CLINICAL TRIAL PROTOCOL

Study title:	TACTI-002 (**T**wo **ACT**ive **I**mmunotherapeutics): A multicenter, open label, Phase II study in patients with previously untreated unresectable or metastatic non-small cell lung cancer (NSCLC), or recurrent PD-X refractory NSCLC or with recurrent or metastatic squamous head and neck cancer (HNSCC) receiving the soluble LAG-3 fusion protein eftilagimod alpha (IMP321) in combination with pembrolizumab (PD-1 antagonist)
Sponsor:	Immutep S.A.S. Parc Les Algorithmes Bâtiment 7 - Le Pythagore Route de l'Orme - RD 128 91190 SAINT-AUBIN France
Protocol No.	TACTI-002 (IMP321-P015); Keynote-PN798
Clinical Phase	II
Protocol date:	Version 5.0 final, dated 18th August 2023
IMPs	eftilagimod alpha (efti, IMP321, LAG3-Ig; INN: eftilagimod alfa) pembrolizumab (Keytruda®; MK-3475)
EudraCT:	2018-001994-25
IND:	139659
NCT:	03625323

STATEMENT OF CONFIDENTIALITY

TABLE OF REVISIONS

Version	Section	Changes
1.2	All sections	Editorial
1.2	Section 3.2.2	Added "as assessed by investigators" to the description of several SAEs as requested
1.2	Section 5	Corrected error in patient sample numbers according to Section 10.1 and synopsis
1.2	Section 6.7.1	Specified medical wording according to FDA requirements
1.2.1	Section 5.6.2 Exclusion criterion 20	Deleted "a known severe ≥ grade 3" as requested by MHRA
1.2.1	Section 6.10	Added wording on avoiding live vaccinations for four months after last IMP dose
1.3	Synopsis, section 5 and; section 10	Introduction of a confirmatory scan prior to study enrolment for part B, extension of the informed consent period for biopsies and confirmatory scans, adaptation of statistical assumptions for part A and additional references
2.0	All sections	Editorial, clarifications, typographical corrections
2.0	Section 3.2.1 and 3.5	Update on pembrolizumab's relevant approved indication
2.0	Section 3.2.2	Update of clinical data of eftilagimod alpha
2.0	Section 5.2	Study Stopping Rules have been updated acc to CA comments
2.0	Section 5.6.1 Inclusion criteria	Specification of NSCLC patient population eligible for the study e.g. clarification on the prior use of durvalumab
2.0	Section 5.6.2 Exclusion criteria	Specification of NSCLC patient population e.g. clarification on the wash-out for patients receiving pembrolizumab Clarification on the definition/detection of hepatitis
2.0	Section 3.2.2 / 3.5	CCI and related risk language added
2.0	Section 8.1.2 vs 8.1.3	Updating requirements on confirmation of iUPD acc to the guideline
2.0	Section 7.2. and 8.2	Addition of minimum further 10 patients from Stage 2 (if opened) to the PK subset.
2.1	Section 6.7.1	CCI
3.0	Synopsis, section 5	Clarification regarding patient selection for Part B
3.0	Synopsis, section 5	Clarification of Inclusion criterion 2.2, 3.1 and Exclusion criterion 9.1 and 18.1; Addition to Exclusion criterion 1.2
3.0	Synopsis, Section5, Section 10.1, 10.9 and 10.13	Concept of cohort extension and details on Part A cohort extension
3.0	Section 3.3, 3.5	Reference to Investigator's Brochure, Benefit and Risk Ratio updated
3.0	Section 6.7.1 and 6.8 and 6.11	Clarification on rules of efti treatment delay and allowed study treatment interruptions
3.0	Table 8	Update to pembrolizumab dose modification rules
3.0	Section 7.1	Elaboration on patient re-screening
3.0	Synopsis, Table 10	Elaboration on pregnancy test
3.0	Section 7.3.3	Replacement of patients early discontinued due to COVID-19
3.0	Synopsis, Section 8.2	PK sampling window extended for late PK timepoints
3.0	Section 8.3.2	Clarification on laboratory analyses used for tumour tissue

		samples
3.0	Section 10.6 and 10.7	Clarification on interim analyses and timing
3.0	Section 12	Adding wording on remote monitoring under special circumstances (e.g. COVID pandemic)
3.1	Multiple sections	Editorial, typographical clarifications
3.1	Synopsis	Addition of new countries and sites
3.1	Section 3.5	Update benefit and risk with details re COVID-19
3.1	Table 8	Update to pembrolizumab dose modification rules
3.1	Section 6.10	Clarification concomitant systemic corticosteroids and vaccination
3.1	Section 9.4	Clarification on screening adverse events
3.1	Section 10.1	Explanation on statistical considerations around clinically meaningful benefit in Part B
3.1	Section 14.2	Clarification on protocol deviations due to COVID-19
3.1.1./4.0	Contact Details	Update
3.1.1/4.0	Synopsis, Section 6.1.2 and Section 6.4	Reference to powder formulation of pembrolizumab removed
3.1.1./4.0	Section 10.9.2.	Typo corrected
4.0	Table 8	Update to pembrolizumab dose modification rules
4.0	Section 6.5	Clarification on methods of patient assignment
4.0	Section 9.3	Clarifying reporting deadline for Events of Clinical Interest
4.1	Front page	Sponsor's address
5.0	Multiple sections	Adding efti INN name and harmonization of name use
5.0	Multiple sections	Updating various contact details
5.0	Synopsis, Section 5.3	Update on study timelines, extending study end by 12 month to collect additional PFS/OS FU data
5.0	CCI	CCI
5.0	Section 6.4	Clarification to instructions on diluted pembrolizumab solution storage
5.0	Section 8.1.5	Clarification to guiding source for date of disease progression or censoring

Signature Page for Sponsor

IMPs:	eftilagimod alfa and pembrolizumab
Protocol No.:	TACTI-002 (IMP321-P015)
Title:	TACTI-002 (Two ACTive Immunotherapeutics): A multicenter, open label, Phase II study in patients with previously untreated unresectable or metastatic non-small cell lung cancer (NSCLC), or recurrent PD-X refractory NSCLC or with recurrent or metastatic squamous head and neck cancer (HNSCC) receiving the soluble LAG-3 fusion protein eftilagimod alpha (IMP321) in combination with pembrolizumab (PD-1 antagonist)

Approved by the following:

PPD

18-Aug-2023

Date

Signature Page for Investigator:

IMPs: eftilagimod alfa and pembrolizumab

Protocol No.: TACTI-002 (IMP321-P015)

Title: TACTI-002 (**T**wo **ACT**ive **I**mmunotherapeutics): A multicenter, open label, Phase II study in patients with previously untreated unresectable or metastatic non-small cell lung cancer (NSCLC), or recurrent PD-X refractory NSCLC or with recurrent or metastatic squamous head and neck cancer (HNSCC) receiving the soluble LAG-3 fusion protein eftilagimod alpha (IMP321) in combination with pembrolizumab (PD-1 antagonist)

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with all relevant local regulations, the current International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice (GCP), and with the principles of the most recent version of the Declaration of Helsinki.

