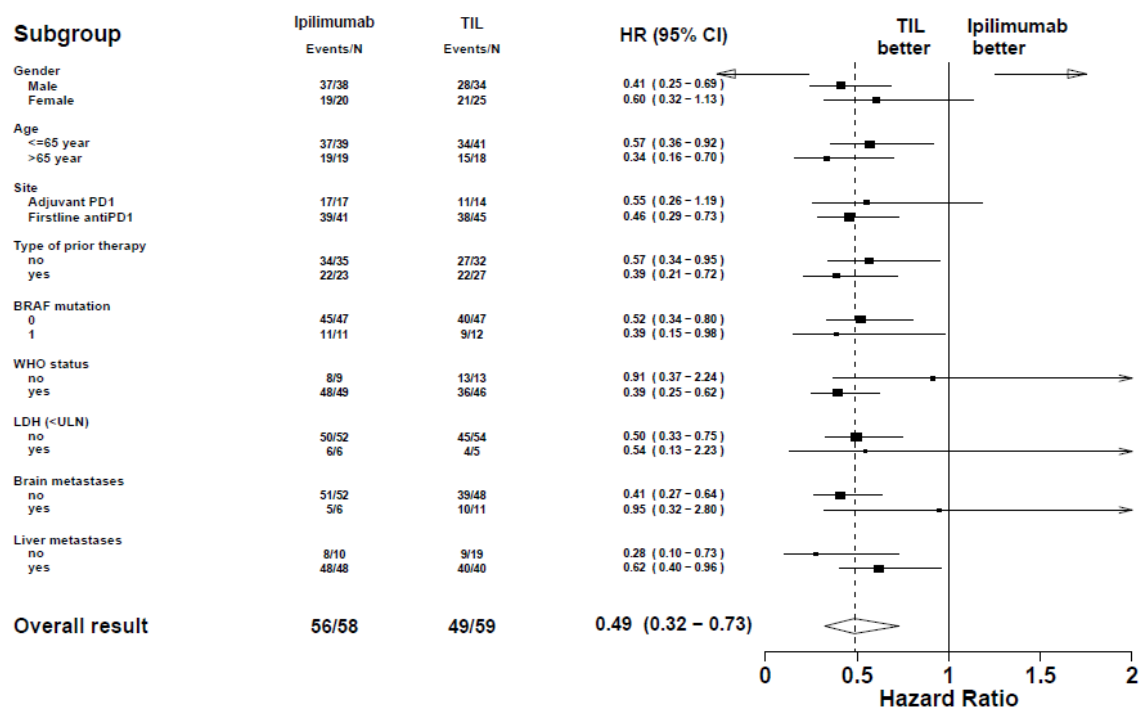
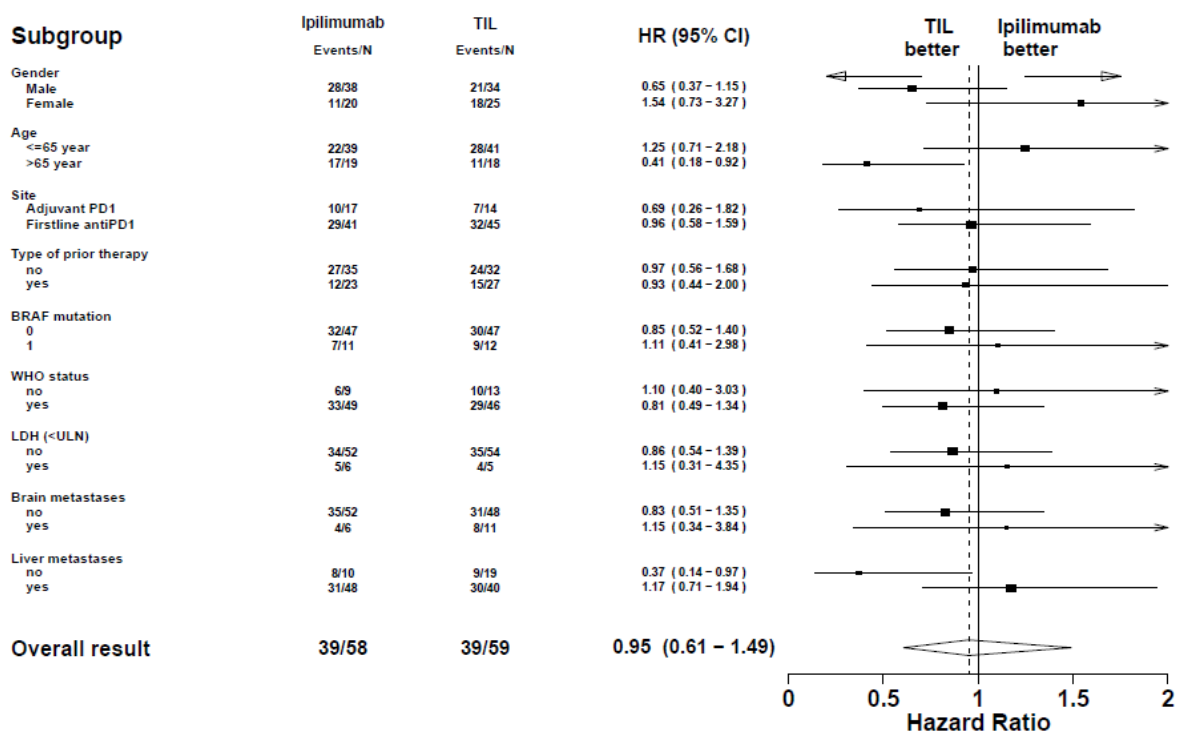


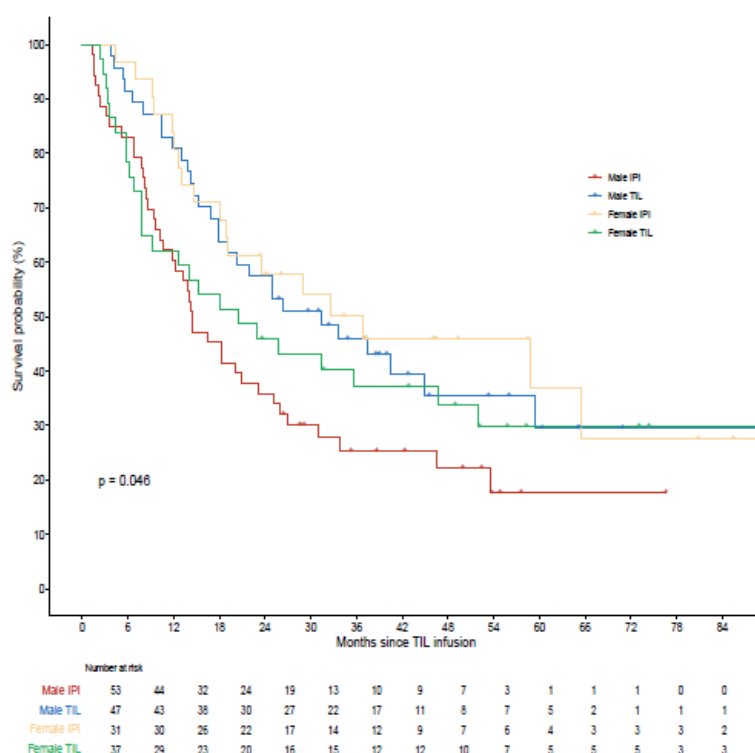
Figure 22. Forest plot overall survival



Difference OS males and females explained

A stratified cox regression using sex, treatment arm and their interaction as predictors was performed to investigate whether the indicated interaction between sex and treatment arm on OS was significant. The interaction effect had a p-value of 0.0376284.

Figure 23. Overall survival by Gender and arm



5.3.3. Clinical studies in special populations

Dedicated studies in renal and hepatic impaired patient have not been carried out.

	Age < 18	Age 75-84 (Older subjects number /total number)	Pregnant or breastfeeding women	Patients with moderate renal dysfunction or hepatic dysfunction
M14TIL	0	2 Male patients in ipilimumab arm	0	no patients in this subgroup were treated

5.3.4. Supportive studies

5.3.4.1. M14TIL Side Study

Based on the outcome of the phase III trial, the Dutch regulatory authorities allowed to start a side study under the same protocol in the Netherlands to bridge the period between the completed confirmatory phase III trial and the start of the hospital exemption. Randomization was stopped (after protocol amendment) and patients in the side study of the confirmatory phase III trial received TM001 therapy. The side study was further performed according to the clinical protocol of the confirmatory phase III trial. Since the side study included only 4, non-randomized, patients, the original study objectives and endpoints of the phase III trial were not applicable and clinical data for the patients in the side study are only descriptive. Of the 4 patients 3 presented progressive disease within 18 weeks, 12 weeks and 6 weeks respectively from the infusion and 1 patient showed a complete metabolic remission (also complete remission according to RECIST), which remained ongoing as of the last

follow-up. Considering the low number of patients enrolled the data do not bring further information on the overall analysis of the product.

5.3.4.2. Hospital Exemption program (study H23TIL)

Study population

On 15 January 2023 the Dutch Health and Youth Care Inspectorate (IGJ) / Ministry of Health, Welfare and Sport granted hospital exemption to the Netherlands Cancer Institute to give TM001 therapy to 50 patients with metastasized melanoma per year. IGJ granted renewals of the hospital exemption for TM001 therapy for 50 patients/year in 2024 and 2025. The TM001 therapy given to patients in this program is performed in line with the clinical protocol of the phase III trial M14TIL (Rohaani et al, NEJM, 2022). All patients included in the H23TIL hospital exemption program have received prior anti-Programmed Death-1 (PD-1)-based checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease, or given as (neo)adjuvant therapy. The TM001 therapy given to patients within the H23TIL hospital exemption program is performed in line with the clinical protocol of the confirmatory phase III trial..

Participant flow and numbers analysed

The main efficacy analysis set consisted of the 50 patients enrolled in the H23TIL hospital exemption program between 15 January 2023 (start of the program) and 06 November 2024 (data cutoff point), who received TM001 therapy and completed their first evaluation scan at 6-weeks post TM001 infusion. Within the hospital exemption program, the patients are to be followed until disease progression, death or until 5 years after TM001 treatment, whatever comes first. Further currently data for n=91 patients (data cut-off 08 October 2025) are available and used below for part of the presentation/indirect comparison of efficacy.

Baseline data

In Table 16 the baseline characteristics of the 50 TM001-treated patients included in this analysis are presented.

Table 16. Baseline characteristics (n=50 patients)

Gender	
Male	31 (62%)
Female	19 (38%)
Age in years	
Median	59
Min - Max	32-75
Stage at HE program entry	
Stage IV	50 (100%)
Stage IIIC - unresectable	0 (0%)
LDH screening <ULN	
no	9 (18%)
yes	41 (82%)
LDH screening 1-2x ULN	
no	42 (84%)
yes	8 (16%)
Prior anti-PD-1 treatment	
Adjuvant anti-PD-1	22 (44%)
First line anti-PD-1	9 (18%)
Ipilimumab-Nivolumab	17 (34%)
Other	2 (4%)

Follow-up

At time of data cut-off (06 November 2024), the overall median follow-up time was 9.36 months (95% Confidence Interval [CI] = 6.74 – 16.36).

Progression free survival

The complete PFS curve is shown Figure 24.

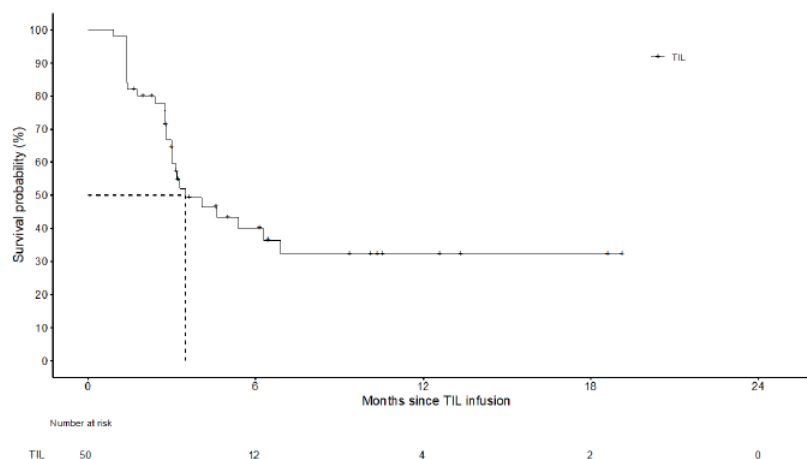
Figure 24. Progression free survival (n=50)

Figure 25 shows the comparison of the PFS after Tacquell therapy (in months from the day of Tacquell infusion) in the Tacquell target population in the M14TIL trial (n=57 PPS, end of study data) and H23TIL hospital exemption program with the latest available data (n=91, data cut-off 08 October 2025).

Figure 25. Progression-free survival (PFS) in days from day of Tacquell infusion in Tacquell target populations within the confirmatory phase III trial (A: M14TIL; n=57 PPS, data cut-off 31DEC2023) and hospital exemption program (B: H23TIL; n=91, data cut-off 08OCT2025)

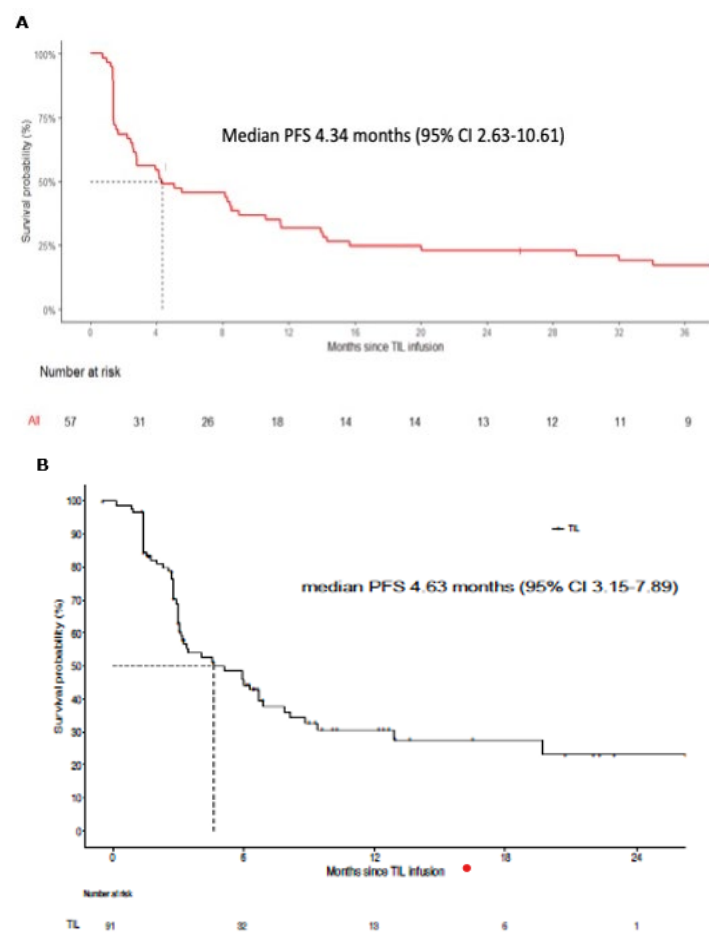


Table 17. Progression Free Survival after TM001 therapy– H23TIL Hospital Exemption Program (data cut-off 06NOV2024)

	TM001
RECIST 1.1	
Median PFS (months)	3.48 months
95% Confidence interval	3.02 – NA
PFS at six months (%)	39.96%
95% Confidence interval	27.17 – 58.79

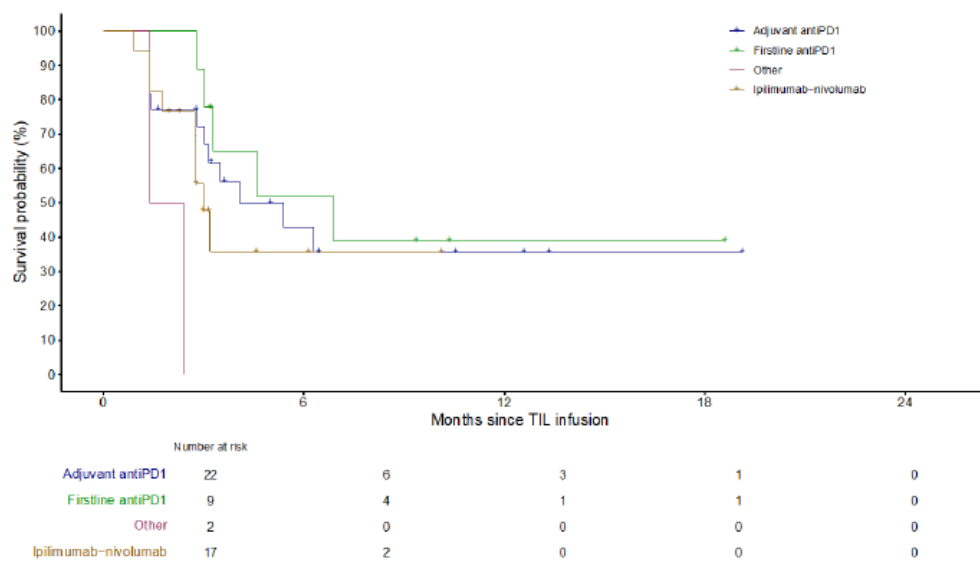
Abbreviated Clinical Report H23TIL Sections 10.2.1 and 10.2.3
 NA=Not applicable

It should be noted that PFS in the hospital exemption program was calculated from the day of TM001 infusion, whereas in the confirmatory phase III trial PFS was calculated from the day of randomization, with a median time between randomization and infusion of 49 days (range 29 - 356 days).