Investigator Name	Signature	Date
[PRINT IN BLOCK CAPITAL LETTERS]		

Institution Name	Site #

City and State/Province	Country

1 CONTACT DETAILS

Sponsor

Chief Medical Officer & Medical Expert	PPD Immutep Email: PPD

CRO

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Safety Database	Allucent (formerly CATO-SMS) Stationsplein Noord-Oost 438 1117 CL Schiphol The Netherlands Phone: PPD
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Other vendors

IMP Management Vendor	Clinigen Clinical Supplies Management SA (formerly: CSM Europe sa) Watson & Crick Hill Rue Granbonpré 11 B-1435 Mont-Saint-Guibert, Belgium Phone: PPD

Central Lab for PD-L1 analyses	Covance Central Laboratory Services Attn: Special Handling 7, Rue Moïse-Marcinhes 1217 Meyrin, Switzerland Phone : PPD
Central lab for gene expression profiling	Labcorp Central Laboratory Services Limited Partnership Covance Genomics Laboratory (CGL) – Indianapolis 8211 SciCor Dr. Dock 17 Indianapolis, IN 46214 USA Phone PPD
Central Laboratory for Pharmacokinetics of efti and Anti-drug Antibodies (efti) and Th1 biomarkers	Charles River Laboratories Evreux RN13 / Route de Pacy 27930 Miserey France PPD
Shipment of Central Laboratory Kits and Samples	MLM Medical Labs GmbH Dohrweg 63 41066 Mönchengladbach, Germany Phone: PPD
Central Imaging Laboratory	Median Technologies Les Deux Arcs, Bldg.B 1800, Route des Crêtes 06560 Valbonne, France Phone: PPD
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2 SYNOPSIS

STUDY TITLE

TACTI-002 (**T**wo **ACT**ive **I**mmunotherapeutics): A multicenter, open label, Phase II study in patients with previously untreated unresectable or metastatic non-small cell lung cancer (NSCLC), or recurrent PD-X refractory NSCLC or with recurrent or metastatic squamous head and neck cancer (HNSCC) receiving the soluble LAG-3 fusion protein eftilagimod alpha (IMP321) in combination with pembrolizumab (PD-1 antagonist)

SPONSOR

Immutep S.A.S.

BACKGROUND:

Lymphocyte activation gene 3 protein (LAG-3) is a transmembrane protein found on activated T and natural killer (NK) cells and a key mediator of immune responses. Eftilagimod alfa (efti, eftilagimod alpha, IMP321) is a recombinant soluble human LAG-3Ig fusion protein which is under development as a cancer immunotherapeutic agent. Like endogenous LAG-3, efti binds to major histocompatibility complex (MHC) class II antigen presenting cells (APCs) such as dendritic cells (DCs) and triggers a T helper (Th) 1 response and T cell proliferation. Efti has an excellent preclinical safety profile. Clinical studies have been/are conducted in the following settings: efti monotherapy or as part of chemo-immunotherapy or as part of a combination with PD-1 antagonists in patients with advanced and/or metastatic malignancies or as a vaccine adjuvant in patients with advanced malignancies.

Pembrolizumab (Brand name: Keytruda®, MK-3475) is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (i.v.) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure. Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

STUDY RATIONALE

Treatment of advanced solid tumors remains challenging despite the progress which has been made over the last years especially with targeted therapies like tyrosine kinase inhibitors, monoclonal antibodies, and immunotherapies like PD-1/PD-L1 and CTLA-4 antagonists. Recently, immune therapies like anti CTLA-4 and anti PD-1 antagonist have been approved by the Food and Drug Administration (FDA) in many different solid tumors. In general immune therapies as single agents achieved response rates between 12 % (ovarian cancer) and 40 % (melanoma, MSI-high) in a high number of solid tumors (i.e. NSCLC; small cell lung cancer (SCLC), renal cell cancer (RCC), HNSCC, triple negative breast cancer (TNBC), hepatocellular cancer (HCC), gastroesophageal cancer (GEC) and others) (1-6).

Understanding the reasons why a majority of patients do not respond to PD-1/PD-L1 blockade is key to developing new therapy combinations. On-treatment tumor biopsies have shown that non-responding patients have either little or no tumor-infiltrating lymphocytes (TILs) in the tumor bed or a non-functional immune response (i.e. no intratumoral IFNγ) with PD-1/PD-L1 negative TILs (7). Thus, immunogenic signals that induce tumor antigen-loaded DCs to escape peripheral tolerance and better

prime and activate effector T cells are expected to reactivate the deficient early steps of the cancer-immunity cycle (8).

In a mouse model of [redacted]
CCI
[redacted].

In clinical studies with efti it has been shown that efti as an APC activator at a dose of ≥ 1 mg/injection induced a sustained increase in monocyte and dendritic cells blood counts as well as a sustained activation of blood monocytes over 6 months. Moreover, this APC activation led to a sustained increase of activated CD8 T cells over 6 months and a sustained increase in serum IFNγ, a Th1 cytokine.

In the cross-talk between immune system and cancer, PD-1 antagonists like pembrolizumab address the immune escape (T cell downregulation). On the other hand, the capacity of the immune cells to recognize the tumor cells and prime an efficient effector response can be increased by an APC activator like efti.

In patients eligible to anti-PD-1 therapy, the addition of a well-tolerated APC activator like efti may help to activate the cellular immune response mechanisms to mediate tumor recognition and killing and thus may lead to higher frequency of durable responses compared to pembrolizumab monotherapy in different solid tumor without adding substantial toxicity.

The study will investigate three different patient populations as described below. This study aims to determine the response rate, safety and further antitumor activity of efti in combination with the anti-PD-1 antagonist pembrolizumab in a larger patient population. Based on the complementary mechanism of action, the presented preclinical and clinical data it is believed that the addition of efti to pembrolizumab therapy increases the response rates of pembrolizumab in these indications. Patients will be enrolled regardless of their PD-L1 status and tumor samples will be collected and the PD-L1 status will be assessed centrally.

The proposed statistical design (Simon`s 2 stage) ensures that initially a small number of patients is exposed to the combination of efti and pembrolizumab.

STUDY LOCATION

The study is planned to be conducted in Europe (Spain, Ukraine, United Kingdom, Poland), United States of America and Australia in 20-25 experienced clinical sites.

STUDY OBJECTIVES

Primary Objectives:

- To evaluate the response rate of eftilagimod alfa in combination with pembrolizumab in patients with advanced, metastatic, recurrent NSCLC and HNSCC

Secondary Objectives:

- To evaluate the safety and tolerability of eftilagimod alfa when combined with pembrolizumab
- To further evaluate the antitumor activity of eftilagimod alfa when combined with pembrolizumab
- To assess the pharmacokinetic and immunogenic properties of eftilagimod alfa

Exploratory Objectives:

- To identify and characterize relevant biomarkers

- To further characterize the antitumor activity of eftilagimod alfa in combination with pembrolizumab

STUDY ENDPOINTS

Primary Endpoints:

- To determine best overall response rate (ORR) according to iRECIST

Secondary Endpoints:

- Safety profile in terms of frequency, severity and duration of Adverse events (AEs) and serious adverse events (SAEs) and events of clinical interest (ECI) and abnormalities in vital signs, physical examination, 12-lead ECG and safety laboratory assessments
- To assess time to and duration of responses according to iRECIST and RECIST 1.1
- To assess the response rate according to RECIST 1.1
- To assess the disease control rate according to iRECIST and RECIST 1.1
- To assess progression free survival (PFS) and overall survival (OS)
- To assess occurrence of anti- eftilagimod alfa -specific antibodies
- To assess the plasma concentration time profile and derived PK parameters of eftilagimod alfa

Exploratory Endpoints:

- To asses PD-L1 expression assessed by central laboratory
- CCI
- To assess Gene signature acc. to PanCancer Immune code set assessed by a central laboratory
- To assess circulating level of Th1 biomarkers (i.e. IFN- γ, CXCL10) assessed by a central laboratory
- CCI

STUDY DESIGN

The study is designed according to Simon's optimal two-stage design (9). During the first stage of the study the number of N1 patients will be recruited for each indication into this multicenter, open label, phase II study. In case there are more responses than threshold r1 observed in patients recruited in the initial stage (N1), additional patients (N2) will be recruited. Following the completion of the initial stage, the decision to recruit the additional patients (N2) will be taken by the Data Monitoring Committee (DMC), as described later.

Indication	Threshold r1	Initial No of pts (N1)	Add. No. of pts (N2)	N total
NSCLC 1st line	4	17	19	36

NSCLC 2nd line	1	23	13	36
HNSCC	2	18	19	37

In case ORR in any part meets a predefined threshold an extension of this cohort may be set up to combine the patients of stages 1, 2, and newly enrolled patients in that respective part to provide a reasonable basis in sample size considerations for further clinical studies. For sample size considerations in the extension phase please refer to the section "sample size calculations" in the synopsis and chapter 10 of the protocol.

To be eligible for participation, patients must have either:

Part A: Histologically- or cytologically confirmed diagnosis of non-small cell lung cancer stage IIIB not amenable to curative treatment or stage IV not amenable to EGFR/ALK based therapy, treatment naïve for advanced/metastatic disease.

Note: patients who received durvalumab or any other PD-1 or PD-L1 therapy as maintenance therapy to the adjuvant chemotherapy regimen and hence are not naïve to anti-PD-X agents, can be recruited provided that all other necessary requirements are met.

Part B: Histologically- or cytologically-confirmed diagnosis of NSCLC after failure of first-line treatment (for metastatic/advanced disease) with at least 2 cycles of any PD-1/PD-L1 therapy (e.g. nivolumab, pembrolizumab, avelumab, etc.) alone, or in combination with any other immunotherapeutic or chemotherapy given as part of first-line treatment.

Note: Failure on therapy is defined as progress acc. to RECIST 1.1 and would require confirmation by a second assessment no less than four weeks from the first documented PD in the absence of rapid clinical progression. If patients discontinue PD-1/PD-L1 after being treated for at least 2 cycles for reasons other than progression, they may enroll in the study if initial progression occurs within 12 weeks after end of PD-1/PD-L1 therapy and progression is confirmed. Only patients to be receiving treatment in true second-line setting can be enrolled to Part B. Patients who have received durvalumab or any other PD-1 or PD-L1 therapy as part of their adjuvant therapy and no other PD-1/PD-L1 therapy in the first line treatment are not eligible for Part B.

Note: in Parts A and B patients with neuroendocrine or sarcomatoid NSCLC tumor types are not eligible. Patients with undifferentiated lung carcinoma with some neuroendocrine features can be recruited.

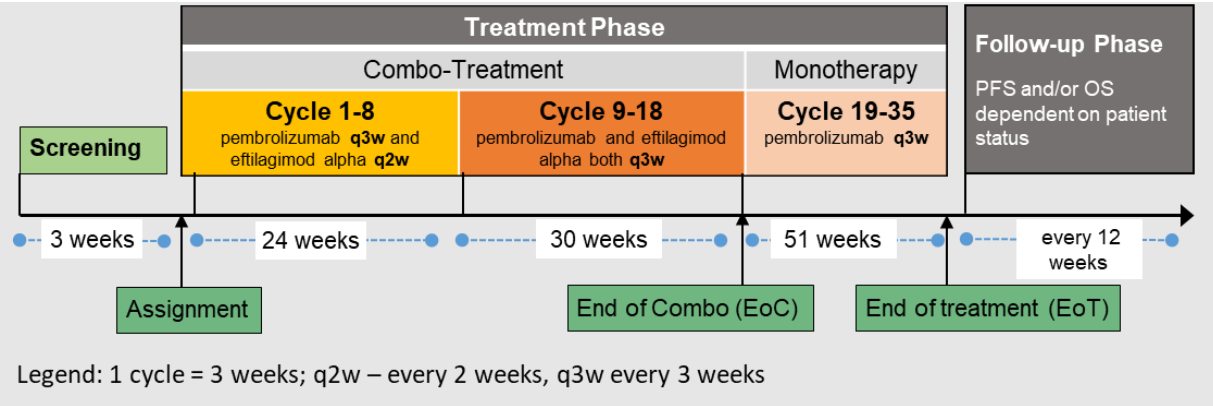
Part C: Histologically- or cytologically-confirmed recurrent disease not amenable to curative treatment with local or systemic therapy, or metastatic (disseminated) head and neck squamous cell carcinoma (HNSCC) of the oral cavity, oropharynx, hypopharynx, or larynx that is considered incurable by local therapies after failure of prior platinum-based therapy.

Note: in all three parts patients will be enrolled regardless of their PD-L1 expression.

Part A+B+C:

Patients will receive pembrolizumab and efti starting from cycle 1 day 1 as follows:

- 200 mg pembrolizumab every 3 weeks i.v. (30 min) for up to 35 cycles; 1 cycle = 3 weeks
- 30 mg of efti every 2 weeks s.c. for the first six months (until including cycle 8) and shifted to every three weeks s.c. thereafter (cycle 9 to 18); 1 cycle = 3 weeks



Screening of patients for eligibility to enter this study will be done in the three weeks prior to cycle 1 day 1. Patients will be enrolled in parallel except for the first three patients in each part who are to be enrolled at least 1 week apart. A patient will stay on treatment until disease progression, unacceptable toxicity, completion of 35 cycles of pembrolizumab (~2 yrs.; completion of study treatment) or discontinuation for any other reason. Three (3) weeks after the end of the combination therapy (cycle 18) end of combination (EOC) therapy assessments will be performed. Three (3) weeks after end of any study treatment (cycle 35) an end of treatment (EOT) visit will be performed. Upon start of study treatment, patients will be followed for PFS and OS. PFS will be radiologically assessed at the study sites until progressive disease (PD), death, withdrawal of consent, loss to follow-up, or until the end of the study, whichever occurs first. Radiological assessment will be performed at intervals of 9 weeks until week 36 (week 9, 18, 27, 36) and every 12 weeks thereafter (after week 36). OS will be monitored until death, withdrawal of consent, loss to follow-up or until the end of the study, whichever occurs first. Measurability will be assessed according to iRECIST. Response to treatment and treatment decisions will be assessed according to iRECIST. Objective response (iPR, iCR) should be confirmed by a repeat imaging assessment at least 4 weeks after the first response is observed. Per iRECIST, disease progression should be confirmed 4 to 8 weeks after site-assessed first radiologic evidence of iUPD. Patients, who have unconfirmed disease progression (iUPD) should stay on treatment (if clinically stable) until progression is confirmed (iCPD), provided they have met the conditions detailed in Section 8.1.3.

Radiological scans and related information will be evaluated at the study sites for treatment decision and for primary objective and will be collected for potential later central evaluation by blinded independent radiologists.

Any adverse event (AE) or events of clinical interest (ECI) that occurs during the first 30 days following the last dose of any study drug will be considered treatment emergent and must be recorded. Same accounts for all serious adverse events (SAEs) occurring during the first 90 days after last study drug administration.

Data Monitoring Committee (DMC):

The DMC will review the available safety data of all patients (part A-C) after 18 patients have completed at least two cycles (6 weeks) of therapy. In addition, the DMC will review the efficacy and safety data after the last patient N1 has been enrolled or the minimum number of responses is reached for each part of the study, whatever is first. The DMC will give a recommendation for each part of the study if stage 2 or an extension can be opened independently. Patients included in this decision must have had at least one tumor imaging after treatment was initiated. Further details are described in the DMC charter.

Furthermore, the DMC will monitor safety and efficacy data at regular intervals and in accordance with the DMC charter. The DMC may recommend stopping/changing the study if at any time during the trial there are unacceptable adverse events or safety concerns. Unless immediate action is required to protect

the safety and well-being of study patients, the sponsor will consult with appropriate regulatory authorities prior to early termination of the study based on any DMC recommendation.

Study Visits:

An overview of study visits is shown in the schedule of assessments (see Table 1).

STUDY POPULATION

Inclusion Criteria:

Patients may be enrolled if they meet all of the following criteria at screening:

1. Willing to give written informed consent and to comply with the protocol.

2.2 Part A (1st line, PD-X naïve in metastatic setting NSCLC): histologically- or cytologically-confirmed diagnosis of non-small cell lung carcinoma stage IIIB not amenable to curative treatment or stage IV not amenable to EGFR/ALK based therapy, treatment naïve for systemic therapy given for advanced/metastatic disease (previous palliative radiotherapy for advanced/metastatic disease acceptable).

Note: patients who received durvalumab or any other PD-1 or PD-L1 therapy as maintenance therapy to the adjuvant chemotherapy regimen and hence are not naïve to anti-PD-X agents, can be recruited provided that all other necessary requirements are met.

Part B (2nd line, PD-X refractory NSCLC): histologically- or cytologically-confirmed diagnosis of NSCLC after failure of first-line treatment (for metastatic/advanced disease) with at least 2 cycles of any PD-1/PD-L1 containing based therapy (e.g. nivolumab, pembrolizumab, avelumab, durvalumab, etc.) alone, or in combination with any other immunotherapeutic or chemotherapy given as part of first-line treatment.