Progression free survival by prior anti-PD-1 treatment type

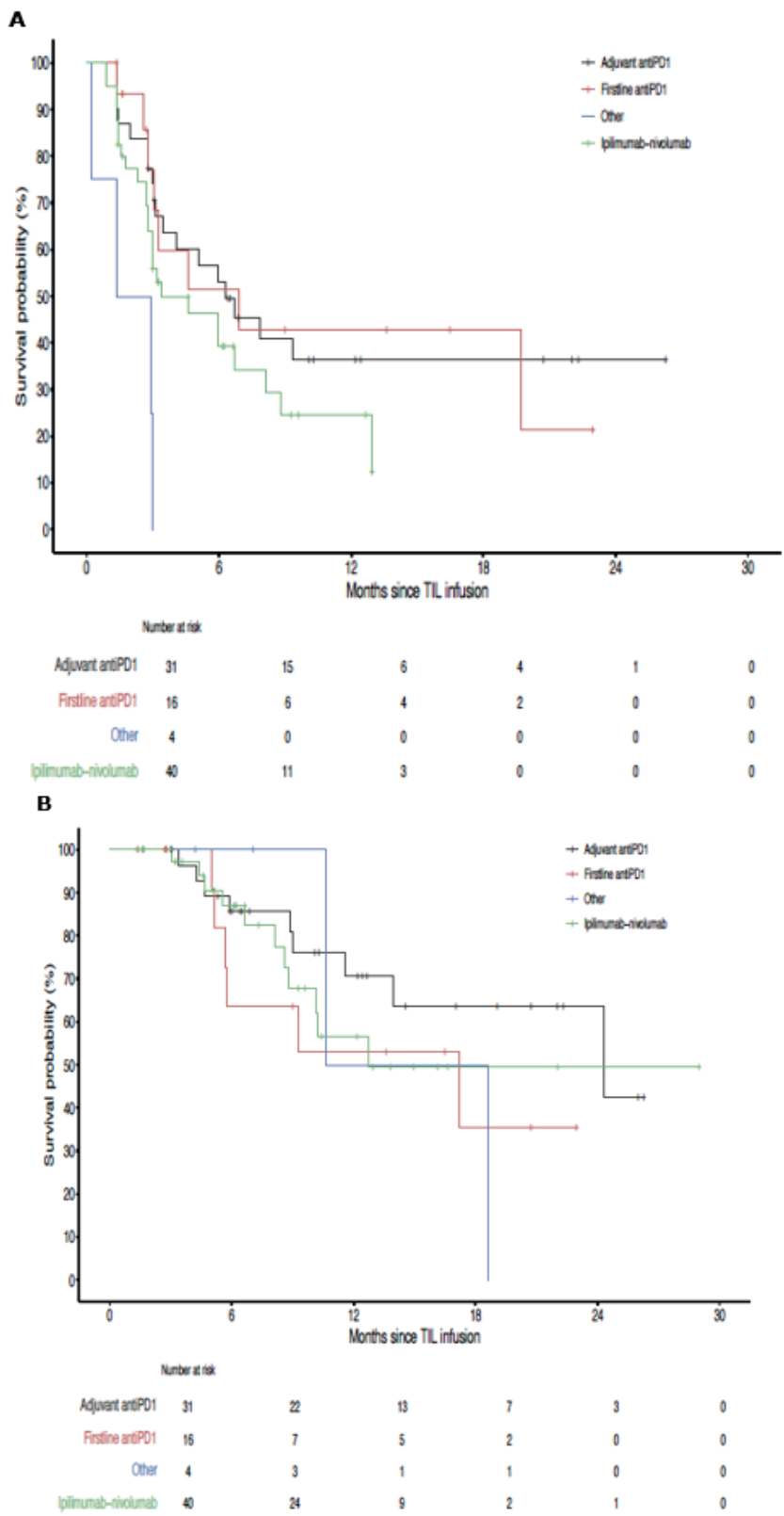
A subgroup analysis was performed on PFS according to RECIST 1.1 after TM001 therapy, based on the type of prior anti-PD-1 treatment i.e. adjuvant, first-line, Ipi/Nivo or other (Figure 26).

Figure 26. Progression free survival – by prior anti-PD-1 treatment type (n=50) (data cut off 6 November 2024)



In **Figure 27** the PFS and overall survival (OS) after Tacquell therapy (in months from the day of Tacquell infusion) is shown for the Tacquell target population in the H23TIL hospital exemption program (n=91, data cut-off 08 October 2025) by prior anti-PD-1-based therapy regimen.

Figure 27. Progression-free survival (A: PFS) and overall survival (B: OS) in days from day of Tacquell infusion by type of prior anti-PD-1-based therapy in Tacquell target population within the hospital exemption program H23TIL (n=91, data cut-off 08OCT2025).



Overall survival

The complete OS curve is shown in **Figure 28**.

Figure 28. Overall survival (n=50) (data cut off 6 November 2024)

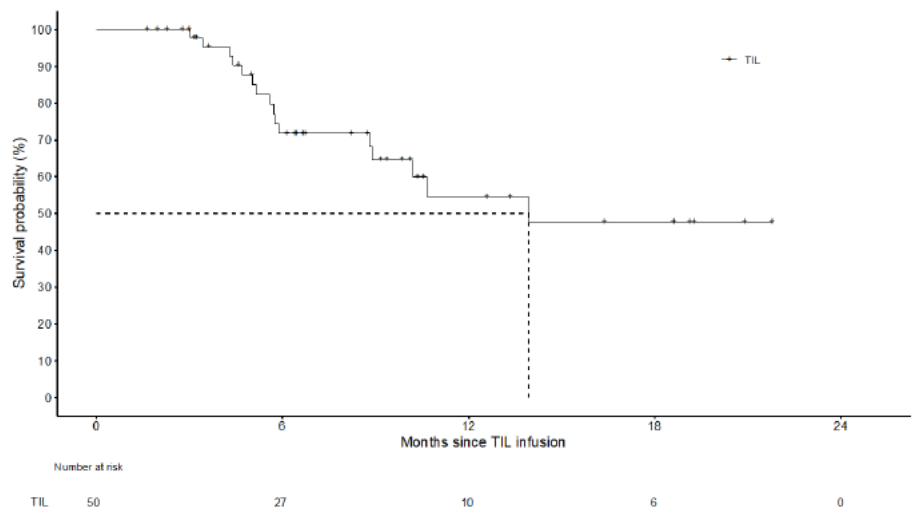
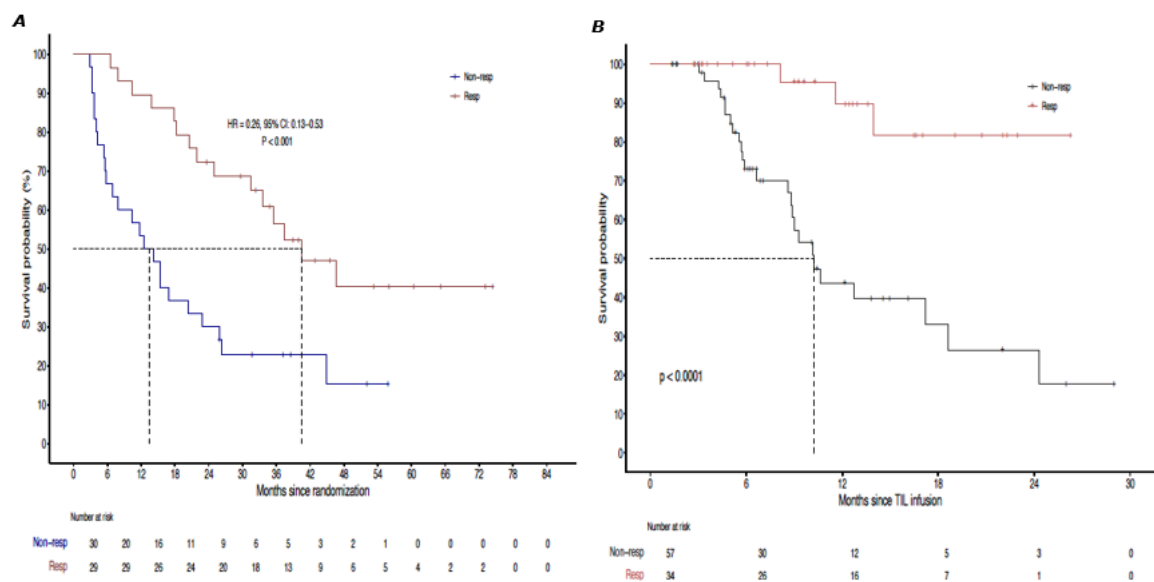


Figure 29 shows the durability of the responses seen in patients responding to Tacquell therapy (in months from the day of Tacquell infusion) in the Tacquell target population in the M14TIL trial (n=59 IIT, end of study data) and H23TIL hospital exemption program (n=91, data cut-off 08OCT2025). These data show OS in patients responding to Tacquell therapy, reflected by a 2-year OS of 72% (95%CI: 57-91%) in the M14TIL trial and a 1-year OS of 90% (95%CI: 77-100%) in the H23TIL.

Figure 29. Overall survival (OS) in days from day of Tacquell infusion in Tacquell target populations within the confirmatory phase III trial (A: M14TIL; n=59 IIT, data cut-off 31DEC2023) and hospital exemption program (B: H23TIL; n=91, data cut-off 08OCT2025) for patients that responded (CR or PR) or did not respond (SD or PD) to Tacquell therapy



Objective Response Rate

Response was assessed according to RECIST 1.1 according to the investigator review. Response was assessed as complete response (CR), partial response (PR), stable disease (SD), progressive disease

(PD), or as could not be evaluated (NE) or not determined (ND). The Objective Response Rate (ORR) is defined as best overall response CR or PR. Clinical benefit is defined as best overall response CR, PR or SD.

Table 18. Objective Response Rate (n=50) (data cut off 6 November 2024)

Best Overall Response	
CR	4 (8%)
PR	13 (26%)
SD	21 (42%)
PD	11 (22%)
NE	1 (2%)
Objective Response Rate	
CR+PR	34%
Clinical Benefit	
CR+PR+SD	76%

TM001 dose and relationship to response (data cut off 6 November 2024)

The median dose of TM001 administered was 47.2E9 viable cells, with a range of 26.4E9 to 86.9E9 viable cells. The relationship between the infused TM001 dose and the clinical response is positive withborderline significance (**Table 19**).

Table 19. Results of logistic regression: relationship total number of cells infused and Response

	OR	2.5 %	97.5 %	P-value
Total number of cells infused	1.05	1.00	1.11	0.05

5.3.4.3. Additional M14TIL-SWOG S1616 comparison provided at the second round

During the assessment, the Applicant provided an additional M14TIL–SWOG S1616 indirect comparison to contextualise the M14TIL TIL/Tacquell results against an external dataset including patients treated with ipilimumab or nivolumab plus ipilimumab.

The applicant created a virtual comparator dataset for Tacquell versus IPI monotherapy and IPI/NIVO combination therapy by applying exclusion criteria of the confirmatory phase III trial for Tacquell (M14TIL trial) on the SWOG1616 dataset (i.e. excluding patients with mucosal melanoma, a clinical ECOG performance status of >1, or with LDH levels >2 times the upper limit of normal). The patient group selected from the SWOG1616 dataset comprised 19 patients treated with IPI monotherapy and 52 patients treated with IPI/NIVO combination therapy.

The report describes four analyses: an unadjusted Cox analysis, a multivariable Cox regression, propensity score full matching, and propensity score weighting. The propensity score model included age, sex, WHO performance status, brain metastases, liver metastases and metastatic category. The report also notes baseline imbalances between the M14TIL and SWOG populations, including older patients in the SWOG population

A propensity score matching model was employed to reduce potential confounding and to achieve maximal comparability between the M14TIL-Tacquell patient cohort and the SWOG1616-IPI/NIVO cohort. Propensity scores, which represent the probability of a patient receiving one treatment versus the other based on observed baseline covariates, were estimated using a logistic regression model including age (dichotomized as age 75), sex, WHO performance status, presence of brain metastases, liver metastases, and metastatic category. A full matching method was applied for pairing each patient in the M14TIL-Tacquell group with a weighted sum of similar patients from the SWOG1616-IPI/NIVO

group based on their propensity scores. The results showed a median PFS after Tacquell therapy versus after IPI/NIVO combination therapy, with a 6-months PFS.

5.3.5. Overall discussion and conclusions on clinical efficacy

5.3.5.1. Discussion

Tacquell consists of autologous viable CD45+CD3+ T cells, isolated and expanded ex vivo from a melanoma metastasis (TM001DS), with the goal of generating immune reactions against the patient's own tumour.

The sought indication is: treatment of adult patients with unresectable stage IIIC to IV melanoma following prior anti-Programmed Death-1 (PD-1)-based checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease, or given as (neo)adjuvant therapy.

The clinical development program included 2 phase I/II and a phase III study M14TIL. Supportive data come from a side-study of the pivotal phase III trial (4 subjects) and a hospital exemption program (91 subjects).

The Applicant submitted the publications by Andersen et al, 2016 and van den Berg et al, 2020 of the two phase I/II clinical trials. These studies were carried out using developmental TIL products that contributed in principle to the design and final manufacturing process applied in the confirmatory phase III trial and were performed in the same clinical sites. They are therefore considered supportive. As the applied manufacturing processes in the phase I/II feasibility studies differ from the commercial process, no formal study reports are available, and only corresponding publications have been provided. The manufacturing process of the TIL was mainly based on established methods published.

Since the results of the phase I/II feasibility studies are not expected to have an impact of the efficacy results of the phase III M14TIL study, no concerns are raised in this regard.

The proposed minimum dose of 10E9 viable CD45+CD3+ cells (see also discussion on clinical pharmacology) has not been exhaustively justified. The lower range of the cell dose of viable CD45+CD3 cell administered to patients should be the lowest number of cells administered to patients that had an objective response in the confirmatory phase III study. A provided logistic regression model may suggest that for lower doses, there may be a probability of response. At the stage of a MAA, it is not accepted to claim an efficacy dose for a medicinal product based on probability of response and the dose should be clinically qualified. To overcome this aspect the applicant has proposed to monitor dosages (batch sizes) as part of the continuous process validation (CPV) which is not endorsed as an acceptable argument to set this minimal dose. As well, no upper dose limit was proposed in the clinical aspects which is also not acceptable.

In all studies the administration of the TIL was preceded by a preparative standard non-myeloablative lymphodepleting chemotherapy regimen and was followed by supportive intravenous administration of IL-2. The non myeloablative conditioning regimen consists of Cyclophosphamide 60 mg/kg/day which is administered on days -7 and -6 IV and of Fludarabine 25 mg/m2/day which is administered from Day -5 to Day-1 IV. The interleukin-2 (IL-2) 600,000 IU/kg IV is used from Day 0 to Day 5.

These dosing regimen for the preparative chemotherapy were used in line with their authorisation. As regards to the IL-2 dose, the Applicant stated that these regimens were used in previous phase I/II TIL without specifying if this corresponds to the Applicant's study or to other clinical studies. It is noteworthy that IL-2 (Aldesleukin) is authorized by US FDA for the treatment of adults with metastatic melanoma. Although no formal demonstration was made to attribute the antitumour activity to the TIL

and not the IL-2 and to isolate the IL-2 activity from the TIL activity, different literatures show the use of IL2 for the expansion and the survival of the lymphocytes (Diaz-Cano et al, 2022). The IL-2 administration is regarded as supportive to promote persistence and outgrowth, rather than as the main driver of the clinical efficacy (Rosenberg et al, 2009). In addition, tables summarising number of IL-2 administrations stratified by BOR for study M14TIL and H23TIL respectively have been provided and patients with an objective response (CR or PR) after Tacquell therapy have received between 1 and 5 doses of supportive IL-2. This number is in line with results from Goff SL et al 2016, showing data from 99 patients with melanoma treated with TIL. The numerically highest ORR was observed in the subgroup of patients who received 3 to 5 doses of IL-2.