Note: failure = failure on therapy is defined as progress acc. to RECIST 1.1 and would require confirmation by a second assessment no less than four weeks from the first documented PD in the absence of rapid clinical progression. If patients discontinue PD-1/PD-L1 after being treated for at least 2 cycles for reasons other than progression, they may enroll in the study if initial progression occurs within 12 weeks after end of PD-1/PD-L1 therapy and progression is confirmed. Only patients to be receiving treatment in true second-line setting can be enrolled to Part B. Patients who have received durvalumab or any other PD-1 or PD-L1 therapy as part of their adjuvant therapy and no other PD-1/PD-L1 therapy in the first line treatment are not eligible for Part B.

Note: in Parts A and B patients with neuroendocrine or sarcomatoid NSCLC tumor types are not eligible. Patients with undifferentiated lung carcinoma with some neuroendocrine features can be recruited.

Part C (2nd line PD-X naive HNSCC): Histologically- or cytologically confirmed recurrent disease not amenable to curative treatment with local or systemic therapy, or metastatic (disseminated) HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx that is considered incurable by local therapies after failure of prior platinum-based therapy.

3.1 Availability of formalin-fixed diagnostic tumor tissue (in the case of participants having received adjuvant therapy, the tissue should be taken after completion of this therapy).

4. Female or male ≥18 years of age on the day of signing the informed consent.

5. All female patients of childbearing potential must have a negative highly sensitive pregnancy test at screening (within 72 hours prior to cycle 1 day 1); all patients of reproductive potential must agree to use highly effective method for contraception from study entry until at least 4 months after the last administration of any study treatment.

   A woman must either be,
   - not of childbearing potential: postmenopausal (≥ 60 years of age, or < 60 years of age and amenorrhoeic for 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression with follicle-stimulating hormone (FSH) above 40 U/L and estradiol below 30 ng/L, or if taking tamoxifen or toremifene, and age < 60 years, then FSH and estradiol in the postmenopausal range), permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy), or otherwise incapable of pregnancy
   - of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; male partner sterilization (the vasectomized partner should be the sole partner for that subject).

6. A man who is sexually active and has not had a vasectomy must agree to use a barrier method of birth control e.g., either condom or partner with occlusive cap (diaphragm or cervical/vault caps) from study entry until at least 4 months after the last administration of study treatment. All men must also not donate sperm from time of study entry until at least 4 months after the last administration of study treatment.
7. ECOG performance status 0-1.
8. Expected survival > 3 months.
9. Evidence of measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 modified for immune-based therapeutics (iRECIST). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
10. Laboratory criteria (collected ≤ 10 days prior to cycle 1 day 1):
    - Absolute neutrophil count > 1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
    - Hemoglobin ≥ 9 g/dL or 5.58 mmol/L[1]
    - Serum creatinine ≤ 1.5 × ULN, or if > 1.5 ULN with a clearance of ≥ 50 mL/min acc to. Gault-Cockcroft formula
    - Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ ULN for patients with total bilirubin > 1.5 x ULN
    - AST (=SGOT) and ALT (=SGPT) ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases are present.

[1] Must be met without erythropoietin dependency and without packed red blood cell transfusion within the last 2 weeks prior to screening.

- International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN unless patient is receiving anticoagulant therapy as long as PT or activated partial thromboplastin time (aPTT) is within therapeutic range of intended use of anticoagulants

Exclusion Criteria:

Patients are to be excluded from the study at the time of screening for any of the following reasons:

1.2 For part A (1st line, PD-X naïve in metastatic setting NSCLC):

- The NSCLC can be treated with curative intent with either surgical resection and/or chemoradiation and/or radiation.
- Has received systemic therapy for the treatment of their stage IV NSCLC. Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.
- Epidermal growth factor receptor (EGFR)-sensitizing mutation and/or is echinoderm microtubule-associated protein-like 4(EML4) gene/anaplastic lymphoma kinase (ALK) gene fusion positive (ALK translocation).
- Has received lung radiation therapy that is >30Gy within 6 months of the first dose of trial treatment.

For Part B (2nd line, PD-X refractory NSCLC):

- Symptomatic ascites or pleural effusion.
- > 1 line of any systemic anticancer therapy for advanced or metastatic disease.
- Has received lung radiation therapy that is >30Gy within 6 months of the first dose of trial treatment.

For Part C (2nd line PD-X naive HNSCC):

- Disease is suitable for local therapy administered with curative intent.
- Previously treated with > 1 systemic regimen for recurrent and/or metastatic disease.

2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) **(Part A and C only)**.
3. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE **(Part B only**).
4. No tumor specimen evaluable for PD-L1 expression by the central study laboratory.

5.1 Prior anti LAG-3 therapy (e.g. anti-LAG-3 antibodies).

6. Prior high-dose chemotherapy requiring hematopoietic stem cell rescue.
7. Prior targeted small molecule therapy (i.e. kinase inhibitors), or radiation therapy within 2 weeks prior to cycle 1 day 1.

Note: Patients must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Patients with ≤Grade 2 neuropathy, alopecia and elevated transaminases in case of

liver metastases may be eligible. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNs disease

8.1 Has received prior chemotherapy, anti-cancer monoclonal antibody, major surgery, another systemic cancer therapy or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to cycle 1 day 1.

Note: Patients must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Patients with ≤Grade 2 neuropathy, alopecia and elevated transaminases in case of liver metastases may be eligible. If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment. Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
Note: wash-out period for pembrolizumab is not applicable to patients having received pembrolizumab and are to be enrolled into Part B. These patients are allowed to enter as long as the last pembrolizumab dose is ≥ 2 weeks prior to cycle 1 day 1 and they fulfill all other requirements in terms of adverse events.

9.1 Known active central nervous system metastasis and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable: i.e. without evidence of progression documented by repeat imaging performed after therapy completed for CNS metastasis and with at least 4 weeks difference, clinically stable and without requirement for steroid treatment for at least 14 days prior to cycle 1 day 1.

10. Women who are pregnant or lactating. A woman of child-bearing potential who has a positive serum pregnancy test (within 72 hours) prior to cycle 1 day 1.

11. Serious intercurrent infection within 4 weeks prior to cycle 1 day 1 or active acute or chronic infection.

12.1 Evidence of severe or uncontrolled cardiac disease within 6 months prior to first dose of study treatment including: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 5.0 Grade ≥ 2, atrial fibrillation > grade 2 not controlled by a pacemaker, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (NYHA III-IV), cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

13. Has interstitial lung disease or history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

14. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

15. Has a known history of human immunodeficiency virus (HIV) infection.

Note: No HIV testing is required unless mandated by local health authority.

16.1 Has a known history of Hepatitis B (defined as a known Hepatitis B surface antigen [HBsAg] positive result) or known active Hepatitis C virus (defined as a known positive anti-Hepatitis C antibody result and known detectable level of HCV RNA [qualitative] on PCR) infection.

Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority. No treatment with antiviral therapy allowed.

17. Has a life-threatening illness unrelated to cancer.

18.1 Has previous malignancies within the last three years other than described in inclusion criterion 2, except successfully treated basal or squamous cell carcinoma of the skin, superficial bladder cancer, ductal carcinoma in situ of the breast, and in situ carcinoma of the cervix.

19. Receives continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days prior to cycle 1 day 1. Inhaled or topical steroids and physiological replacement doses of up to 10 mg daily prednisone equivalents are permitted in the absence of active auto-immune disease.

20.1 Has a hypersensitivity to eftilagimod alfa and/or pembrolizumab and/or any of its excipients.

21. Live vaccine within 30 days of planned cycle 1 day 1. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

23. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

INVESTIGATIONAL PRODUCTS, DOSE AND MODE OF ADMINISTRATION

Eftilagimod alfa (efti, eftilagimod alpha, IMP321):

The efti drug product is a single-use, preservative-free, sterile solution of efti [redacted] for subcutaneous injections (s.c.) at a concentration of 25 [redacted] mg/mL. The drug product is filled into [redacted] mL glass vials with an extractable volume of [redacted] mL to be stored at [redacted].