In study M14TIL study the comparator, ipilimumab, YERVOY, is an authorised medicinal product in the EEA (EU/1/11/698/001-002), indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older as monotherapy or in combination with nivolumab. The dose and regimen used are in line with the marketing authorization.

Design and conduct of clinical studies

Main study: M14TIL

Study M14TIL is a Phase III multicenter, randomized, open-label, trial to evaluate the efficacy and the safety of TIL-IMP therapy, compared to ipilimumab (IPI) in patients with histologically confirmed American Joint Committee of Cancer (AJCC) version 7 unresectable stage IIIC to IV melanoma.

The 5-year follow-up of the pivotal trial is considered as sufficient to assess the efficacy of the TIL in this indication however the threshold of >50% is further discussed in the safety section.

Based on the design of the Phase III, multicenter, open-label, randomized, controlled trial, the primary objective which is the comparison of progression-free survival according to RECIST 1.1 between ipilimumab arm and TIL-IMP arm is endorsed. It was calculated in the efficacy analysis set (FAS) from the date of randomization to the date of progression or death (whatever came first). This definition aligns with the recommendations outlined in the Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.6) and is considered appropriate for studies in this indication. The secondary objectives, PFS at 6 months (according to RECIST 1.1), PFS according to irRC, Overall response rate, Complete response rate and Overall survival were adequately defined so as to support the results of the median PFS and to demonstrate additional effects on the disease. PFS at 6 months (according to RECIST 1.1) was initially the primary endpoint and, when reclassified, was retained as a secondary endpoint, which is the recommended approach. Taking into account the targeted therapeutic indication, ie. unresectable stage IIIC to IV melanoma, the overall survival could have been proposed as a key secondary endpoint. Several amendments have been made to the primary endpoint between 2014 to 2021, with total PFS listed as the primary endpoint in protocol version 1 (Feb 2014), then PFS at 6 months listed in protocol version 2 (Dec 2014) and then total PFS again in protocol version 7 (23 Apr 2021). PFS at six months became a secondary objective in protocol version 7 [E29.1]. Although the final primary endpoint chosen may make sense methodologically, the integrity of the study is not considered preserved, and no reassuring justification has been provided on such terms.

During the conduct of the study the approval of anti-PD1 based immune check-point inhibitors in 2016 changed the standard of care for patients with unresectable stage IIIC to IV melanoma from Ipilimumab to anti-PD1 treatment in the 1st line setting and this would have been the appropriate control arm in the proposed indication. To address this issue, the applicant presented an indirect comparison (study S1616) of Tacquell with IPI-NIVO in the second-line setting, referring to the SWOG1616 trial, which evaluates IPI and IPI-NIVO in patients refractory/resistant to PD1 (see section 5.3.5). However, the indirect comparison is limited by cross trial differences, residual baseline imbalances, and lack of alignment in PFS assessment. To address confounding factors, the Applicant

performed an unadjusted Cox analysis and adjusted analyses using a multivariable Cox model and propensity score based on full matching with weighting (see section 5.3.5). The propensity score model included age dichotomised at 75 years, sex, WHO performance status, presence of brain metastases, presence of liver metastases, and metastatic category. Across analyses, PFS results numerically favoured Tacquell, but estimates were imprecise. The unadjusted analysis and the propensity score weighted analyses showed similar effect estimates with wide confidence intervals overlapping unity. Given the limited size of the external comparator cohort and the use of weighting, the robustness of these estimates is uncertain. Key information required to assess the validity of the propensity score approach is insufficiently documented, including balance diagnostics, assessment of overlap and positivity, distribution of weights, and effective sample size. Thus, based on the answer provided it is still entirely unclear if the treatment effect holds in the current treatment landscape. Of further note, patients in the SWOG1616 comparator dataset were relapsed/refractory to PD-1, and most had received anti-PD1 as first-line therapy for unresectable stage IIIC-IV melanoma, i.e. they received IPI-NIVO in a second-line setting. While indeed IPI-NIVO may be used after first-line anti-PD1 according to the ESMO guidelines, the additional benefit of adding nivolumab to ipilimumab in this setting may be expected to be less than when IPI-NIVO is given in the first line treatment, only after prior (neo)adjuvant anti-PD1. Of note, the sought indication for Tacquell would also permit use in the "first line" after only prior (neo)adjuvant anti-PD1 and an indirect comparison versus IPI-NIVO in this setting has not been carried out.

Therefore, based on the above, to draw robust conclusions, a prospective, randomized trial directly comparing TIL therapy with IPI/NIVO in this population would be the most appropriate approach.

In the total population of study M14TIL, it appears that only 17.9% (ipilimumab arm) and 16.7% (TIL arm) received the trial treatment as their first line of treatment. An incorrect use of "first line treatment" definition was applied using such parameter for stratification of patients and affecting the randomisation. Despite the applicant's justification indicating that the stratification variable was misinterpreted consistently across sites and did not impact the randomization process or study integrity, this is considered incorrect: these patients would be randomised according to an incorrect value for this stratification factor.

In addition, the applicant clarified that the term "second line" was used for both patients previously treated with adjuvant anti-PD1 and those treated with prior anti-PD1 in the first-line setting, thus "first line treatment" refers only to patients with no prior exposure to anti-PD1. Only 19 patients received the TIL in this "first line" setting. Therefore, the vast majority of subjects had already received a prior "first-line" of therapy and received the trial treatment as "second-line therapy". Considering the major shortcomings of the dossier on the conduct of the study and the relevant uncertainties in assessing the benefit/risk balance of Tacquell, the definition of the proper indication with respect to treatment line or prior therapies is not possible.

A complete estimands table aligned with ICH E9(R1) for the primary endpoint, including a clear classification and handling strategy for each intercurrent event was provided. The intercurrent events and the handling of these events are appropriate for the population included in the M14TIL clinical study. Supplementary and sensitivity analyses for the primary estimand were performed, including the Fleming-Harrington weighted log-rank test, a landmark analysis and the restricted mean survival time (RMST) approach. These analyses constitute sensitivity analyses, as they rely on the same primary estimand while applying alternative estimators or analytical approaches. No supplementary estimands, as defined in ICH E9(R1), were introduced.

An overall administrative censoring rule defined as the earliest of last date known alive or data cut off, together with a statement that non administrative censoring was limited to patients who did not receive treatment, with no loss to follow up or withdrawals, and a limited description of two

intercurrent events handled under a treatment policy strategy was provided. This does not constitute a complete, operationally reproducible specification for a RECIST based PFS derivation, where censoring is typically anchored to the date of the last adequate tumour assessment. Moreover, the provided patient listing shows at least one apparent internal inconsistency, for example a patient coded as died 0 and progressed 0 but not flagged as administratively censored, suggesting either listing errors or missing censoring categories not described. Finally, in the inspection context of incomplete or unclear audit trails (see section 2.4.3), post data cut off changes and the inability to confirm the integrity of CSR data outputs, the reliability of event and censoring derivations cannot be supported by a binary flag table alone. The Applicant stated that these sensitivity analyses were pre-specified, however, the estimand framework was not used in the SAP but implemented during the analytical phase post-hoc. The censoring rules were not completely described in the SAP and CSR which could jeopardize the integrity of the study and is considered of post-hoc nature. As well, death for other reason than melanoma was not used as censoring reason for PFS in the confirmatory phase III trial (M14TIL). Given the extent of issues uncovered during the GCP inspection (see section 2.4.3) and the open-label nature of the trial, this is seen as problematic.

The inclusion and exclusion criteria are overall adequate. Randomisation was stratified based on BRAF V600 mutation, line of treatment and treatment center which is appropriate. The reasons for longer intervals between randomisation and TIL infusion in some patients, mainly identified in metastasectomy related complications as described in section 5.3.2.1.2 can be understood.

In addition to the scans described in the study design above, in the IPI arm, a CT scan is performed prior to the 3rd ipilimumab infusion, approximately 5 weeks after the first dose, but it is not used for tumor response assessment. This scan can lead to early discontinuation of treatment if disease progression is detected, which may affect the apparent benefit of the ipilimumab control arm, as only 47.62% of patients completed all four cycles of treatment. The applicant noted that early discontinuation due to disease progression only occurred in 9 patients, based on clear signs of progression, but the specific criteria and potential impact on response rates are unclear. In addition, the applicant didn't provide a timeline of CT scans from the time of randomisation in the IPI arm. In the IPI arm, there was a "baseline scan" performed at screening, within 4 weeks prior to randomisation. Yet, given that the article published on the pivotal study (Rohan et al., 2022) states that the CT scan closest to start of treatment was used as baseline in both treatment groups, this could imply that the 5-week scan was used as baseline in some patients, if closer to the start of treatment than the "baseline scan". The issue remains unclear. In the Tacquell arm, patients undergo evaluations for response at 6, 12, and 18 weeks after Tacquell infusion, and then every 3 months thereafter. The scan conducted before Tacquell therapy ((before start of the preparative lymphodepleting chemotherapy) serves as the baseline for assessing tumor response in the Tacquell arm. Overall, the timeline of baseline and evaluation scans in the IPI arm is still unclear and remains an uncertainty.

The study was not blinded, and assessment of tumour response was per investigator. The Dutch National Health Care Institute (Zorginstituut Nederland) advised at an early stage that an independent radiologist should perform blinded central review of CT scans for determination of the primary endpoint. Then, between protocol versions 7 and 8, the study protocol was amended to indicate that the radiologic response was investigator assessed, as patients randomised for TIL-IMP therapy all underwent surgical resection of a tumour lesion, and the radiologist could therefore not be treatment blinded. A fully blinded central review is claimed infeasible because surgical resection for Tacquell manufacturing functionally identifies the treatment arm, a feasible independent mitigation to strengthen endpoint credibility (e.g. independent central review and/or independent adjudication/confirmation of progression events and dates under a predefined charter) has not been provided. Therefore, this major issue is not considered resolved.

As regards to the concomitant medications, it was only specified that filgrastim could be used to treat the neutropenia and the concomitant medication prescribed for the treatment-related adverse events were recorded throughout the study. Moreover, the use of systemic corticoids for the treatment of AEs after Tacquell infusion should be avoided, unless absolutely required from a safety perspective. Antibiotics were allowed and were used after Tacquell infusion. For both arms, co-interventions were permitted, namely palliative (limited-field) radiation therapy for pain control to sites of bone disease present at baseline that were not target lesions, as well as surgical resection for palliative reasons for non-target lesions present at baseline.

The primary analysis used standard methods for time-to-event outcomes, including Kaplan–Meier estimates, stratified log-rank test, and Cox proportional hazards regression. However, these were not explicitly linked to a predefined estimand, and the sensitivity analyses presented (including RMST and Fleming-Harrington weighted tests) were not described in a way that allows assessment of their relevance to missing data, intercurrent events or potential informative censoring. In particular, the use of a complete-case approach without justification raises concerns regarding potential bias from informative censoring. Additional analyses such as RMST and Fleming-Harrington weighted tests were performed but were not prespecified in the SAP. The absence of formal multiplicity control for secondary endpoints further limits confirmatory strength. Overall, while the statistical methods applied are standard, they fall short of current regulatory expectations in the absence of fully defined estimands and supporting sensitivity analyses. In addition, in the context of the amendments made to the protocol and the open label nature of the study, these changes and the methodological considerations regarding the use of the weighted-log rank analysis and the RMST approach lacks of justification and contextualisation (for instance in light of any exchanges with the DSMB) to ensure that the integrity of the study was maintained at all times.

Overall, the open-label design of the study is acknowledged. Nonetheless, several important changes occurred during the study, including the restriction of the primary analysis to the TM001 subgroup introduced post hoc due to comparability issues. These adaptations, while possibly justified, reduce the confirmatory nature of the trial and impact the generalizability of the findings. In addition, the routine GCP inspection conclusion adds to the difficulty to interpret the results.

Indeed, the GCP inspection reported multiple findings, affecting the quality of the data reported (see section 2.4.3 for the specific criticalities and major findings). There were multiple serious and significant shortcomings in the data management processes, a general lack of control over key computerised systems used in the trial as well as significant shortcomings in the statistical analysis processes. At the sponsor location, “not all key clinical trial processes were governed by QMS documents such as SOPs. For multiple key processes, SOPs had only been put in place late, well after the start of the trial.” At the investigator site, Inadequate Deviation Management and Documentation was observed.

Altogether, these findings make impossible for the inspectors to confirm integrity of the data represented in the CSR and warned that the trial results could be used in an MAA-procedure only with major reservations. Following this inspection outcome, the committee considered that there are major concerns in the pivotal clinical trial which impact the reliability, integrity, traceability, and re-constructability of the clinical data package and finally that the quality of the data cannot be acceptable. To mitigate these shortcomings the applicant provided additional source data verification activities for CAPA measures and other corrective actions including replication of the statistical analysis of the efficacy and safety parameters by an independent statistician. However, this exercise does not fully alleviate concerns regarding data integrity in the eCRF; the reliability of the pivotal evidence package remains not established.

From 199 patients who were screened at the start of the phase III study, 168 patients were randomized with 84 patients who were assigned to the TIL arm and 84 patients to the IPI arm, this was the total FAS population. The Full Analysis Set population corresponds to the randomized patients and is the same as the intention-to-treat (ITT). The Per Protocol Analysis Set (PPS) consisted of all patients that received treatment. Given the proposed indication, the applicant has also defined an FAS including patients with prior anti-PD-1 treatment, which comprises 145 patients in total (117 at the NKI site and 28 at the CCIT site). Considering the patients who received a prior anti-PD-1 treatment at the NKI sites, 58 were assigned to ipilimumab arm of which 57 were treated and 59 were assigned to the TIL arm of which 57 were infused with TM001. Compared to clinical trial with other immunotherapies the numbers of patients randomised per arm is limited. Nevertheless, considering the nature of the medicinal products and the limitation related to the manufacturing process, no concerns will be raised.

The protocol deviation log omitted multiple protocol deviations, as also highlighted in the GCP inspection report, and hence the CSR contains insufficient information on potentially significant protocol deviations that occurred during the trial. In some cases contradictory information have been provided on same patient in regards to screening (patient with screening failure but with metastasectomy done to be save for later and the patient was not included or randomised), randomisation to the respective arm (a patient was initially reported as randomised to IPI arm of the study when later was confirmed to have been randomised to the TIL Arm), etc. Therefore, the conflicting information provided regarding these patients illustrates the lack of data control and concerns remain related to the screening and randomization process, as well as the handling of protocol deviations.

Following a post-trial comparability exercise performed by the Applicant, it was concluded that the cells manufactured on the Dutch sites were not similar to the cells manufactured on the Danish site. The Applicant therefore decided to separate data from the Dutch sites and the Danish site and present data from the Dutch sites as pivotal data for this MAA. Separate clinical results for each manufacturing site and per treatment centre (NKI and CCIT) for patients who received prior anti-PD1 treatment as well as the pooled data of the patients who received prior anti-PD1 treatment (N=145) were requested during the assessment. Further, the Applicant was asked to submit comparative KM curves for PFS and OS versus the Dutch site, NKI and discuss any deviation between sites. while the non-comparability is acknowledged. To justify this exclusion, the applicant claims that, as the sub-analysis (of Dutch patients with prior anti-PD-1 treatment) was performed after completion of patient enrolment, influence of potential bias in the execution of the trial was limited. However, this does not address the inspection-related concerns on data integrity and reconstructability of key analysis datasets and outputs and this statement does not include a specific reconciliation showing that the key efficacy endpoints and analysis datasets underpinning the restricted claim can be considered accurate and complete given the inspection conclusions affecting the full data package and the CSR outputs, including data management and statistical analysis processes.

Overall, the credibility of the efficacy demonstration remains methodologically poor. While it is acknowledged that the non-comparability between the Danish and the Dutch sites and the changing therapeutic landscape are arguments for the performed subgroup analysis, the justification for breaking the ITT principle is considered not acceptable as indeed the full ITT (n=168) is considered the main efficacy population. Furthermore, the lack of comparative efficacy data between the sites is considered highly concerning.

Supportive studies

Although the program was conducted in similar situations to the pivotal M14TIL study (since patients have been included according to same eligibility criteria), the hopsital exemption program is considered

as a supportive study because the dataset is non randomized, and the patient population differs from that of the pivotal randomized trial due to the evolving treatment landscape. Baseline characteristics and prior therapies have also changed over time, which limits comparability.