Efti will be injected at a dose of 30 mg every 2 weeks for the first 8 cycles (1 cycle = 3 weeks) and every 3 weeks thereafter (starting cycle 9) until cycle 18. The maximum number of 22 efti injections may be administered (18 cycles). Efti is to be given always ≥ 30 minutes after pembrolizumab infusion is finished.

The route of administration for efti will be subcutaneous injection (s.c., single anatomical site) in the anterior face of the thigh. The location of the injection site should be rotated with each injection and alternating left and right thighs (if, for example, the first injection is on the left thigh, the subsequent one will be on the right and so on). The injection should be performed slowly to avoid discomfort at the site of injection.

No dose reductions of efti are allowed. Dose delays are allowed and are described in section 6.7.

Efti will be provided by the sponsor.

Pembrolizumab:

Pembrolizumab Solution for Infusion 100 mg/vial is a liquid DP. The vials are stored at 2°C to 8°C (36°F to 46°F). The liquid DP is clear to opalescent solution, essentially free of visible particles.

Pembrolizumab will be given at a dose of 200 mg (flat) as a 30-minute i.v. infusion every 3 weeks. The maximum number of 35 pembrolizumab infusions (35 cycles) may be administered. Dose modifications and dosing interruptions will be performed as described section 6.7. Pembrolizumab will be provided by the sponsor.

DURATION OF THE STUDY

Individual patients will undergo up to 3 weeks screening period, followed by a 54-weeks combination treatment phase (18 cycles). Patients who benefit from the treatment may continue with another 51-weeks of pembrolizumab monotherapy (17 cycles). Three (3) weeks after the last study drug administration an end of treatment visit (EOT) is to be conducted. Patient will be followed-up for progression and/or survival (dependent on patient status at EOT) until PD, death, study end, withdrawal of consent or loss to follow-up, whatever occurs first.

The timelines are as follows: first patient first visit occurred March 2019. The recruitment time for stage 1 was completed with last patient recruited in Nov 2021. The recruitment time for stage 2 ended in August 2021. Recruitment to extension for part A was completed with last patient recruited in Nov 2021. The last patient last visit in part A is expected to occur in H2 2023.

The end of study is defined as 36 months after last patient first visit.

STATISTICAL ANALYSIS

Sample Size Calculation:

The null hypothesis that the true response rate is [p0] will be tested against a one-sided alternative. In the first stage, [n1] patients will be accrued. If there are [r1] or fewer responses in these [n1] patients, the study will be stopped. Otherwise, [n - n1] additional patients will be accrued for a total of [n]. The null hypothesis will be rejected if [r2 + 1] or more responses are observed in [n] patients. This design yields a one-sided type I error rate of CCI and power of CCI when the true response rate is [p1].

Mini-max results of this calculation were used for this clinical trial.

Indication	response rate p_0	Alternative p_1	r_1	r2	Initial No of pts (n_1)	Add. No. of pts (n_2)	N total
NSCLC 1st line	23%	CCI %	4	CCI	17	19	36
NSCLC 2nd line	7 %	CCI %	1	CCI	23	13	36
HNSCC	15 %	CCI %	2	CCI	18	19	37

The "true response rates" for 1st line NSCLC were extracted from Keynote-024 and Keynote-042 under consideration that for PD-L1 all comers response rate will be lower (10, 11). For 2nd line NSCLC there are no available publications for pembrolizumab alone in PD-1/PD-L1 refractory patients, but due to the confirmation of progression it (p_0) is considered close to 0 % for pembrolizumab alone. The alternative (p_1) of [redacted] % was considered clinically relevant especially in comparison to available standard chemotherapy. For HNSCC relevant publications from Keynote 012 and Keynote-040 were used (2, 12) for p_0.

For part A an extension (Part A extension) is anticipated based on the ORR of efti in combination with pembrolizumab as test group in a single arm design. The true ORR of monotherapy pembrolizumab in NSCLC 1st line is expected to be 23%, whereas a rate of [redacted]% is expected for the test group (in case PD-L1 distribution is as expected from historical studies with ~70% of patients with <50% TPS PD-L1expression). Using these assumptions with a power of [redacted]% and a one-sided level of significance of [redacted]% in this phase II trial, a sample size of 105 patients would be required for analysis. With a drop-out rate of 5%, a total of 110 patients need to be enrolled. With the 36 patients of stages 1 and 2, another 74 patients would be needed to be enrolled in total in this extension. This sample size is regarded sufficient to provide a reasonable precision for the estimate of ORR as basis for sample size considerations for further clinical studies.

Possible extensions of part B and C will be introduced via substantial amendments.

Analysis Populations:

- The Full Analysis Set (FAS) follows the intent to treat principles and includes all assigned patients who received at least one dose of study drug (i.e. one dose of either pembrolizumab or efti). This population will be the primary population for the analyses of efficacy endpoints and baseline characteristics.
- The safety set is defined analogously to the full analysis set and includes all assigned patients who received at least one dose of study drug (i.e. one dose of either pembrolizumab or efti). This population will be the primary population for the analyses of safety.
- In addition, a per protocol population and a PK population are defined.

Baseline and Demographic Characteristics:

Baseline characteristics and demographic information at baseline will be summarized with descriptive statistics for each part of the study independently. Medications will be coded using the most current version of the World Health Organization (WHO) Drug dictionary and will be summarized as treated for all patients in the safety population. Prior medications, medications used at study and concomitant medications will be described separately.

Safety Analysis:

Safety data will be summarized for the safety population. The baseline value for safety analysis is defined as the value collected at the time closest to and prior to the start of any study drug administration. The number and percentage of patients with at least 1 AE will be summarized by preferred term and system organ class. AEs will also be summarized by severity and relationship to study drug (i.e., either efti or pembrolizumab). Vital signs, 12-lead ECG variables, body weight, and safety laboratory parameters will be presented (each time point and changes from baseline) using descriptive statistics (mean, standard deviation, median, minimum, and maximum). Other safety data will be summarized and/or listed.

For indications with an extension, the patients of stages 1 and 2 will be combined with the newly enrolled patients of the extension as combined dataset for analysis. Certain endpoints will in addition be analyzed in the subgroups "patients of stage 1+2" and "newly enrolled patients" to assess any effect of later

enrollment on the outcome. All endpoints assessed in stages 1 and 2 will also be assessed for the extension as described above. Details will be given in the SAP.

Immunogenicity analyses:

The development of anti-efti antibodies will be evaluated. Autoantibodies will also be evaluated.

Pharmacokinetic analyses:

The plasma concentration time profile of efti will be summarized and PK parameters such as area under the curve (AUC), peak serum concentration (C_{max}), time to reach C_{max} (t_{max}), systemic clearance (CL), elimination half-life ($t_{1/2}$) and volume of distribution (VD) will be calculated.

Efficacy Analysis:

All efficacy analyses will be based on Investigator's assessment according to iRECIST. Overall response rate (ORR) will be summarized for each part A to C separately by binomial response rate with two-sided 95% exact confidence intervals. using the Clopper-Pearson method.

The DOR (based on iRECIST) will be summarized using the Kaplan-Meier product-limit method. The median time to event will be calculated along with 95% CIs using the Kaplan-Meier method. In addition, the proportion of responders still in response at different timepoints will be assessed based on a Kaplan-Meier Plot.

All secondary analyses will be performed descriptively. The time-to-event endpoints (PFS (based on iRECIST), CCI , OS) will be summarized using the Kaplan-Meier product-limit method. The median time to event will be calculated along with 95% CIs using the Kaplan-Meier method. The PFS and OS rate at 3, 6, 12, 18 and 24 months and corresponding 95 % confidence intervals will be estimated using the Kaplan-Meier method.

As a sensitivity analysis ORR, DOR, PFS will be assessed based on RECIST 1.1. All efficacy analyses are based on local investigator assessments. A central independent assessment will be conducted, respective analyses will be specified in the SAP.

For indications with an extension, the patients of stages 1 and 2 will be combined with the newly enrolled patients of the extension as combined dataset for analysis. Certain endpoints will in addition be analyzed in the subgroups "patients of stage 1+2" and "newly enrolled patients" to assess any effect of later enrollment on the outcome. All endpoints assessed in stages 1 and 2 will also be assessed for the extension as described above. Details will be given in the SAP.

Tumor Biomarker Analysis:

Archival tumor material or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated will be provided by patients on a mandatory basis. These samples will be assessed for PD-L1 staining intensity using a standardized diagnostic test. TH1 biomarker and gene expression profile according to the PanCancer immune code will be measured in the blood. Exploratory analyses to assess correlations between biomarkers and response endpoints will be done, depending on the available data.

Table 1: Schedule of Assessments (Part A + B + C)

Phase	**Screening[22]**	**Combined Immunotherapy (pembrolizumab + efti)**					**EOC[17]**	**Pembrolizumab monotherapy**	**EOT [18]**	**PFS-FU**	**OS-FU**
Cycle (1 cycle = 3 weeks)		**Cycle 1 / 3 / 5 / 7**		**Cycle 2 / 4 / 6 / 8**		**Cycle 9 / 10 / 11 / … / 18**	**Cycle 19**	**Cycle 20-35**	**NA**	**NA**	**NA**
Visit	**Screening**	1 / 5 / 9 / 13	2 / 6 / 10 / 14	3 / 7 / 11 / 15	4 / 8 / 12 / 16	17 / 18 / …/26	27	28- 43	44	every 12 wks[19]	every 12 wks[20]
Reference Day (per period)	**Day -21 to -1**	D1	D15	D1	D8	D1	D1	D1	NA	NA	NA
Visit Week		1/ 7 / 13 / 19	3 / 9 / 15 / 21	4 / 10 / 16 / 22	5 / 11 / 17 / 23	25 / 28 / 31 / … 52	55	58-105	108	NA	NA
Visit Window		± 2 days				± 3 days	± 4 days	± 4 days	± 7 days	± 9 days	± 4 wks.
Written informed consent[22]	x										
Inclusion/exclusion criteria	x	Only C1									
Assignment to treatment		Only C1									
Medical history / demographics[1]	x										
CT/MRI scan[2]	x	9-weekly until week 36 thereafter every 12 weeks until PD (from date of assignment; independent from study treatment)									
Tumor tissue sample[3]	x										
Gene expression profile[4]	x	only C5									
Physical examination[5]	x	x		x		x	x	x	x		
Body weight / height[5]	x	x		x		x	x	x	x	x	
ECOG PS + survival	x	x		x		x	x	x	x	x [16]	Survival
Vital signs[6]	x	x	x	x	x	x	x	x	x		
ECG[7]	x	x		x		x	x	x	x		
Safety laboratory[8]	x	x		x		x	x	x	x		
Thyroid function tests[23]	x			x		Only C10, 12, 14,16,18		Only C20, 22, 24, 26, 28, 30, 32, 34	x		
Pregnancy test[9]	x	x		x		x	x	x	x		
HIV, HCV and HBV[10]	x										
Auto-antibodies (pre-dose)[21]		only C1				only C9	x		x		
PK efti[11]		only C1, C5				only C9					
Anti-drug (efti) antibodies (pre-dose)[12]		only C1, C5	only C3		Only C2	only C9, C13	x		x		
Th1 Biomarker[13]		only C1, C5				only C9, C13	x		x		
Pembrolizumab		x		x		x	x	x			
Efti[14]		x	x		x	x					
Adverse events [15]	x	x	x	x	x	x	x	x	x	x[15]	x[15]
Concomitant medications/procedures[15]	x	x	x	x	x	x	x	x	x		

DEFINITIONS: ECG=Electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=End of Treatment; PFS=Progression-Free Survival; FU=Follow-Up; PD=Progressive Disease, PS-Performance Status;

List of Footnotes

1. Patient medical history should include the complete cancer medical history. Inclusion-/exclusion criteria requiring documented medical history must be verified at a minimum by subject interview or other protocol-required assessment (e.g., physical examination, laboratory assessment) and documented in the source documents. Details are described in section 7.
2. Patients need to undergo CT (contrast enhanced preferred) or MRI scan for assessment of eligibility at screening (historical images ≤28 days prior cycle 1 day 1 allowed), and for radiological assessments every 9 weeks until week 36 (scans may be performed ± 6 days) and every 12 weeks thereafter (scans may be performed ±9 days). In case brain imaging is required MRI is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated. Patients with HNSCC will have a CT of the neck and head as needed.
3. If tumor tissue from the archived formalin-fixed block is not available, a tumor tissue sample will be collected at screening to assess PD-L1 (all study parts) and HPV positivity (for HNSCC only, if applicable).
4. Whole blood samples will be collected from each patient at screening and pre-dose day 1 cycle 5 for gene expression profiling.
5. The physical examination includes the following: head, eyes, ears, nose and throat; respiratory system/chest; cardiovascular system/heart; abdomen; skin, lymph nodes; extremities and (at the investigator's discretion) genitourinary system/pelvis. Height should only be obtained once at screening.
6. During the treatment phase, vital signs (resting blood pressure, heart rate and body temperature) will be assessed prior to administration of study drugs on each treatment day.
7. During the treatment phase, single 12-lead ECGs in rest will be assessed prior to administration of study drugs on Day 1 of each Cycle and on EOT.
8. The safety laboratory tests include hematology, biochemistry, coagulation and urinalysis. They may be performed up to 2 days before the dosing day except for screening where 10 days are allowed. All tests to be performed at screening and pre-dose on day 1 of each cycle.
9. Women of childbearing potential must have a negative pregnancy test at screening (serum) and on Day 1 of each Cycle (urine) prior to any treatment. The test may be performed up to 3 days before the dosing day. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required
10. HIV, HCV* and HBV** if necessary according to local laws. *anti-HCV antibody (and HCV RNA quantitative PC R if anti-HCV antibody positive), **HBsAg
11. Blood samples for PK assessment of efti will be collected in a subset of 20 patients in Stage 1 (selected sites in UK, ES) and an additional subset of at least 10 patients in Stage 2, at selected sites in cycle 1, cycle 5 and cycle 9. PK sampling will be performed pre-dose, after 1 hour, after 2 hours, after 4 hours, after 8 hours, after 24, 48, 72 and 96 hours after efti injection. The following windows are permitted on the assessment time points for PK: up to 1 hour for the PRE-dose assessment, ±5 minutes for the 1-hour assessment, ±15 minutes for the 2 hour and 4-hour assessments, ±30 minutes for the 8-hour assessments, ±2 hours for the 24, 48-hour assessments and -4 hours or up to +48 hours window for the 72 and 96-hour timepoints.
12. Blood samples for assessment of potential anti-efti ADAs will always be collected pre-dose of efti and pembrolizumab administration day 1 of cycle 1, day 8 of cycle 2, day 15 of cycle 3, day 1 of cycle 5, day 1 of cycle 9, day 1 of cycle 13, EOC and EOT.
13. Blood samples for Th1 biomarker assessment will be collected for all patients on day 1 of Cycle 1, Cycle 5, Cycle 9, Cycle 13, End of Combo (EOC) and EOT prior to dosing with Pembrolizumab and/or efti. In subsets of patients with PK assessment, Th1 biomarkers will be additionally assessed in selected samples collected as part of PK assessment after dosing at cycle 1, cycle 5 and cycle 9 (no additional blood sampling needed).
14. Eftilagimod alfa (efti, eftilagimod alpha, IMP321) administration will be every 2 weeks until week 23. Thereafter efti will be administered every 3 weeks until week 52 (starting week 25). Patients must stay for 30 minutes at the site after each efti administration. The combined immunotherapy of pembrolizumab and efti requires on several occasions that both treatments will be given on the same day. In these cases, efti will be given ≥ 30 minutes after end of the pembrolizumab infusion.
15. Adverse events, events of clinical interest and concomitant medications will be recorded from the time of informed consent until 30 days after the last study treatment. SAEs (pregnancy or breastfeeding) will be recorded from the time of informed consent until 90 (120) after last study drug treatment. In case patients receive subsequent antitumor

therapy, the period is reduced accordingly. SAEs potentially related to the any of the study drugs will be reported also beyond the 90 days. Safety follow-up will be performed for each AE, SAE or ECI.