Efficacy data and additional analyses

Main study M14TIL

In the full ITT population (N=168), patient characteristics were well-balanced between the arms. Similarly, the baseline characteristics were mostly similar between the TM001 and IPI treatment arms at the NKI site (N=117). No information on the race or ethnic background of patients in the confirmatory phase III trial (M14TIL) and hospital exemption program (H23TIL) was collected. The majority of the patients had stage IV melanoma, with only 2 patients in each study arm with unresectable IIIC melanoma at study entry. Since there is no biological rationale for expecting less response to immunotherapy in these patients than in patients with stage IV melanoma, and that treatment guidelines also generally recommend the same first-line treatment approach in these patients, the extrapolation of data from stage IV patients to stage IIIC is acceptable. Treatment arms were balanced in terms of baseline brain and liver metastases, M-category and LDH levels.

Patients were stratified by BRAF mutation status. Among patients who received prior anti-PD1 therapy, 27 (45.76%) patients in the TM001 arm and 23 patients (39.66%) in the IPI arm had a BRAF V600 mutation melanoma. While the CSR only mentioned anti-PD1 as prior systemic therapies, based on the list of prior systemic therapies and in the total FAS, some patients were treated with BRAF inhibitor with or without MEK inhibitors.

In the ITT population of the M14TIL trial, four patients (two per arm) had prior BRAF/MEK inhibitor therapy; none were in the target (mITT) population, where anti-PD-1 was the only permitted prior treatment. Most patients received TIL before BRAF/MEK inhibitors. Two patients (4%) received BRAF/MEK inhibitors after adjuvant anti-PD-1 and before starting the Tacquell therapy, but it is unclear whether others had multiple prior lines (e.g., anti-PD-1 followed by IPI/NIVO).

Very scant information on the use of BRAF/MEKi as first-line therapy in the unresectable Stage III/IV setting prior to Tacquell therapy from both the M14TIL study and the H23HE programme are available. As rationale to treat patients with Tacquell before the inhibitors, the Applicant cited some publications (Dennison, 2021; Dushyanthen, 2017; Liu et al., 2015; Vella et al., 2014) showing that MEK inhibitors impaired activation of TILs in in vitro and in vivo settings.

The ORR of BRAF/MEKi as the first line of treatment after Tacquell therapy was 10/14 (71%) and after IPI treatment was 18/19 (95%), results that the applicant does not consider substantially different given the low patients numbers. These ORR rates are also in line with what would be expected for BRAF/MEKi in these patients. A retrospective study (Pedersen 2021) showing similar OS/PFS in patients receiving BRAF/MEK inhibitors post-Tacquell versus those without prior TIL therapy was provided. However, the indirect comparison lacks statistical rigor. No proper clinical trial was performed to establish non inferiority or superiority of TIL over MEK inhibitor /BRAF inhibitor after anti-PD1 progression in patients with BRAFV600 mutated melanoma.

Overall, the available evidence does not exclude a potential loss of treatment opportunity for patients with BRAF-mutant melanoma treated with TACQUEL before BRAF/MEK inhibitors.

Outcomes and estimation

At the DCO 31-Dec-2023, the median follow-up time in the FAS/ITT (n=168) was 52.42 months (95% CI 46.14 - 58.56) being 55.80 months (95% CI, 45.52 - 70.92) and 49.95 months (95% CI, 42.37 to 58.56) in the TIL-IMP and IPI arm, respectively. The follow-up time is considered adequate for the claimed indication.

In the FAS (ITT population), the median PFS assessed according to RECIST was 6.81 months (95% CI, 4.19 - 12.47) in the TIL-IMP arm, compared to 3.06 (95% CI, 2.97 - 4.32) months in the IPI arm; the analysis of the curves showed an HR between ipilimumab and TM001 arms of 0.52 [95% CI 0.37-0.73; P-value <0.001]). The proportional hazards assumption was found not to be violated. The statistical analysis plan specified that PFS was to be compared between the ipilimumab and TIL arms using a log-rank test, and the Fleming-Harrington weighted log rank test putting more weight on events that occur later in time, as well as the Restricted Mean Survival Time (RMST) analysis as sensitivity analyses. A significant difference in PFS between ipilimumab and TIL in favor of TIL ($\chi^2 = 8.69$, $p = 0.003$) was observed when using the Fleming-Harrington weighted log rank test. In the RMST analysis, the restricted mean survival time for the ipilimumab arm was 7.9 months and for the TIL arm was 16.7 ($p = 3.96 \times 10^{-4}$). Thus, the primary endpoint can be said to be met, again bearing in mind the methodological concerns described above.

In the FAS/ITT, the 6-month PFS event-free rate was 21.4% (95%CI: 14.23-32.27) in the ipilimumab arm and 52.4% (95%CI: 42.72-64.23) in the TIL arm. PFS at six months for the PPS population was 52.5% (95% CI, 42.62 - 64.67) in the TIL-IMP arm and 19.5% (95% CI, 12.57 - 30.28) in the IPI arm. PFS according to irRC was similar to PFS per RECIST.

In the modified ITT population (ie the patients from the NKI site, previously treated with anti-PD-1), at time of data cut-off on 31 December 2023, the overall median follow-up time was 45.52 months (95% CI = 38.62 - 54.82 being 45.52 months (95% CI, 38.98 - 60.37) and 42.37 months (85% CI, 37.20 - 57.64) in the TM001 and IPI arm, respectively

The primary endpoint, progression free survival (PFS) according to RECIST 1.1, showed that the median PFS is 2-fold longer after the TIL treatment compared to ipilimumab arm (6.65 months (95% CI, 4.06 - 12.47) in TIL arm, compared to 3.08 months in the IPI arm (95% CI, 3.01 - 4.48)). The analysis of the curves showed an HR between ipilimumab and TM001 arms of 0.49 [95% CI 0.32-0.73; P-value <0.001]).

In general, PFS was shown to be largely consistent across subgroups based on gender, age, site, type of prior therapy, BRAF mutation, WHO status, LDH (<ULN), disease stage, brain metastasis, liver metastasis, and follow-up systemic therapy.

For the patients from the NKI site, previously treated with anti-PD-1, the PFS rate at 6 months was of 50.85% (95% CI, 39.57 - 65.35) in TM001 arm compared to 18.97% (95% CI, 11.14 - 32.28) in IPI arm. Assessment of PFS according to irRC also showed a PFS of 5.4 months (95% CI, 3.96 - 12.83) in patients treated with TM001 compared to 3.55 months (95% CI, 3.03 - 4.84) in patients treated with IPI which is line with the mPFS assessed according to RECIST 1.1. These results suggest a clinical response for the patients treated in the TIL. However, bearing in mind the methodological concerns described above, no conclusion will be drawn with regards to clinical benefit.

The ORR in the FAS/ITT population was 50.0% (95% CI, 38.9 - 61.1) in the TIL-IMP arm, as compared to 21.4% (95% CI, 13.2 - 31.7 [$p < 0.001$]) in the IPI arm. CR was observed in 20.2% (95% CI, 12.3 - 30.4 [$p < 0.001$]) of patients in the TIL-IMP arm and in 8.3% (95% CI, 3.4 - 16.4) of patients in the IPI arm. The ORR results in the IPI arm are equivalent to those seen in comparable trials. Median DOR was 359.5 days (Q1, Q3: 168.5, 900.25), i.e. approximately 12.0 months in the IPI arm and 392.5 days (Q1, Q3: 202.75, 1221.75), i.e. approximately 13.1 months in the TIL arm. Thus, response rates in the TIL arm appear substantially higher than those in the control arm, while duration of response rates are more comparable between the two arms.

For the patients from the NKI site, previously treated with anti-PD-1, the percentage of patients with an objective response according to RECIST 1.1 was found to be significantly higher ($p < 0.001$) in patients that received TM001 therapy, compared to patients that received the comparator IPI

treatment with 29 patients corresponding to 49.15% (95% CI, 65.9 – 62.5) in TM001 arm compared to 12 patients corresponding to 20.69% of (95% CI, 111.2 - 33.4) in ipilimumab arm. Patients for which no response was determined were 6 in ipilimumab arm vs. 1 in TM001. The Applicant noted that ORR in the CSR was already computed under a conservative approach counting all NE/ND as non-responders. However, the requested sensitivity analyses - including recalculated ORR estimates and treatment contrasts under alternative assumptions - were not provided. Additionally, it was not assessed whether evaluability differed between arms, potentially biasing the ORR comparison. The claim that NE/ND cases "factually" correspond to PD lacks RECIST confirmation and does not substitute for the required robustness assessment. The ORR is a secondary endpoint limited by the absence of multiplicity adjustment.

Median overall survival (FAS/ITT population) was 25.04 months (95% CI, 17.82 - 44.93) in the TIL-IMP arm compared to 19.04 months (95% CI, 14.31 - 30.90) in the IPI arm. Considering the follow up of the patients in the clinical trial, the overall survival rate at 18 months, 24 months and 36 months for the patients pre-treated with anti-PD1 treated at NKI site was provided. Although there is a trend in favour of the TIL arm, this is not statistically significant since the 95% CI overlap. OS data indicate non-proportional hazards and crossing of the curves around the 6-7 months mark. Regarding any clinical significance of the crossing of the curves, the applicant argues that the OS curves for patients in the Tacquell and IPI arm are in fact superimposable, and that the divergence of the curves cannot easily be attributed to the M14TIL study treatment (Tacquell therapy versus IPI treatment) alone, but could be related to differences in subsequent treatment lines for the two arms. This is acknowledged.

An analysis of OS based on no prior systemic therapy, adjuvant anti-PD-1 therapy or first-line anti-PD-1 as prior treatment was performed. The numbered results of the modified ITT or so-called Tacquell target population by the Applicant were provided and confirmed the absence of difference between both groups. The data were not submitted for the ITT population, which is not acceptable. However, this has not been further pursued considering the other unresolvable issues in the dossier.

Patients with BRAF mutation have better OS results than those without, likely due to treatment with BRAF/MEK inhibitors following disease progression on TIL therapy.

A significant interaction between sex and treatment arm on OS was found in subgroup analyses. The applicant provided Kaplan-Meier plots of OS by gender and arm, both for the ITT (n=168) and for the "Tacquell target population", namely NL patients with prior anti-PD1 (n=59 in TIL arm and n=58 in IPI arm). In both populations, females have poorer OS results on TIL than on IPI, as evidenced by the curves and by median OS. While the interaction effect between gender and treatment arm was not found to be significant for the target population, for the ITT (n=168), the interaction was indeed significant (p=0.038). The results seen in female patients in the pivotal trial are concerning. However, OS is a secondary endpoint, which is descriptive only due to lacking formal multiplicity adjustment, and there appears to be no biological rationale for this difference. The applicant proposed to further monitor potential gender differences in the ongoing H23TIL hospital exemption program post-approval, this would have been supported if a marketing authorisation would have been granted..

For the patients from the NKI site, previously treated with anti-PD-1, the median OS of 25.04 months [95% CI, 16.90 – 44.93] in patients treated with TM001 was slightly higher than the median OS of 18.22 months [95% CI, 13.98 – 36.81] in patients treated with IPI (HR = 0.95, 95% CI: 0.61 – 1.49; P-value =0.082) but the difference was not statistically significant. In addition, the Kaplan-Meier curve illustrate that both TM001 and ipilimumab curves overlap upon prolonged follow-up, which strengthen the issue raised as regards the limited efficacy result observed with the TIL.

Dedicated studies in renal and hepatic impaired patient have not been carried out and the Applicant clarified that for the renal function, the patients with liver metastases could be included with slightly higher serum ALAT/ASAT levels.

Supportive studies

M14TIL side study: The M14TIL-side-study included 4 patients, and based on the very limited information provided, the side-study is not considered to provide further evidence to the dossier.

Hospital Exemption program: The median PFS assessed according to RECIST 1.1 was 3.48 months after the TIL infusion for the 50 TM001-treated patients included in this analysis and the PFS at six months after TM001 infusion was 39.96% (95% CI 27.17 – 58.79) for these patients. This result of 3.48 months is different to the median PFS of 6.665 months obtained in the pivotal study because PFS in the hospital exemption program was calculated from the day of TM001 infusion, whereas in the confirmatory phase III trial PFS was calculated from the day of randomization, with a median time between randomization and infusion of 49 days (range 29 - 356 days).

The overall survival was also shorter than in the pivotal study, at 13.93 months, as compared to 25.04 months in the TIL arm in the pivotal study. However, the median follow-up for OS was only median 9.36 months. Response rates were also somewhat lower than in the pivotal study, with an ORR of 34%, including 8% with a CR. The efficacy results from the HE programme are numerically somewhat lower than those in the pivotal study but still provide some corroboration of the results seen in the pivotal study.

Updated results were provided for 91 patients treated in the hospital exemption program (data cut-off 08OCT2025) showing similar results as for the first analysis of 50 Patients. Updated PFS and OS results of patients who received the IPI/NIVO in first-line setting were also provided, showing same trends as the results from patients who received first-line anti-PD-1 and adjuvant anti-PD1.

5.3.5.2. Conclusions on the clinical efficacy

The routine GCP inspection (EMA/IN/0000276203) concluded that multiple significant findings constituting (often significant) non-compliance with ICH-GCP E6 R2 have been raised. Given the inspection conclusion that data integrity, completeness and correctness of the CSR could not be unambiguously established, it remains insufficient to re-establish the reliability of the pivotal evidence package.

The several methodological and statistical issue as described above which are supported by the GCP inspection, prevents from providing clear evidence of efficacy for Tacquel. Indeed, the methodological explanations provided do not reconcile the primary efficacy endpoints and analysis outputs with the documented limitations affecting computerised systems, data management/audit trail, and re-constructability of statistical outputs. Furthermore, given the changing treatment landscape during the extended time period in which the clinical trial was run, it is not clear whether, and in which setting the product might provide a clinical benefit. Further, given the concerns with GCP and study methodology in general, including the violation of the ITT principle through the exclusion of data from the Danish site, the reliability of the data from the study is in question.

In this context, it remains to be demonstrated, for the pivotal efficacy evidence package, that the key efficacy source data and derived endpoints (notably PFS events and censoring) are reliable and consistently derived from traceable source documentation and final locked datasets.

All in all, no positive efficacy outcome has been shown in the sought indication.

The CHMP endorses the CAT conclusion on clinical efficacy as described above.

5.4. Clinical safety

5.4.1. Safety data collection

Overall, 169 patients were exposed to TIL throughout the clinical development: 35 patients in 2 phase 1/2 studies, 80 in the M14TIL, 4 in the side study, and 50 in the hospital exemption program H23TIL program. Only data from study M14TIL, where 80 patients received TIL (64 at NKI and 16 at CCIT) is considered for assessing safety.

The safety data was collected at a reasonable frequency (during chemotherapy, at TIL infusion, and during IL2 treatment, with complete AE assessment at 6, 12, 18, 24 weeks, then every 3 months up to 3 years and every 6 months up to 5 years or end of study. Causality was assessed by investigator by phase of treatment and overall. Nevertheless, the 3 treatment phases cannot be dissociated and the whole regimen is to be considered for safety assessment.

The first patient was enrolled in the study on 23 September 2014 and end of study was 31 December 2023.

5.4.2. Patient exposure

Phase 3 confirmatory Study: M14TIL

Patients assigned to the TIL-investigational medicinal product (TIL-IMP) therapy group received a single intravenous TIL-IMP infusion containing 5E9 to 2E11 viable cells. The TIL-IMP infusion was preceded by a preparative non-myeloablative lymphodepleting chemotherapy regimen and followed by supportive intravenous administration of IL-2.

Preparative chemotherapy consisted of a NMA-LD regimen of cyclophosphamide (60 mg/kg/day x 2 days IV and Mesna 300mg/m²) and fludarabine (25 mg/m²/day x 5 days IV). After TIL-IMP infusion, in-vivo outgrowth of T-cells from the TIL-IMP was supported by high dose IL-2 IV (600,000 IU/kg/dose every 8 hours) for a maximum of 15 times.

Patients assigned to the IPI group received 3 mg/kg IPI administered intravenously every 3 weeks, for a maximum of 4 doses, following SmPC recommendations of Yervoy.

For the phase 3 study, TIL was manufactured at 3 sites. Clinical outcome of the confirmatory phase III trial was positive and there appeared no differences between the clinical sites in clinical outcome parameters, however, a post-trial product quality comparability analysis showed the manufacturing process differences between the Dutch manufacturing sites and the Danish manufacturing site. For this reason, TIL-IMP includes any TIL product administered in the confirmatory phase III trial, while TM001 is the TIL-IMP product manufactured by the Dutch sites that is subject to this MAA.

An overview of patient numbers in the confirmatory phase 3 trial in relation to treatment received, clinical site of trial, and prior anti-PD-1 treatment is provided in **Table 20**.

Table 20. Patient numbers in the confirmatory phase III trial M14TIL

	NKI site	CCIT site	TOTAL
Nr of patients included (FAS/ITT)	132 TM001 : 66 IPI : 66	36 TIL-IMP : 18 IPI : 18	168 TM001/TIL-IMP : 84 IPI : 84
Nr of patients treated (PPS)	128 TM001 : 64 IPI : 64	34 TIL-IMP : 16 IPI : 18	162 TM001/TIL-IMP : 80 IPI : 82
Nr of patients with prior-anti-PD-1 treatment (FAS)	117 TM001 : 59 IPI : 58	28 TIL-IMP : 14 IPI : 14	145 TM001/TIL-IMP : 73 IPI : 72
Nr of patients with prior anti-PD-1 treatment (PPS)	114 TM001 : 57 IPI : 57	26 TIL-IMP : 12 IPI : 14	140 TM001/TIL-IMP : 69 IPI : 71

FAS: full analysis set; ITT: intention to treat; PPS: per protocol analysis set; TM001 and SmPC Safety Analysis Sets in grey

Overall, 169 patients were exposed to TIL throughout the clinical development: 35 patients in 2 phase 1/2 studies, 80 in the M14TIL, 4 in the side study, and 91 in the hospital exemption program H23TIL in the Netherlands.

Demographics

Baseline characteristics of patients in M14TIL study: refer to the efficacy section.

5.4.3. Adverse events

Summary of adverse events (full analysis set)

Table 21. Overview of Treatment Emergent Adverse Events - NKI and CCIT site -Safety Analysis Set

Event	IPI arm, N= 82	TIL-IMP arm, N= 80	P-value
Any TEAE	82 (100%)	80 (100%)	1.00
Any TEAE grade ≥3	59 (71.95%)	80 (100%)	0.00
Any SAE	36 (43.9%)	13 (16.25%)	0.00
Any treatment related TEAE	79 (96.34%)	80 (100%)	0.24
Any treatment related TEAE grade ≥3	47 (57.32%)	80 (100%)	0.00

Event	IPI arm, N= 82	TIL-IMP arm, N= 80	P-value
Any cyclophosphamide related TEAE	0 (0%)	80 (100%)	NA
Any cyclophosphamide related TEAE grade ≥ 3	0 (0%)	80 (100%)	NA
Any fludarabine related TEAE	0 (0%)	80 (100%)	NA
Any fludarabine related TEAE grade ≥ 3	0 (0%)	80 (100%)	NA
Any TIL related TEAE	0 (0%)	76 (95%)	NA
Any TIL related TEAE grade ≥ 3	0 (0%)	56 (70%)	NA
Any IL-2 related TEAE	0 (0%)	79 (98.75%)	NA
Any IL-2 related TEAE grade ≥ 3	0 (0%)	74 (92.5%)	NA
Any TIL/IL-2 related TEAE	0 (0%)	80 (100%)	NA
Any TIL/IL-2 related TEAE grade ≥ 3	0 (0%)	78 (97.5%)	NA
Any treatment related SAE	22 (26.83%)	12 (15%)	0.08

All patients in both arms experienced at least 1 Treatment Emergent Adverse Event (TEAE). In the TIL-IMP arm 100% of the patients experienced Any TEAE grade ≥ 3 , compared to 71.95% in the IPI arm. However, 16.25% of the patients in TIL-IMP arm had an SAE compared to 43.9% in the IPI arm.

All patients (100%) in the TIL-IMP arm experienced chemotherapy-related TEAEs (cyclophosphamide and fludarabine). Any IL-2-related TEAE was reported for 98.75% of the TIL-IMP treated patients.

Most common treatment related AEs ($\geq 25\%$) by worst grade per patient in the TIL-IMP group.

Table 22. Most common treatment related adverse events TIL-IMP arm by worst grade - Safety Analysis Set

AE	TIL-IMP arm, N=80 Grade (CTCAE)					
	1	2	3	4	5	Total
Neutrophil count decreased	NA	NA	3 (3.75%)	77 (96.25%)	NA	80 (100%)
Fever	6 (7.5%)	32 (40%)	36 (45%)	NA	NA	74 (92.5%)
Anemia	7 (8.75%)	50 (62.5%)	16 (20%)	NA	NA	73 (91.25%)
Nausea	26 (32.5%)	45 (56.25%)	2 (2.5%)	NA	NA	73 (91.25%)
Platelet count decreased	2 (2.5%)	NA	17 (21.25%)	54 (67.5%)	NA	73 (91.25%)
Febrile neutropenia	NA	NA	70 (87.5%)	1 (1.25%)	NA	71 (88.75%)
Chills	9 (11.25%)	52 (65%)	6 (7.5%)	NA	NA	67 (83.75%)
Dyspnea	23 (28.75%)	25 (31.25%)	14 (17.5%)	1 (1.25%)	NA	63 (78.75%)
Hypophosphatemia	1 (1.25%)	8 (10%)	50 (62.5%)	3 (3.75%)	NA	62 (77.5%)
Fatigue	27 (33.75%)	25 (31.25%)	8 (10%)	NA	NA	60 (75%)
White blood cells decreased	NA	NA	1 (1.25%)	56 (70%)	NA	57 (71.25%)
Diarrhea	32 (40%)	13 (16.25%)	3 (3.75%)	NA	NA	48 (60%)
Hypocalcemia	15 (18.75%)	31 (38.75%)	1 (1.25%)	NA	NA	47 (58.75%)
Rash	16 (20%)	18 (22.5%)	10 (12.5%)	NA	NA	44 (55%)
Hypoalbuminemia	9 (11.25%)	34 (42.5%)	NA	NA	NA	43 (53.75%)
Sinus tachycardia	42 (52.5%)	NA	1 (1.25%)	NA	NA	43 (53.75%)
Alopecia	2 (2.5%)	35 (43.75%)	NA	NA	NA	37 (46.25%)
Weight gain	25 (31.25%)	11 (13.75%)	NA	NA	NA	36 (45%)
Hypotension	18 (22.5%)	10 (12.5%)	6 (7.5%)	NA	NA	34 (42.5%)
Vomiting	28 (35%)	3 (3.75%)	2 (2.5%)	NA	NA	33 (41.25%)
Headache	22 (27.5%)	10 (12.5%)	NA	NA	NA	32 (40%)
Elevated AST concentration	10 (12.5%)	12 (15%)	9 (11.25%)	NA	NA	31 (38.75%)
CPK increased	16 (20%)	4 (5%)	6 (7.5%)	3 (3.75%)	NA	29 (36.25%)
Edema limbs	27 (33.75%)	2 (2.5%)	NA	NA	NA	29 (36.25%)
Elevated ALT concentration	5 (6.25%)	12 (15%)	11 (13.75%)	NA	NA	28 (35%)
Pulmonary edema	22 (27.5%)	5 (6.25%)	1 (1.25%)	NA	NA	28 (35%)
Capillary leak syndrome	NA	23 (28.75%)	NA	1 (1.25%)	NA	24 (30%)
Hypokalemia	15 (18.75%)	7 (8.75%)	2 (2.5%)	NA	NA	24 (30%)
Elevated alkaline phosphatase concentration	15 (18.75%)	5 (6.25%)	3 (3.75%)	NA	NA	23 (28.75%)

Overview of Adverse events by treatment phase (CSR):

Overview of TEAEs before TIL infusion (following the non-myeloablative lymphocyte depleting therapy):

Table 23. Overview of all TEAEs before TIL-IMP infusion

AE	TIL IMP arm, N = 80
Any TEAE	79 (98.75%)
Any SAE	0 (0%)
Any treatment related TEAE	78 (97.5%)
Any cyclophosphamide related TEAE	78 (97.5%)
Any fludarabine related TEAE	76 (95%)
Any treatment related SAE	0 (0%)

Table 24. Most common chemotherapy related adverse events (25%) by worst grade - TIL-IMP arm - Safety Analysis Set

AE	TIL-IMP arm, N=80 Grade (CTCAE)					Total
	1	2	3	4	5	
Neutrophil count decreased	NA	NA	3 (3.75%)	77 (96.25%)	NA	80 (100%)
Anemia	7 (8.75%)	50 (62.5%)	16 (20%)	NA	NA	73 (91.25%)
Platelet count decreased	2 (2.5%)	NA	17 (21.25%)	54 (67.5%)	NA	73 (91.25%)
Febrile neutropenia	NA	NA	68 (85%)	1 (1.25%)	NA	69 (86.25%)
Nausea	26 (32.5%)	41 (51.25%)	2 (2.5%)	NA	NA	69 (86.25%)
White blood cells decreased	NA	NA	1 (1.25%)	56 (70%)	NA	57 (71.25%)
Fatigue	26 (32.5%)	19 (23.75%)	4 (5%)	NA	NA	49 (61.25%)
Hypophosphatemia	1 (1.25%)	28 (35%)	19 (23.75%)	1 (1.25%)	NA	49 (61.25%)
Alopecia	2 (2.5%)	35 (43.75%)	NA	NA	NA	37 (46.25%)
Diarrhea	23 (28.75%)	11 (13.75%)	2 (2.5%)	NA	NA	36 (45%)
Hypocalcemia	15 (18.75%)	20 (25%)	1 (1.25%)	NA	NA	36 (45%)
Hypoalbuminemia	10 (12.5%)	17 (21.25%)	NA	NA	NA	27 (33.75%)
Vomiting	22 (27.5%)	2 (2.5%)	2 (2.5%)	NA	NA	26 (32.5%)
Headache	15 (18.75%)	5 (6.25%)	NA	NA	NA	20 (25%)
Hypokalemia	15 (18.75%)	3 (3.75%)	2 (2.5%)	NA	NA	20 (25%)

Overview of TEAE related to IL-2, following TIL administration

Table 25. Most common IL-2 related adverse events by worst grade - Safety Analysis Set

AE	1	2	3	4	5	Total
Fever	3 (3.75%)	32 (40%)	34 (42.5%)	NA	NA	69 (86.25%)
Chills	7 (8.75%)	51 (63.75%)	6 (7.5%)	NA	NA	64 (80%)
Dyspnea	24 (30%)	23 (28.75%)	13 (16.25%)	NA	NA	60 (75%)
Febrile neutropenia	NA	NA	57 (71.25%)	NA	NA	57 (71.25%)
Hypophosphatemia	1 (1.25%)	6 (7.5%)	44 (55%)	3 (3.75%)	NA	54 (67.5%)
Fatigue	22 (27.5%)	21 (26.25%)	7 (8.75%)	NA	NA	50 (62.5%)
Sinus tachycardia	39 (48.75%)	NA	1 (1.25%)	NA	NA	40 (50%)
Nausea	20 (25%)	17 (21.25%)	NA	NA	NA	37 (46.25%)
Diarrhea	26 (32.5%)	7 (8.75%)	2 (2.5%)	NA	NA	35 (43.75%)
Hypotension	18 (22.5%)	9 (11.25%)	6 (7.5%)	NA	NA	33 (41.25%)
Hypoalbuminemia	5 (6.25%)	26 (32.5%)	NA	NA	NA	31 (38.75%)
Hypocalcemia	3 (3.75%)	26 (32.5%)	NA	NA	NA	29 (36.25%)
CPK increased	15 (18.75%)	4 (5%)	6 (7.5%)	3 (3.75%)	NA	28 (35%)

In the IPI arm, the Grade 3 AE with highest frequency were colitis 18.29%, diarrhoea 14.63%, elevated ALT/AST 8.54/7.32%. In total 9 AE were Grade 4 (elevated ALT/AST, colitis, GGT increased, lipase increased, and hyperglycaemia).

For the IPI arm, the most common treatment related adverse events reported by worst grade per patient ($\geq 25\%$) are presented in **Table 26** below. Diarrhoea and fatigue were reported by the majority of patients.

Table 26. Most common treatment related adverse events IPI arm by worst grade -Safety Analysis Set

AE	IPI arm, N=82 Grade (CTCAE)					Total
	1	2	3	4	5	
Diarrhea	11 (13.41%)	14 (17.07%)	12 (14.63%)	NA	NA	37 (45.12%)
Fatigue	19 (23.17%)	17 (20.73%)	1 (1.22%)	NA	NA	37 (45.12%)
Pruritus	26 (31.71%)	8 (9.76%)	NA	NA	NA	34 (41.46%)
Nausea	16 (19.51%)	12 (14.63%)	2 (2.44%)	NA	NA	30 (36.59%)
Rash	17 (20.73%)	7 (8.54%)	4 (4.88%)	NA	NA	28 (34.15%)
Elevated ALT concentration	6 (7.32%)	8 (9.76%)	7 (8.54%)	1 (1.22%)	NA	22 (26.83%)
Headache	18 (21.95%)	3 (3.66%)	1 (1.22%)	NA	NA	22 (26.83%)

5.4.3.1. Adverse drug reactions

Summary of ADRs

Adverse drug reactions (ADR)

Since the safety of TM001 is not considered to be influenced by prior anti-PD-1 treatment, the analysis of TM001-related AEs by organ system (**Table 27**) is based on safety data from the total of 64 patients that completed TM001 therapy (patients with and without prior anti-PD1 treatment).

Adverse drug reactions include those AE observed after the TIL infusion (i.e. TIL and IL2 treatment).

Table 27. Adverse reactions to TM001 by worst grade per patient - Phase III trial (M14TIL) (n=64)

System (SOC)	Organ	Class	Frequency	Adverse reactions	Incidence	
					All grades	Grade ≥ 3
Blood and lymphatic system disorders			very common	Febrile neutropenia	45.31%	45.31%

System (SOC)	Organ	Class	Frequency	Adverse reactions	Incidence	
					All grades	Grade ≥3
Cardiac disorders			very common	Sinus tachycardia	28.13%	0%
			common	Atrial fibrillation	3.13%	0%
				Chest pain - cardiac	1.56%	0%
				Palpitations	1.56%	0%
Ear and labyrinth disorders			common	Hearing impaired	4.69%	1.56%
				Tinnitus	1.56%	0%
Eye disorders			very common	Blurred vision	10.94%	0%
			common	Uveitis	9.38%	1.56%
				Conjunctivitis	1.56%	0%
				Dry eye	1.56%	0%
				Photophobia	1.56%	0%
				Retinal detachment	1.56%	0%
Gastrointestinal disorders			very common	Nausea	35.94%	0%
				Diarrhea	21.88%	3.13%
				Vomiting	12.50%	0%
			common	Abdominal pain	1.56%	0%
General disorders and administration site conditions			very common	Fatigue	60.94%	4.69%
				Fever	59.38%	14.06%
				Chills	28.13%	0%
			common	Edema limbs	7.81%	0%
				Non-cardiac chest pain	6.25%	0%
				Edema face	4.69%	0%
				Malaise	4.69%	0%
				Localized edema	3.13%	0%
				Edema trunk	1.56%	0%
				Flu-like symptoms	1.56%	0%
Immune system disorders			common	Allergic reaction	1.56%	0%
Injury, poisoning and procedural complications			common	Fall	1.56%	0%

System (SOC)	Organ	Class	Frequency	Adverse reactions	Incidence	
					All grades	Grade ≥3
Investigations	very common			Elevated AST concentration	15.63%	3.13%
				GGT increased	14.06%	7.81%
				Elevated ALT concentration	12.50%	1.56%
				Weight gain	12.50%	0%
	common			Elevated alkaline phosphatase concentration	9.38%	1.56%
				Weight loss	4.69%	0%
				Blood bilirubin increased	3.13%	0%
				CPK increased	1.56%	0%
				Platelet count decreased	1.56%	0%
				White blood cells decreased	1.56%	0%
Metabolism and nutrition disorders	very common			Hypocalcemia	35.94%	0%
				Hypoalbuminemia	31.25%	0%
				Hypophosphatemia	17.19%	10.94%
	common			Hypokalemia	9.38%	0%
				Anorexia	9.38%	1.56%
Musculoskeletal and connective tissue disorders	common			Myalgia	4.69%	0%
				Pain in extremity	3.13%	0%
Nervous system disorders	very common			Headache	18.75%	0%
	common			Dysgeusia	6.25%	0%
				Dizziness	3.13%	0%
				Concentration impairment	1.56%	0%
				Peripheral sensory neuropathy	1.56%	0%
Psychiatric disorders	common			Agitation	1.56%	0%
				Depression	1.56%	0%
				Libido decreased	1.56%	0%
Renal and urinary disorders	common			Acute kidney injury	3.13%	0%
				Urinary frequency	1.56%	0%

System (SOC)	Organ	Class	Frequency	Adverse reactions	Incidence	
					All grades	Grade ≥ 3
Respiratory, thoracic and mediastinal disorders	very common			Dyspnea	37.50%	10.94%
				Pulmonary edema	20.31%	0%
				Hypoxia	10.94%	3.13%
	common			Cough	6.25%	0%
				Pleural effusion	4.69%	1.56%
				Adult respiratory distress syndrome	3.13%	3.13%
				Bronchospasm	1.56%	0%
Skin and subcutaneous tissue disorders	very common			Rash	48.44%	10.94%
				Skin hypopigmentation	14.06%	0%
	common			Pruritus	7.81%	0%
				Skin hyperpigmentation	4.69%	0%
				Dry skin	3.13%	0%
				Purpura	3.13%	0%
Vascular disorders	common			Hypertension	7.81%	4.69%
				Hypotension	3.13%	0%
				Capillary leak syndrome	1.56%	0%
				Hot flashes	1.56%	0%

5.4.4. Adverse events of special interest, serious adverse events and deaths, other significant events

Serious Adverse events

In total 84 SAEs were reported. In the TIL-IMP arm, 13 patients (16.25%) reported 26 SAEs and in the IPI arm 36 patients (43.9%) reported 58 SAEs. In the TIL-IMP arm 12 patients (15%) reported at least 1 treatment related SAE compared to 22 patients (26.83%) in the IPI arm.