16. Additionally, any next line of anti-cancer therapy and the outcome will be recorded.
17. At end of combination (EoC) therapy visit will be performed three (3) weeks ±4 days after the last combination treatment (cycle 18) in case the patient continues on pembrolizumab monotherapy.
18. Patients who discontinue the treatment phase prior to regular EOT have an EOT visit within 3 weeks (±7 days) after discontinuation or their last study drug administration.
19. Progression free survival follow-up will be performed every 12 weeks ±9 days. The first PFS-FU will take place 12 weeks after last radiological scan under treatment and then every 12 weeks thereafter. PFS-FU is to be conducted until confirmed PD (iCPD), study end or any other reason, whatever occurs first.
20. Overall survival follow-up will be performed every 12 weeks ±4 weeks. The first overall survival will take place 12 weeks after the last visit of the treatment phase (if not EOT took place), EOT or PFS-FU whatever was last. OS-FU is to be conducted until study end, death, withdrawal of consent or lost to follow-up whatever occurs first.
21. Autoantibodies (i.e. antimitochondrial antibodies, rheumatoid factor, antithyroid (antithyroglobulin) antibodies, and antinuclear antibodies) will be evaluated at the local laboratory
22. Patient can be consented up to 35 days before cycle 1 day 1 to allow planning of fresh tumor biopsy and/or perform CT scan for assessment of eligibility at screening (the latter for Part B only). All screening assessments including the biopsy or confirmatory tumor assessment for part B (to confirm progression) itself are still to be performed between -21 days and -1.
23. Thyroid function tests (Triiodothyronine (T3) or Free Triiodothyronine (FT3), Free thyroxine (FT4) and Thyroid stimulating hormone (TSH)) are to be performed up to 2 days before the dosing day except for screening where 10 days are allowed. All tests to be performed at screening and pre-dose every 2nd cycle starting with cycle 2. Thyroid function test will also be performed at EoT.

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GLOSSARY OF TERMS AND ABBREVIATIONS

Abbreviation	Definition
5-FU	5-Fluorouracil
AACR	American Association for Cancer Research
ADA	Anti-Drug Antibodies (in this context against eftilagimod alpha)
AE	Adverse Event
ALAT	Alanine Aminotransferase
ALK	Anaplastic Lymphoma Kinase
AMA	Antimitochondrial Antibodies
ANA	Antinuclear Antibodies
ANC	Absolute Neutrophil Count
APC	Antigen-Presenting Cells
APTT	Activated Partial Thromboplastin Time
ASAT	Aspartate Aminotransferase
ATA	Antithyroid (Antithyroglobulin) Antibodies
AUC	Area Under the Curve
BCG	Bacillus Calmette–Guérin
BOR	Best Overall Response
CCDS	Company Core Data Sheet
CD	Cluster of Differentiation
CI	Confidence Interval
CL	Systemic Clearance
C_{max}	Maximum (or Peak) Serum Concentration
CMH	Cochran-Mantel Haenszel
COVID-19	infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CR	Complete Response
CRF	Case Record Form
CRP	C-reactive Protein
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T Lymphocyte(s)
CXCL	C-X-C motif chemokine
DC	Dendritic Cell
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
DP	Drug Product
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
ECI	Event of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
efti	Eftilagimod alfa (eftilagimod alpha, IMP321)
EGFR	Epidermal Growth Factor Receptor
EoC	End of Combo (visit)
EoT	End of Treatment (visit)
EORTC	European Organization for Research and Treatment of Cancer
EU	European Union

Abbreviation	Definition
EudraCT	European Clinical Study s Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
FU	Follow Up
GCP	Good Clinical Practice
GEC	Gastroesophageal Cancer
GGT	Gamma-Glutamyl Transpeptidase
GMP	Good Manufacturing Practice
HBV	Hepatitis B Virus
HCC	Hepatocellular Cancer
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HNSCC	Head and Neck squamous cell carcinoma
HR	Hazard Ratio
i.v. IV	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iCPD	Confirmed progressive disease according to iRECIST
iCR	Complete Response acc to iRECIST
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
INF-g	Interferon Gamma
IP 10	Interferon gamma-induced protein 10
iPR	Partial Response acc to iRECIST
irAE	Immune-Related Adverse Event
IRB	Institutional Review Board
iRECIST	Guidelines for response criteria for use in trials testing Immunotherapeutics
iSD	Stable Disease acc to iRECIST
iUPD	Unconfirmed progressive disease
LAG-3	Lymphocyte Activation Gene 3
LAG-3Ig	Lymphocyte Activation Gene 3 Immunoglobulin (=Efti or IMP321)
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
MBC	Metastatic Breast Cancer
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
MICD	Minimal Important Clinical Difference
mLAG-3Ig	Murine homologue of IMP321 (hLAG-3Ig)
MNC	Mononuclear Cell
MoA	Mechanism/Mode of Action
MRCC	Metastatic Renal Cell Cancer
MRI	Magnetic Resonance Imaging

Abbreviation	Definition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Non-Evaluable
NK cell	Natural Killer Cell
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over the Counter
PBMC	Peripheral Blood Mononuclear Cell
PBPK	Physiologically-based PK
PD	Progressive Disease or Pharmacodynamic dependent on the context
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death Ligand 2
PD-X	PD-1 or PD-L1 (targeted therapy)
PFS	Progression-Free Survival
cci	cci
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
PR interval	ECG parameter (represents the time the impulse takes to reach the ventricles from the sinus node)
Q3W	Every 3 weeks
QOL	Quality of Life
QRS complex	ECG parameter (represents the time for ventricular depolarization)
QT interval	ECG parameter (represents the time from depolarization to repolarization of the ventricles)
QTc	Heart rate-corrected QT interval
RBC	Red Blood Cell
RCC	Renal Cell Cancer
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RHF	Rheumatoid Factor
ROC	Recurrent Ovarian Cancer
RPTD	Recommended Phase Two Dose
RR interval	ECG parameter (represents the duration of one complete cardiac cycle, a measure of the heart rate)
RSD	Reference Safety Database
SAD	Short Axis Diameter
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC s.c.	Subcutaneous
SD	Stable Disease
SIM	Site Imaging Manual
sLAG-3	Soluble LAG-3 (Lymphocyte Activation Gene-3) Protein
SOP	Standard Operating Procedure
Study agent/drug	Every IMP used in this study (i.e. efti or pembrolizumab). The Terminology Study agent is used as equal to Study drug
Study treatment	Any combination of pembrolizumab + efti
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Tesla
t1/2	Elimination Half-Life

Abbreviation	Definition
TdP	Torsade de Pointes
TEAE	Treatment-emergent Adverse Events
Th1	Helper T Cells Type 1
TIL	Tumor Infiltrating Lymphocytes
TLR	Toll-like Receptor
T_{max}	Time to Reach C_{max}
TMDD	Target-mediated Drug Disposition
TNBC	Triple Negative Breast Cancer
Treg	Regulatory T Cell
TTNT	Time to Next Treatment
ULN	Upper Limit of Normal
US, USA	United States
VD	Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization

3 INTRODUCTION

The information given in this section is an overview of the pre-clinical and clinical development program for eftilagimod alfa (efti, eftilagimod alpha, IMP321) and pembrolizumab to date that underpin the proposed Phase II clinical study. Further specific and more detailed information is provided in the Investigator's Brochure (IB) for efti. The IB will be updated at regular intervals and whenever new safety relevant data become available.

3.1. Standard Treatment Options

3.1.1. Advanced non-small cell lung cancer (NSCLC)

Almost 800.000 new cases of NSCLC are reported worldwide every year accounting for approximately 85 % of all lung cancers (13). NSCLC can be divided into adeno-, large cell and squamous cell carcinoma representing approximately 50-60 %, 30-40 % and 2-10 % with differences between the regions.

NSCLC is the indication leading to the most cancer related death worldwide as it is mostly diagnosed relatively late. In the US approximately 180.000 new cases were recorded in 2015 (13). The 5-year survival rate published by the American Cancer Society in 2017 for patients with stage IIIA NSCLC is about 36 %. For stage IIIB cancers the survival rate is about 26 %. For stage IIIC cancers the survival rate is about 13 %. (14). Approximately 41 % are diagnosed with stage IVA with a 5-year survival rate of ~ 10 % or stage IVB with a survival rate of <1 % (13).