SAEs that occurred in the TIL-IMP arm by worst grade per patient are shown in **Table 28**. The majority of the patients experienced $\geq$ Grade 3 serious adverse events. One patient experienced a Grade 5 serious adverse event, a venous thromboembolism, according to the investigator not related to treatment.

Table 28. All serious adverse events that occurred in the TIL-IMP arm by worst grade - Safety Analysis Set

	TIL-IMP arm, N=80 Grade (CTCAE)				
SAE	1	2	3	4	5
Adult respiratory distress syndrome	NA	NA	1 (1.25%)	2 (2.5%)	NA
Anemia	NA	NA	1 (1.25%)	NA	NA
Cardiac troponin T increased	NA	NA	2 (2.5%)	NA	NA
Intracranial hemorrhage	NA	NA	1 (1.25%)	NA	NA
Myocarditis	NA	NA	1 (1.25%)	1 (1.25%)	NA
Peripheral motor neuropathy	NA	NA	1 (1.25%)	NA	NA
Platelet count decreased	NA	NA	NA	1 (1.25%)	NA
Pleural effusion	NA	NA	1 (1.25%)	NA	NA
Pneumonia	NA	NA	NA	1 (1.25%)	NA
Pneumonitis	NA	NA	1 (1.25%)	NA	NA
Uveitis	NA	1 (1.25%)	1 (1.25%)	NA	NA
Venous thromboembolism	NA	NA	1 (1.25%)	NA	1 (1.25%)
Vision loss	NA	NA	NA	1 (1.25%)	NA
Wound infection	NA	NA	1 (1.25%)	NA	NA

Hospitalization is part of the TIL treatment procedure, starting with chemotherapy (day -7).

Hospitalization for the administration of the TIL treatment will therefore not be reported as a 'serious adverse event'. If the patient experiences an event that falls under the above mentioned criteria and/or the event requires IV or other treatment that cannot be given outside the hospital and/or the patient is admitted to an Intensive Care Unit, the event will be reported as an SAE.

SAEs that occurred in the IPI arm by worst grade per patient are presented in **Table 29**. One patient experienced a Grade 5 serious adverse event, an intracranial haemorrhage, according to the investigator not related to treatment.

Table 29. All serious adverse events that occurred in the IPI arm by worst grade - Safety Analysis Set

	IPI arm, N=82 Grade (CTCAE)				
AE	1	2	3	4	5
Acute kidney injury	1 (1.22%)	NA	2 (2.44%)	NA	NA
Adrenal insufficiency	NA	1 (1.22%)	NA	NA	NA
Anemia	NA	1 (1.22%)	NA	NA	NA
Biliary tract infection	NA	NA	1 (1.22%)	NA	NA

	IPI arm, N=82 Grade (CTCAE)				
AE	1	2	3	4	5
Chills	NA	NA	1 (1.22%)	NA	NA
Colitis	NA	1 (1.22%)	6 (7.32%)	1 (1.22%)	NA
Constipation	NA	1 (1.22%)	NA	NA	NA
Dehydration	NA	NA	1 (1.22%)	NA	NA
Diarrhea	NA	NA	2 (2.44%)	NA	NA
Dizziness	NA	NA	1 (1.22%)	NA	NA
Duodenal perforation	NA	NA	1 (1.22%)	NA	NA
Dyspnea	NA	1 (1.22%)	1 (1.22%)	NA	NA
Elevated ALT concentration	NA	NA	2 (2.44%)	NA	NA
Enterocolitis infectious	NA	NA	1 (1.22%)	NA	NA
Fever	NA	1 (1.22%)	NA	NA	NA
Flu-like symptoms	NA	NA	1 (1.22%)	NA	NA
Gastric ulcer	NA	1 (1.22%)	NA	NA	NA
Headache	NA	NA	1 (1.22%)	NA	NA
Hemodynamic instability	NA	NA	1 (1.22%)	NA	NA
Hepatitis	NA	NA	2 (2.44%)	NA	NA
Hyperglycemia	NA	NA	NA	2 (2.44%)	NA
Hypophysitis	NA	NA	2 (2.44%)	NA	NA
Ileus	NA	NA	1 (1.22%)	NA	NA
Immune system disorder-other, bronchiolitis	NA	NA	1 (1.22%)	NA	NA
Intracranial hemorrhage	NA	NA	NA	NA	1 (1.22%)
Malaise	NA	2 (2.44%)	NA	NA	NA
Myocarditis	NA	NA	NA	NA	NA
Non-cardiac chest pain	NA	NA	1 (1.22%)	NA	NA
Pneumonitis	NA	1 (1.22%)	1 (1.22%)	NA	NA
Pulmonary thromboembolism	NA	NA	NA	1 (1.22%)	NA
Rash	NA	NA	2 (2.44%)	NA	NA
Sinus tachycardia	NA	1 (1.22%)	NA	NA	NA
Skin infection	NA	NA	2 (2.44%)	NA	NA
Small intestinal obstruction	NA	1 (1.22%)	1 (1.22%)	NA	NA
Stevens-Johnson syndrome	NA	NA	NA	1 (1.22%)	NA
Stomach pain	NA	NA	1 (1.22%)	NA	NA
Tumor pain	NA	2 (2.44%)	NA	NA	NA

Treatment emergent SAE

Thirteen patients reported a total of 21 treatment emergent SAEs in the TIL-IMP arm and in the IPI arm 37 patients reported 58 treatment emergent SAEs.

Of the 21 treatment emergent SAEs in the TIL-IMP arm, 6 were considered related to TIL-IMP. Of the 58 treatment emergent SAEs in the IPI arm, 34 were considered related to IPI.

Deaths

There were no deaths related to TM001 and no patients died within the official follow-up period of the confirmatory phase III trial (M14TIL), the M14TIL side study or the H23TIL hospital exemption program.

Of the 80 patients in the TIL-IMP arm, one patient died after TIL-IMP infusion due to toxicity that was, according to the investigator, not related to TIL-IMP treatment. A tabulated overview of death cases has been provided later on in the procedure, where 5 cases of death are not attributed to disease progression and at least 1 was due to an AE (vasculitis).

In the IPI arm, no patients died within the study.

Other significant SAE

There were no other significant adverse events identified that led to an intervention, withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events.

Serious ADR:

In the TM001 safety analysis set there were 5 reports of SAEs related to TM001 (**Table 30**).

Table 30. SAEs related to TM001 by worst grade per patient-phase III trial (M14TIL)- TM001 Safety Analysis Set

Serious Adverse Reactions	Number of patients	CTCAE grading
Adult respiratory distress syndrome (ARDS)	2	4, 3
Pleural effusion	1	3
Uveitis	2	3, 2

The DLP for the writing of this report was the point when >50% of patients died and the median overall survival time could be defined. Death of patients in this study is correlated with the disease. Due to this no analysis has been done.

Adverse events of special interest

In the TIL-IMP arm expected autoimmune toxic effects associated with melanocyte-directed reactivity were uveitis, and hearing loss. Pleural effusion, adult respiratory distress and uveitis were considered related to the treatment with TIL-IMP. The majority of the reported serious adverse events related to the preparative NMA-LD chemotherapy, however, as IL-2 is administered directly after TIL-IMP infusion, the role of TIL-IMP in the reported (serious) adverse events cannot be excluded.

5.4.5. Discontinuation due to adverse events

In the TIL-IMP arm, 84 patients received preparative non-myeloablative lymphocyte depleting regimen of chemotherapy and 80 patients received TIL-IMP infusion. All dosed patients in the TIL-IMP arm completed TIL-IMP therapy.

Table 31. Reason for end of IPI treatment - total group IPI arm (FAS population)

	IPI (N=84)
Reason end of treatment	N (%)
According to protocol	40 (47.62%)
Disease progression	15 (17.86%)
Toxicity	26 (30.95%)
Patients refusal	2 (2.38%)
Other	1 (1.19%)

5.4.6. Safety in special populations

All studies with TM001 were conducted in adults and elderly (≥ 18 years and ≤ 75 years of age) with unresectable stage IIIC to IV melanoma. No analyses with respect to intrinsic factors related to safety of TM001, including age, were performed.

Use in pregnancy and lactation

Pregnant and breastfeeding women were excluded from the TM001 clinical development program, and a pregnancy test was performed on all women of child-bearing potential before the start of TM001 therapy.

Overdose

No information relevant to overdose, including signs and/or symptoms, laboratory findings, and therapeutic measures and/or treatments and antidotes was retrieved in any of the performed studies/clinical use of TM001.

5.4.7. Immunological events

Immune-mediated toxicities recorded after Tacquell therapy were uveitis, skin hypopigmentation, and hearing impairment. Skin hypopigmentation was reported for 14% while hearing impaired was observed in 5% (2% grade 3 or higher) of the patients. Uveitis occurred in 11% (2% grade 3 or higher) of the patients that received Tacquell.

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

No interaction studies have been performed. The use of systemic corticosteroids may interfere with the activity of TM001. The use of systemic corticosteroids is therefore not recommended in combination with TM001. Co-administration of TM001 and agents known to stimulate T cell function (e.g. checkpoint inhibitors) has not been investigated and the effects are unknown.

5.4.9. Vital signs and laboratory findings

Clinical chemistry, urinalysis, hematology, TSH and FT4 were assessed for each patient and when out of range reported as (S)AEs. No additional clinical laboratory evaluations have been performed. (see section 5.4.3.1).

5.4.10. Post-marketing experience

Not applicable

5.4.11. Overall discussion and conclusions on clinical safety

5.4.11.1. Discussion

5.4.11.1.1. Overall assessment of available safety data

The safety analysis is based on the data from the phase 3 pivotal study (M14TIL), a multicenter, open-label, randomized phase III trial comparing TM001 to standard ipilimumab treatment in patients with unresectable stage IIIC to IV melanoma. Data from the M14TIL 'side study' and the hospital exemption program H23TIL in The Netherlands are supportive. According to the Applicant, number and severity of AEs from the H23TIL hospital exemption programme is in line with the previously gained knowledge on TIL therapy. However, this cannot be assessed at present due to the uncertainties of the safety data from the phase III trial.

The treatment regimen consisted of Cyclophosphamide on D-7 and D-6 and Fludarabine on D-5 to D-1, TIL infusion on D0, and interleukin IL2 on D0 to D5. Cyclophosphamide and Fludarabine dose was as recommended in the SmPC (60mg/kg/day and respectively 25mg/m²/day). Proleukin planned dose was 600,000UI/Kg every 8 hours, in line with the product label approved by FDA, but considerably higher than recommended in the SmPC (18 *10⁶UI/m²/day) in the EU labelling (of note, Proleukin is not centrally authorized in the EU). Adverse events were collected and graded by the investigator by phase of treatment and overall. Nevertheless, the treatment phases cannot be dissociated and the whole regimen is to be considered for safety assessment.

Overall, 169 patients were exposed to TIL throughout the clinical development: 35 patients in 2 phase 1/2 studies, 80 in the M14TIL, 4 in the side study, and 50 in the hospital exemption program H23TIL. For the phase 1/2 studies, the applicant states that no CSRs were compiled as the data was reported in publications and therefore safety data does not contribute to this MAA.

The pivotal phase 3 study M14TIL was conducted at 2 sites (CCIT in Denmark and NKI in the Netherlands). The first patient was enrolled on 23SEP2014 and the end of study was 31DEC2023.

The safety data in the application is focussed on the M14TIL study and is therefore limited. In study M14TIL, 80 patients received TIL (64 at NKI and 16 at CCIT). While the manufacturing process of TIL differed in terms of quality characteristics between the two sites, no difference in terms of safety is observed.

The duration of follow-up for the M14TIL study was 54.4 months (46 - 58 months). Data cut-off was 31DEC2023 in the 'side study' and 06NOV2024 in the H23TIL program. The applicant states that the standard safety follow-up period in the M14TIL trial was 28 days following the last study treatment (defined as the day of discharge in the Tacquell arm or the day of administration of the last IPI dose in the IPI arm) for AEs and 100 days following the last study treatment for SAEs and AEs clearly related to the study treatment. Unresolved AEs within the 28-day period were monitored until resolution, up to 100 days post-treatment. The lack of systematic follow-up for AEs beyond 100 days is an important limitation to the ability to fully characterize the long-term safety of Tacquell. The absence of detailed data on mean, median, minimum, and maximum safety follow-up durations remain a gap in the safety assessment.

In terms of dose of TIL, the target dose range in the M14TIL, 'side study', and H23TIL was 5E9 to 2E11 viable cells. The median dose administered in the M14-TIL was 40.90 E9 with a range of 4.90 - 110.40 E9 cells. There seems to be no relation between the TIL dose and the safety profile.

Adverse events

MedDRA version 28.1 has been used for coding adverse events.

The safety analysis set is the PPS and consists of all patients treated with Tacquell (n=80). In the TIL arm, it is noted that the frequency of adverse events is comparable between the patients with prior anti-PD1 treatment (n=69) and the total number of patients treated (n=80).

The summary of clinical safety (SCS) submitted by the Applicant is not considered acceptable. The document contains very few organised data. Usual tabulated overview of all AEs/SAE regardless of causality, by SOC frequencies and at the PT level (all and grade 3-4) are not included in the SCS or in the Clinical study report (CSR). Tabulated treatment-related AEs with onset prior to TIL infusion and respectively after the TIL infusion, and by stage of the treatment regimen (tumour cell harvesting, NMA-LD, TIL-infusion or IL-2), by SOC and PT and by grade are not included as well. Only raw data are available, with the exception of data specific to AEs that occurred following the tumour harvest, which are not suitable for the expected assessment.

Clinically significant abnormal findings or other abnormal assessments that were associated with the disease being studied, unless considered by the investigator as more severe than expected for the patient's condition, or that presented or were detected at the start of the study and did not worsen, were not reported as AEs or SAEs. Events that clearly occurred due to progressive disease were not reported as an SAE. It remains unclear if the AE/SAE were reported in line with the ICH scientific guidelines, which states: "All adverse events occurring after initiation of study treatments (including events likely to be related to the underlying disease or likely to represent concomitant illness, unless there is a prior agreement with the regulatory authority to consider specified events as disease related) should be displayed in summary tables." While the applicant argues that the exclusion of disease-related events does not lead to the underreporting of treatment-related (S)AEs or inaccurate ADR frequencies, this assumption is not substantiated. The exclusion of events such as liver dysfunction, respiratory compromise, and malignant effusions, despite being attributed to disease progression, could theoretically overlap with known toxicities of Tacquell therapy. As such, the applicant's approach to AE/SAE reporting is not supported and does not comply with EMA guidelines.

The figures included in this report are based on the CSR dated 10DEC2025, unless otherwise specified.

Overall in the TIL-IMP arm 80 patients reported a total of 3852 AEs, with 3 times higher frequency than in the IPI-arm (82 patients reported a total of 1090 AEs). The frequency of any TEAE was the same in both arms (100%); the frequency of Grade ≥ 3 TEAE and Grade ≥ 3 treatment-related TEAE was higher in the TIL than IPI arm (100% vs 71.95% and 100% vs 57.3%). The frequency of SAE and treatment-related SAE was higher in the IPI than TIL group (43.9% vs 16.3% and 26.8% vs 15%); this imbalance should be interpreted with caution due to potential misclassification of SAE in the TIL arm.

As stated above, only the most common 'treatment related TEAE' (i.e. whole regimen) are reported in the most recent SCS and include, amongst others by PT: neutrophil count decreased 100%[EA1.1][STeo1.2], fever 93%, anaemia and nausea 91% each, febrile neutropenia 89%, chills 84%, platelet count decreased 83%, fatigue 75%. Information on the time to onset and duration/time to resolution of events has not been provided. According to the applicant, "the majority of AEs are resolved before discharge of the patients from the hospital and within the first 1-3 months after Tacquell therapy" This raises concerns on the consistency and adequacy of the safety follow-up.

By phase of treatment, in the TIL arm, frequency of adverse events reported as related to the NMA-LD treatment (cyclophosphamide and fludarabine) was 100%, to IL-2 98.75%, to TM-001 95%, and to TM-001/IL2 100%. However, one cannot distinguish to which specific treatment the events are related.

Most common TEAE reported before TIL infusion includes by PT: neutrophil count decreased, platelet count decreased, anaemia, febrile neutropenia, nausea, and white blood cells decreased, consistent with the chemotherapy known safety profile.

The most common TEAE reported after the TIL infusion were anaemia, fatigue, fever, rash, febrile neutropenia, dyspnoea, nausea, hypoalbuminemia, and sinus tachycardia.

The study protocol allowed up to 15 doses of IL2; however, in practice only a median of 5 doses could be administered due to toxicity. There was no relation between the dose of TIL, the number of doses of IL2 and the safety profile. The most common TR-TEAE reported as related to IL2 were fever, chills, dyspnea, febrile neutropenia, hypophosphatemia, fatigue. Most events were of Grade 1-3.

In the IPI arm, the most common treatment-related TEAE are: diarrhoea and fatigue (45.1% each), pruritus (41.6%), nausea (36.6%), consistent with the known safety profile of IPI. Most of the events were Grade ≤ 3 .

In the updated SCS, the most common Grade ≥ 3 TR-TEAE reported in the TIL arm were neutrophil count decreased 95%, febrile neutropenia 89%, platelet count decreased 80%, WBC decreased 71%, hypophosphatemia 66%, fever 45%, anaemia 20%.

The most common Grade 4 treatment related TEAE were neutrophil count decreased 91%, WBC decreased 70%, platelet count decreased 60%. These are consistent with the safety profile of cyclophosphamide, fludarabine, and IL2. Median duration of Grade 3-4 neutrophil count decreased was 7 days (2-58 days).

In the IPI arm, the Grade 3 AE with highest frequency were colitis 18.29%, diarrhoea 14.63%, elevated ALT/AST 8.54/7.32%. In total 9 AE were Grade 4 (elevated ALT/AST, colitis, GGT increased, lipase increased, and hyperglycemia).

In the supportive EAP program H23TIL, the safety profile appears consistent with the pivotal M14TIL study (data not shown), however due to uncertainties on safety data collection it is not possible to consider these data as contributing to the assessment.

Adverse drug reactions (ADR)

ADRs are considered those related to any component of the treatment regimen (tumour harvest, NMA-LD, TIL and IL-2. It is not possible to isolate the events really related to TIL alone due to the fact that IL2 treatment starts the same day as TIL infusion. In addition, since the IL2 dose is considerably higher than in the Proleukin product authorized in some EU countries, the ADR will capture the TIL and the likely higher toxicity of IL2.

AESI (adverse events of special interest)

No AESI were pre-planned. It is stated that autoimmune toxic effects associated with melanocyte-directed reactivity are expected. The applicant states that expected (due to the mechanism of action) immune related side effects (skin/hair colour hypopigmentation, impaired vision and uveitis, impaired hearing) occurred in few patients (data not shown). Cytokine release syndrome (CRS), typically observed with CAR-T cell therapies, was not observed with Tacquell. However, it should be noted that CRS has been observed with other TILs, and its absence with Tacquell may be due to the fact that it was not specifically investigated or monitored in the study.

According to the provided appendices, elevation of IL-6 was reported during the study, which may be a symptom of cytokine release syndrome (CRS). However, levels of IL-6 were not systematically measured and CRS was not systematically assessed. This may give rise to underestimation of this effect.

Capillary leak syndrome (CLS) is reported in 30% of patients in the M14TIL study and is a potentially life-threatening AE considered related to treatment with IL-2. Uveitis has been reported in 6 patients,

including 2 SAE considered related to the TIL infusion. In one of the phase 2 studies, vitiligo was reported in 37% of patients, and hypopigmentation was reported in 9/80 patients in M14TIL study. Immune-related side effects associated with the mechanism of action of Tacquell, especially recognition of healthy melanocytes in organs like the eye, the skin and the ear, that were observed after Tacquell therapy in a minority of the M14TIL and H23TIL Tacquell target population, is to be considered among the selected ADRs.

SAE (serious adverse events)

In study M14TIL, the number of SAE in the IPI arm was almost 3 times higher than in the TIL arm.

The incidence of SAEs in the TIL-IMP arm is unexpectedly low, given that the treatment protocol involves tumour harvest, chemotherapy and IL-2. One would anticipate a higher frequency of SAEs, such as infections and cytopenias, with febrile neutropenia also being a potentially expected SAE.

Since patients were already hospitalized for the procedure, only AE which led to transfer to ICU, resulted in prolonged hospitalization or death were considered SAE. The median duration of hospitalization was 17 days (12-38 days) and 8 patients (10%) were admitted to ICU for a median duration of 4 days (1-24 days). Hospitalization was not considered an SAE and the applicant states that there were no AEs which resulted in prolonged hospitalization. However, AE which would have required hospitalization (e.g. Grade 4 AE) if the patient was not already hospitalized were not reported. This induces important uncertainties on the classification and reporting of SAE and the rate of SAE cannot be reliably estimated.

With this caveat, the SAE considered by the applicant related to TIL were Grade 3 and Grade 4 (1 patient each) acute respiratory distress syndrome (ARDS), Grade 3 pleural effusion (1 patient), and Grade 2 and Grade 3 (1 patient each) uveitis, Grade 3 pneumonitis. According to the narratives, the Grade 4 ARDS has not resolved; all other Serious ADR either stabilized or resolved.

In the IPI arm, the majority of SAE were Grade 3 and occurred in 1-2 patients each. There were 4 Grade 4 AE: colitis, pulmonary thromboembolism, and Stevens-Johnson syndrome (1 patient each) and hyperglycaemia (2 patients). There was 1 SAE of Grade 5: intracranial haemorrhage. Of the 58 SAE reported, 34 were considered related to IPI.

Deaths

With respect to deaths, the safety data provided are inconsistent and incomplete. The clinical study report (CSR) indicates that only one patient died during the study (TIL-IMP arm), but the SAE narratives indicate a total of four deaths, which also appears to be inaccurate when compared to the provided overall survival (OS) data.

The applicant argues that patients went off-study upon disease progression after Tacquell therapy (according to the agreed protocol) and often they returned to their referring treating physicians for follow-up treatment. Therefore, any information on long-term safety aspects needs to be collected from those centers. Since no provision for collecting these data was built into the M14TIL clinical protocol, detailed death narratives and detailed information on AEs at the time of death could not be reconstructed. As such, death was considered related to progression of the disease. This is not acceptable because AE could go-on or occur after disease progression. While it is acknowledged that the study protocol allowed for patients with disease progression to exit the study, this does not exempt the applicant from the responsibility to provide narratives for all deaths. The fact that these deaths occurred after disease progression does not exclude the possibility that they may still be related to the treatment. Initially it was reported that one death due to toxicity occurred, however not considered related to study treatment, in a patient who experienced pneumonia, ARDS (RSV infection) and a thromboembolic event. A tabulated overview of death cases has been provided later

[EA2.1][STeo2.2]on in the procedure, where 5 cases of death are not attributed to disease progression and at least 1 was due to an AE (vasculitis). There is no discussion of these events.

Discontinuations

The treatment consists of preparative non-myeloablative lymphodepleting chemotherapy (NMA-LD), a single infusion of TIL, followed by up to 15 doses of high dose IL2 . The median number of doses of IL2 actually administered was 4 (0-10). [EA3.1][STeo3.2]

Safety in special populations

The applicant states that none of special populations have been studied. The clinical development included adults and elderly (< 75 years of age); Median age was 59 years (range 26-77) and about 70% were < 65 years of age. The safety analysis by age (<65 and >= 65 years of age) is not interpretable due to small sample size.

There are no data available on the use of Tacquell in pregnant women as pregnant (and breastfeeding) women were excluded from the clinical development program. Regardless of the impact and potential foetotoxicity of Tacquell during pregnancy, the use of preconditioning and supportive treatment warrants the implementation of pregnancy status verification and effective contraceptive measures.

According to the MAH, women who are breast-feeding should be made aware of the potential risks to the breast-fed infant. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain during or after Tacquell therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. As with the pregnancy considerations, breastfeeding conditions should take into account not only the risks associated with Tacquell itself, but also those related to the supportive and conditioning treatments.

No drug interactions have been performed. This is acceptable for the CT products. Corticosteroids may interfere with the activity of TIL and should not be used in combination with TIL. In the M14TIL study, according to the study protocol, all patients received supportive treatment during chemotherapy, Filgrastim until neutropenia was recovered, and anti-infective therapy to treat emergent infections.

The laboratory bio-chemistry values outside the normal ranges were reported as AE or SAE.

Regarding laboratory values, a critical analysis of the clinical relevance of laboratory and vital sign abnormalities, including how the results support and justify the proposed prescribing information, was not provided. Additionally, claims regarding the transient nature and resolution of abnormalities were not substantiated with time-to-onset and duration summaries.

Apart from haematology (neutropenia, anaemia, thrombocytopenia) discussed as ADR above, hypophosphatemia 78%, hypocalcaemia 59% hypoalbuminaemia 54%, elevated AST/ALT 39/35%, GGT increased 18%, alkaline phosphatase increased 29% and hypokalemia 30%, are reported as adverse reactions to TM001. These are generally consistent with the ADR reported for IL2 (Proleukin). The most common Grade >=3 AE were hypophosphatemia 66%, ALT/AST increased, CpK increased and GGT increased.

Based on the discussion above the final definition of the final ADRs for the treatment and the full safety section informing prescribers is not possible to be finalised. [EA4.1][STeo4.2]

Due to the significant uncertainties in the methodology, including the lack of clarity regarding the reporting and analysis of safety data (i.e. causality assessment classification of AE as SAE), the insufficient duration of safety follow-up and the insufficient provision of death narratives, the safety profile of Tacquell cannot currently be adequately assessed.

5.4.11.2. Conclusions on clinical safety

Overall, there are significant uncertainties related to limited follow-up, classification of SAE and absence of death narratives. The collection methodology, which excluded AEs not classified as "clearly related" beyond 28 days post-discharge, is an important limitation to the completeness of the safety data. The protocol-defined follow-up periods of 28 days for AEs and 100 days for SAEs are not considered sufficient to capture delayed-onset adverse events, which are relevant for assessing the long-term safety of Tacquell. The definition of «treatment related» is not clear, and a proper assessment of causality has not been provided. Consequently, at this time, the ADRs being proposed by the Applicant do not allow to conduct a thorough safety assessment. SAEs were misclassified. The lack of detailed narratives for deaths is highly concerning as they are critical for conducting a thorough benefit-risk assessment. In addition, there are numerous unresolved issues which in totality raise concern about the suitability of the safety clinical package to support a MA dossier.

Furthermore, irrespective of these methodological aspects consideration, the safety profile of Tacquell is considered unfavourable, with very high frequency of adverse events and Grade ≥ 3 , considerably higher than the comparator Ipilimumab. The high toxicity is driven by the pre-TIL chemotherapy (which is mandatory prior to TIL cells infusion) and high doses of IL2 treatment (needed for the TIL in vivo persistence and outgrowth). The toxicity of TIL in itself is not possible to be characterized, due to concomitant IL2 treatment and the complex treatment regimen. In the context of this high toxicity, cases of death attributed to progression of disease but potentially due to adverse events represent an important concern.

In conclusion, the significant uncertainties in the methodology, in particular limited safety data collection and follow-up, potential misclassifications of SAEs as AEs, and lack of detailed death narratives, preclude the assessment of the safety profile of Tacquell.

The CHMP endorses the CAT conclusion on clinical safety as described above.

6. Risk management plan

Due to the negative opinion a satisfactory pharmacovigilance system, summary of safety concerns, risk management plan and post-authorisation measures to address other concerns cannot be agreed at this stage.

7. Product information

Due to the negative opinion a satisfactory summary of product characteristics, labelling, package leaflet, cannot be agreed at this stage.

8. Benefit-risk assessment

8.1. Therapeutic context

The proposed indication for Tacquell is the treatment of adult patients with unresectable stage IIIC to IV melanoma following prior anti-Programmed Death-1 (PD-1)-based checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease, or given as (neo)adjuvant therapy.

8.1.1. Disease or condition, proposed therapeutic indication

Melanoma is a cancer type that derives from melanocytes. Once the melanoma is locally advanced and has spread to the lymph nodes (stage III) or is spread to organs or other parts of the body (stage IV), it is called advanced stage disease. Patient prognosis is related to the disease stage. Cutaneous melanoma is one of the most common malignancies, accounting for 1.7% of global cancer diagnoses according to GLOBOCAN. The risk of developing melanoma increases with age, possibly related to a greater cumulative exposure to UV radiation.

Melanoma has an estimated yearly increasing incidence of >150.000 newly diagnosed cases per year in Europe (Dyba et al., 2021). In Europe, the incidence rate is 10 – 25 new melanoma cases per 100,000 inhabitants, with a dramatic increase seen in the last years in many parts of Europe for all age groups. Most diagnoses are made prior to the development of lymph node or distant metastases (stage III to IV, advanced disease). The risk of developing melanoma increases with age, possibly related to a greater cumulative exposure to ultraviolet (UV) radiation. However, melanoma can also develop on areas of the skin that are not UV-exposed (Dennis et al., 2008; Rozeman et al., 2018; Ting et al., 2007).

8.1.2. Available therapies and unmet medical need

Patients with stage IIIC to IV melanoma were reported to have a poor prognosis in the past before approval of immunotherapy, with a 10-year survival of less than 5%, due to the very limited effect of traditional first-line therapies like radiation and chemotherapy (Balch et al., 2009; Bhatia & Thompson, 2012).

The anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody ipilimumab (IPI) was the first immune checkpoint inhibitor to achieve a significant improvement in survival of advanced stage melanoma and was approved as a Standard of Care (SoC) for the management of those patients in Europe in 2011. A switch in clinical practice occurred with the approval of molecules targeting PD-1 as first-line therapy in 2015 and as adjuvant therapy for patients with unresectable stage IIIC to IV melanoma in 2018.

Nevertheless, after failure of first-line treatment with anti-PD-1 antibodies, 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. The recent ESMO guideline on cutaneous melanoma (T. Amaral et al, 2025), indicates that patients who do not respond to PD-1-based immunotherapy have very limited therapeutic options available (which includes also experimental TILs treatment as potential therapy) and recommends clinical trials as the best option in this setting. This guideline also states that chemotherapy should be considered as a last-line treatment. Due to this limited clinical benefit of second-line treatment with the currently available immune checkpoint inhibitors and targeted therapies, there is a clear unmet medical need for novel treatment modalities for relapsed/refractory patients with advanced stage melanoma.

8.2. Main clinical studies

M14TIL is a Phase III multicenter, open-label, randomized trial to evaluate TIL-IMP therapy or ipilimumab administered intravenously in patients with unresectable stage IIIC to IV melanoma. A total of 168 patients were randomized in a 1:1 ratio to receive either ipilimumab (administered IV 3 mg/kg once every 3 weeks, maximal 4 times as described in the SmPC of Yervoy) or TIL-IMP therapy (a dose of minimum 5E9 up to a maximum of 2E11 viable cells administered IV over 20 to 30 min). Patients that were assigned to the TIL-IMP group underwent a metastasectomy to harvest tumour material required for the manufacturing of TIL-IMP. One week prior to the TIL-IMP infusion, patients were admitted to the

hospital for administration of preparative non-myeloablative lymphodepleting chemotherapy intravenously (cyclophosphamide/fludarabine), followed by the TIL-IMP infusion and subsequent high-dose (600,000 IU/kg IV over 15 min every 8 hours continued for up to 5 days) interleukin-2 (IL-2) intravenously to support the in-vivo outgrowth of T-cells from the TIL-IMP.

At the time of study development, treatment with IPI was standard of care for patients with unresectable stage IIIC to IV melanoma. For that reason, IPI was chosen as comparator for the phase III trial. However, during the course of the trial (2014-2023) the standard of care changed with the approval of anti-programmed death-1 (PD-1) immune checkpoint inhibitors in June 2015, resulting in the majority of patients included in the phase III trial being pre-treated with anti-PD-1-based checkpoint inhibitors. In addition, TIL-IMP products from one of the three manufacturing sites was found to be non-comparable. Therefore, the Applicant considered a subset of the data of the confirmatory phase III trial dataset as relevant to evaluate and this results in 59 patients in the TIL arm and 58 patients in the control arm.

The formal end of study was set to 31 December 2023 based on an event-driven decision (>50% patients died). At this DCO, the overall median follow-up time for all 168 patients (FAS) was 52.42 months (95% CI, 46.14 - 58.56), being 55.80 months (95% CI, 45.52 - 70.92) and 49.95 months (95% CI, 42.37 to 58.56) in the TIL-IMP and IPI arm, respectively. For the patients from the NKI site, previously treated with anti-PD-1, at time of data cut-off, the overall median follow-up time was 45.52 months (95% CI, 38.62 - 54.82), being 45.52 months (95% CI, 38.98 - 60.37) and 42.37 months (85% CI, 37.20 - 57.64) in the TM001 and IPI arm, respectively.

8.3. Favourable effects

Favourable effect are reported for the ITT (n=168) population.

The primary endpoint, progression free survival (PFS) according to RECIST 1.1, showed an HR between ipilimumab and TM001 arms of 0.52 [95% CI 0.37-0.73; P-value <0.001]). Median PFS per investigator according to RECIST 1.1 criteria is 6.81 months (95% CI, 4.19 - 12.47) in the TIL-IMP arm compared to 3.06 (95% CI, 2.97 - 4.32) months in the ipilimumab arm.

Median OS: 25.04 months (95% CI, 17.82 - 44.93) in the TIL-IMP arm, 19.04 months (95% CI, 14.31 - 30.90) in the ipilimumab arm.

ORR: 50.00% (95% CI, 38.9 - 61.1) in the TIL-IMP arm, 21.43% (95% CI, 13.2 - 31.7) in the IPI arm.

Median DOR: 392.5 days (Q1, Q3: 202.75, 1221.75), i.e. approximately 13.1 months in the TIL-IMP arm and 359.5 days (Q1, Q3: 168.5, 900.25), i.e. approximately 12.0 months in the ipilimumab arm.

In the modified ITT which correspond to patients treated at NKI site who received prior anti-PD1 therapy:

The primary endpoint, PFS according to RECIST 1.1, showed an HR between ipilimumab and TM001 arms of 0.49 [95% CI 0.32-0.73; P-value <0.001]). The median PFS is 6.65 months (95% CI, 4.06 - 12.47) in TIL arm, compared to 3.08 months in the IPI arm (95% CI, 3.01 - 4.48)).

Median OS: 25.04 months (95% CI, 16.90 - 44.93) in the TIL-IMP arm, 18.22 months (95% CI, 13.98 - 36.81) in the ipilimumab arm.

ORR: 49.15% (95% CI, 35.9 - 62.5) in the TIL-IMP arm, 20.69% (95% CI, 11.2 - 33.4) in the IPI arm.

Median DOR: 340 days (Q1, Q3: 127, 1049), i.e. approximately 11.3 months in the TIL-IMP arm and 243.5 days (Q1, Q3: 145.5, 517.75), i.e. approximately 8.10 months in the ipilimumab arm.

8.3.1. Uncertainties and limitations about favourable effects

A routine GCP inspection (EMA/IN/0000276203) concluded that from a GCP perspective, reliability, integrity, traceability, and re-constructability of the clinical data package and therefore completeness and correctness of the CSR could not be unambiguously established, and that the trial results could only be used with major reservations and they remain insufficient to provide back the reliability of the pivotal evidence package. Although the applicant presented further actions, undertaken to mitigate the findings from the inspection, including source data verification and repetition of the statistical analysis by an independent statistician, this exercise has not been considered to fully alleviate concerns regarding data integrity in the eCRF. These elements did not alter the assessment conclusion, and the reliability of the pivotal evidence package remains not established.

In addition, the documented limitations affecting computerised systems, data management/audit trail, and re-constructability of statistical outputs further undermine any methodological explanations provided and would not strengthen the primary efficacy endpoints and analysis outputs. In this context, it remains to be demonstrated that the pivotal efficacy data are reliable and traceable to source documentation, and that endpoints (notably PFS events and censoring) are consistently and reproducibly derived from these data and the final locked datasets.

Further, in view of multiple amendments to the primary endpoint definition/analysis approach and the description of DSMB closed-session review including survival information by treatment arm, it remains unclear which comparative efficacy information was reviewed, when this occurred, and how confirmatory interpretability was preserved. Finally, in this open-label trial with investigator-assessed PFS, where a fully blinded central review is deemed infeasible, adequate independent mitigation measures (e.g. independent central review and/or independent adjudication/confirmation of progression events and dates under a predefined charter) have not been put in place to ensure the credibility and robustness of the endpoint. Furthermore, inadequate original pre-specification of censoring rules and the handling of intercurrent events, in an open-label study and key modifications to the primary endpoint framework and analysis strategy provide further level of methodological and statistical concerns limiting the interpretability of the pivotal study,

Therefore, the efficacy results are hampered by major methodological concerns and uncertainties.

Following a post-trial comparability exercise performed by the Applicant, it was concluded that the cells manufactured on the Dutch sites were not similar to the cells manufactured on the Danish site. The Applicant therefore decided to separate data from the Dutch sites and the Danish site and present data from the Dutch sites as pivotal data for this MAA. The indication sought was hence based on a subgroup of the patients in the pivotal trial, specifically those treated at the Dutch site and only those with prior anti-PD1 therapy, given either in the (neo)adjuvant or first-line setting. The ITT principle is not considered to have been followed since data from the Danish site are excluded. No separate clinical results of the patients treated at NKI and at CCIT were submitted and this lack of comparability raises concerns regarding the inability to assess whether efficacy results differ between the Danish and the other sites adding on the fragility of the rationale for the exclusion of the Danish data and the ensuing ITT violation. This also contributes in reducing the robustness and generalisability of the retained dataset, particularly in the context of an MAA based on a single pivotal randomized trial.

Given the start date of this trial, it is acknowledged that the sponsor chose ipilimumab in the control arm which was an appropriate comparator at the time of trial initiation. With ipilimumab/nivolumab becoming standard of care in the first line, the use of ipilimumab in the second line setting has been reduced. Therefore, the absence of a control arm in line with current treatment landscape leads to a challenging interpretation of the magnitude of the treatment effects with regards to the current available therapies used to treat adult patients with unresectable stage IIIC to IV melanoma following prior anti-PD-1-based

checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease, or given as (neo)adjuvant therapy.

In the impossibility to define a clear benefit of the product due to the methodological and statistical aspects described above the efficacy of the proposed minimum dose has not been substantiated, and the proposed dose range still has to be justified.

8.4. Unfavourable effects

Overall, 169 patients were exposed to TIL throughout the clinical development: 35 patients in 2 phase 1/2 studies, 80 in the M14TIL, 4 in the side study, and 50 in the hospital exemption program H23TIL. Only data from study M14TIL, where 80 patients received TIL (64 at NKI and 16 at CCIT) is considered for assessing safety.

Overall in the TIL-IMP arm 80 patients reported a total of 3852 AEs, with 3 times higher frequency than in the IPI-arm (82 patients reported a total of 1090 AEs). The following analysis is based on the M14TIL clinical study report for 80 patients treated with Tacquell.

The frequency of any TEAE was the same in both arms (100%); the frequency of Grade ≥ 3 TEAE and Grade ≥ 3 treatment-related TEAE was higher in the TIL than IPI arm (100% vs 71.95% and 100% vs 57.3%).

The most common Grade ≥ 3 TR-TEAE in the TIL arm were febrile neutropenia 87.5%, hypophosphatemia 62.5%, fever 45%, platelet count decreased 21.25%, anaemia 20%, dyspnoea 17.5%, rash 12.5%.

Frequency of Grade ≥ 3 AE by treatment phase was related to NMA-LD 100%, TM-001 70%, IL2 92.5%, and TM-001/IL2 97.5%.

The most common Grade 4 TEAE were neutrophil count decreased 96.25%, WBC decreased 70%, platelet count decreased 67.5%. These are consistent with the safety profile of cyclophosphamide, fludarabine, and IL2. Median duration of Grade 3-4 neutrophil count decreased was 7 days (2-58 days). The Grade 4 events considered related to TIL were acute respiratory distress syndrome, dyspnoea, and GGT increased (1 patient each). The Grade 4 events related to IL2 were hypophosphatemia and CPK increased (3 patients each).

In the TIL arm, 13 patients (16.25%) reported 26 SAEs and 12 patients (15%) reported at least 1 treatment related SAE compared to 22 patients (26.83%) in the IPI arm. All but one SAE (1 case of uveitis Grade 2) were Grade ≥ 3 .

8.4.1. Uncertainties and limitations about unfavourable effects

The size of the database is very limited, prohibiting the capture of less frequent adverse events.

There are uncertainties about the limited safety data collection and duration of safety follow-up.

The summary of clinical safety is critically incomplete, with very few tables and it lacks a relevant discussion.

Reporting of SAE is not clear and there is a concern of misclassification and underreporting of these events.

It is not clear to what extent death occurred due to the high toxicity of the complex treatment regimen. The number of deaths due to adverse events is uncertain and death narratives have not been provided.

The causality assessments for ADR is not presented.

The safety profile of Tacquell is complicated by the complex regimen including pre-treatment with lymphodepleting agents and the post treatment with IL-2 which does not allow a clear isolation of the safety profile of Tacquell.

8.5. Effects table

Table 32. Effects Table for Tacquell for treatment of adult patients with unresectable stage IIIC to IV melanoma following prior anti-programmed death-1 (PD-1)-based checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease, or given as (neo)adjuvant therapy (data cut-off: 31 December 2023)

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Favourable Effects (in FAS/ITT, n=168)				
	TIL-IMP	ipilimumab arm		
Median PFS per investigator according to RECIST 1.1	6.81 months (95% CI, 4.19 - 12.47)	3.06 (95% CI, 2.97 - 4.32)	SoE: significant PFS differences based on the HR and positive trend for the median PFS Unc: Clinical relevance unclear and considerable methodological/statistical issue	study M14TIL
	HR= 0.52, 95% CI: 0.37-0.73 P<0.001			
OS	25.04 (95% CI, 17.82 - 44.93) months	19.04 (95% CI, 14.31 - 30.90) months		
ORR	50.00% (95% CI, 38.9 - 61.1)	21.43% (95% CI, 13.2 - 31.7)		
DOR	13.1 months	12.0 months		
Favourable Effects in the modified ITT (the subgroup of patients who received prior anti-PD1 at NKI sites , n=117)				
Median PFS according to RECIST 1.1	6.65 months, 95% CI: 4.06-12.47	3.08 months, 95% CI: 3.01-4.48	SoE: significant PFS differences based on the HR and positive trend for the median PFS Unc: Clinical relevance unclear and considerable methodological/statistical issue	CSR M14TIL study
	HR= 0.49, 95% CI: 0.32-0.73 P<0.001			
Median OS	25.04 months (95% CI, 16.90 - 44.93)	18.22 months (95% CI, 13.98 – 36.81)		
ORR	49.15% (95% CI, 35.9 - 62.5)	20.69% (95% CI, 11.2 - 33.4)		
Median DOR	340 days (Q1, Q3: 127, 1049),	243.5 days (Q1, Q3: 145.5, 517.75)		
Unfavourable Effects*				
Neutrophil count decreased	100%		Unc: limited data	Safety databases

Effect (short description)	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Fever	93%		available; uncertainties on safety data collection (including concern on misclassification of events) and duration of safety follow-up	
Anaemia	91%			
Nausea	91%			
Febrile Neutropaenia	89%			

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence; PFS: progression free survival; OS: overall survival; ORR: objective response rate; DOR: duration of response.

* Due to the high degree of uncertainty, the unfavourable effects cannot currently be determined

8.6. Benefit-risk assessment and discussion

8.6.1. Importance of favourable and unfavourable effects

The efficacy results presented from pivotal study M14TIL in patients with unresectable or metastatic melanoma may appear promising if taken in isolation from the methodological and statistical concerns. There is a relevant PFS difference between the study arms which pertains to the proportion of longer term non-progressors. Median PFS is roughly twice that in the ipilimumab control arm, and the median OS is also numerically improved relative to the control arm. In addition, ORR is higher in the TIL arm than the control arm, though the duration of response is comparable. The observed efficacy results could be considered clinically relevant. However, according to the GCP inspection, data integrity, completeness and correctness of the CSR could not be unambiguously established, it remains insufficient to ensure the reliability, integrity, traceability, and re-constructability of the pivotal evidence package.

Indeed, given the documented limitations in computerized systems, data management/ audit trails, and the re-constructability of statistical outputs, the reliability of the key efficacy source data and derived endpoints (including PFS events and censoring) could not be adequately demonstrated. Furthermore, these data could not be consistently verified against traceable source documentation and the final locked datasets.

Further, taking into account the several amendments to the primary endpoint definition/analysis approach and the description of DSMB closed-session review including survival information by treatment arm, it is difficult to derive a correct evaluation of efficacy. Moreover, in the frame of an open label trial, inadequate original pre-specification of censoring rules and the handling of intercurrent events, and the lack of an independent evaluation of PFS data (e.g. through central review and/or independent adjudication/confirmation of progression events and dates under a predefined charter) does not strengthen the endpoints' credibility.

Furthermore, the limitation of the PFS results is all the more marked by the fact that the enrolled patient population was treated under conditions (use of ipilimumab as comparator) that no longer reflect the current therapeutic setting, as the field in the treatment of melanoma has evolved since the randomised pivotal study started.

All in all, multiple methodological and statistical concerns limit the interpretability of the pivotal study. These include inadequate original pre-specification of censoring rules and the handling of intercurrent

events, the lack of an appropriate mitigation strategy for investigator-assessed PFS in an open-label study and key modifications to the primary endpoint framework and analysis strategy, as well, the post hoc restriction of the randomized comparison and the exclusion of a substantial proportion of patients from the primary analysis deviate from the ITT principle, reducing the robustness and generalisability of the retained dataset, particularly in the context of an MAA based on a single pivotal randomized trial.

The extent and severity of uncertainties regarding the safety are deemed critical and highly concerning. The absence of data on deaths, misclassification of SAE, limited safety data collection and the duration of safety follow-up impede an adequate assessment of the safety profile of Tacquell. There are therefore numerous unresolved concerns which in totality raise doubts on the adequacy of the clinical safety package in support of the MA dossier. Nevertheless, even if the safety profile provided is taken in isolation from the methodological concerns reported above, the data suggest an unfavourable safety profile, with very high frequency of adverse events and Grade ≥ 3 adverse events, considerably higher than the comparator Ipilimumab. The most common Grade 3 and 4 events were febrile neutropenia, neutropenia, platelet count decreased, hypophosphatemia, and CPK increased. The high toxicity is driven by the pre-TIL chemotherapy (which is mandatory prior to TIL cells infusion) and IL2 treatment (needed for the TIL in vivo persistence and outgrowth). The toxicity of TIL in itself is not possible to be characterized and isolated, due to concomitant IL2 and pre-TIL chemotherapy treatments. In the context of this high toxicity, cases of death due to adverse events are not clear and death narratives are not available.

All the above should also be seen in the frame of the quality issues which concerns: comparability between the clinical batches from the manufacturing sites, and between the M14TIL clinical trial batches and the commercial batches which is not established; incomplete documentation for the GMP compliance; the control strategy lacks the necessary robustness to ensure consistent quality, safety, and efficacy of the commercial medicinal product and furthermore the control strategy regarding the non-proliferation of feeder cells is inadequate, and aseptic process validation does not encompass the full feeder-cell manufacturing process.

Overall, due to the uncertainties and limitations of the design of the phase III trial, the limited data and the extent and severity of uncertainties regarding efficacy, and safety, together with the major concerns raised in the quality aspect of the dossier, data are not considered sufficient to support positive benefit/risk balance.

8.6.2. Balance of benefits and risks

As described in detail above, based on i) non-established comparability, ii) incomplete documentation about EU GMP compliance, iii) inadequate and non-robust control strategy to ensure consistent quality, safety and efficacy, iv) the critical results of the GCP inspection, v) the multiple methodological and statistical shortcomings, vi) the breaking of the ITT principle and vii) the non-comprehensive safety data set provided, it is currently considered that an adequate assessment of the potential clinical benefit over a not characterized safety profile is not possible at this stage and the clinical benefit of Tacquell in the claimed indication has not been demonstrated.

8.7. Benefit-risk conclusions

Due to all the above-described concerns the benefit-risk balance of Tacquell in the treatment of adult patients with unresectable stage IIIC to IV melanoma following prior anti-Programmed Death-1 (PD-1)-based checkpoint inhibitor treatment given either as first line treatment for unresectable stage III or IV disease, or given as (neo)adjuvant therapy is negative.

The CHMP endorses the CAT conclusion on Benefit Risk balance as described above.