3.1.2. 1st line NSCLC

Treatment of NSCLC is dependent on histological subtypes (squamous vs. non-squamous) and presence of EGFR, BRAF, ALK or ROS1 mutations. Patients with actionable mutations (10-20 % of all NSCLC patients (15)) will receive targeted therapies such as dabrafenib or ceretinib, depending on the mutation (16).

Patients with ≥50 % programmed death ligand 1 (PD-L1) expression and non-squamous NSCLC can be treated with the programmed death 1 (PD-1) blocking antibody pembrolizumab as first line therapy (16). In the Keynote-024 study an objective response rate (ORR) of 45 %, median progression free survival (PFS) of 10.3 and median overall survival (OS) of 30 months were reported (10). These results were confirmed in the Keynote-042 study where single agent pembrolizumab led to a statistically significant overall survival benefit compared to doublet chemotherapy in first line NSCLC patients with either squamous or non-squamous disease and PD-L1 expression of ≥1 % (17). The response rate for pembrolizumab in this patient population was reported with 27 % (11).

For patients not amenable to treatment with therapies targeting the EGFR pathway or pembrolizumab monotherapy will receive (based on the performance status) platinum-based doublet chemotherapy in combination with pemetrexed. The ORR of platinum plus pemetrexed was reported with 28 %. The median PFS was 6 months (10).

Just recently at American association for Cancer Research (AACR) congress April 2018, results from the Keynote-189 trial were reported for the combination of platinum-based chemotherapy plus pemetrexed ± pembrolizumab (18) in first line non-squamous NSCLC patients. An ORR of 47.6 % compared to 18.9 %, and overall survival hazard ratio (HR) of 0.49 was reported regardless of PD-L1 expression. The combination of ipilimumab and nivolumab (CTLA-4 and PD-1 antagonists) also reported superior efficacy (median PFS of 7.2 months) compared to chemotherapy (median PFS of 5.5 months) in a large Phase III trial, in NSCLC patients with high tumor mutational burden (19). Pembrolizumab has been submitted for registration for the patient population investigated in Keynote-189 and accepted for 1st line treatment of

NSCLC not harboring EGFR and ALK driver mutations in combination with pemetrexed and platinum chemotherapy.

3.1.3.2nd line NSCLC

Although it is difficult to estimate the proportion of NSCLC patients receiving 2nd line therapy, it was about 40-50 % in recent clinical trials (20). Single agent chemotherapy was the mainstay for long. Docetaxel, a widely used single agent chemotherapy, results in a ORR of 9-12 %, a median PFS of about 4 months, and a median OS of about 9 months (21, 22). Different PD-1/PD-L1 targeting therapies (pembrolizumab, nivolumab or atezolizumab) are approved and recommended for monotherapy for different 2nd line NSCLC subsets. In PD-X naïve (having not received any PD-1 or PD-L1 antagonist) 2nd line patients with non-squamous NSCLC and PD-L1 expression ≥1 % pembrolizumab at doses of 2 or 10 mg/kg led an ORR of 18 %, a median PFS of ~4 months and a median OS of 10.4-12.7 months (3). Nivolumab obtained comparable results with ORR of 19 %, median PFS of 2.3 and OS of 12.3 months regardless of PD-L1 expression. Both drugs are approved in 2nd line NSCLC after failure of platinum-based 1st line chemotherapy.

The majority of patients with metastatic NSCLC will progress and ultimately succumb to their disease. Based on the results published at AACR 2018 it is assumed that shortly the clear majority of patients not amenable to ALK/EGFR targeted therapy will receive a PD-X antibody in the first line setting. Therefore, new treatment regimens for 1st line in combination with an anti-PD-1 antibody and for PD-X refractory 2nd line NSCLC are needed to improve clinical benefit in this incurable setting.

3.1.4.Recurrent or metastatic head and neck cancer

Worldwide about half a million new cases of head and neck cancer (HNC) are reported every year. For the US 58.115 cases were reported for 2016 with an anticipated annual growth rate of approximately 1.5 % for the next decade. Initial treatment options for stage I-III are, if feasible, surgery and/or radiation therapy together with adjuvant regimes. If the cancer is non-resectable, chemoradiotherapy is offered as standard of care.

HNC has a recurrence rate of 20-50 % depending on the stage of diagnosis and is responsible for about 300.000 death per year worldwide (23, 24). The treatment paradigm for HNC is schematically depicted in Figure **1**.

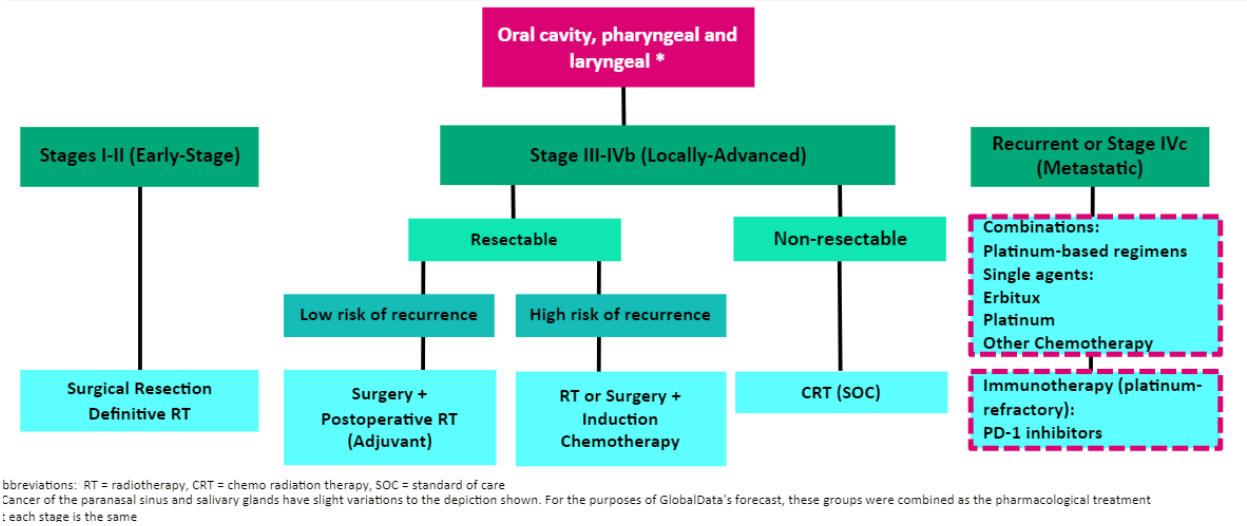

Figure 1: Treatment paradigm HNC. (25)

First line systemic treatment for recurrent or stage IV non-nasopharyngeal HNC consist according to the National Comprehensive Cancer Network (NCCN) guideline mostly of platinum-based combination therapies, especially the combination of cisplatin, 5-FU and cetuximab followed by cetuximab maintenance therapy (23, 24).

Standard 2nd line treatments include methotrexate or docetaxel with an ORR of around 6 % and an OS of about 6 months (24, 26). In the last years, several PD-1 targeted therapies (nivolumab, pembrolizumab) have been approved by the Food and Drug Administration (FDA) with reported ORR of 13.3-16.2 %, median PFS of around 2.1 month and a median OS of 7.1-8.4 month (24, 26). Despite some durable responses observed under pembrolizumab and nivolumab therapy improvement of the treatment options for recurrent head and neck squamous cell carcinoma (HNSCC) patients is warranted. Further improvement for 2nd line recurrent HNSCC patients is urgently needed, given the short OS time and the low response rate.

3.2. Eftilagimod alfa

Eftilagimod alfa (efti, eftilagimod alpha, IMP321) consists of the extracellular portion of the human LAG-3 protein (27, 28) fused to the Fc fraction of a human IgG1 (Figure 2). This soluble LAG-3Ig fusion protein, like the membrane form of LAG-3 naturally expressed on human T cells, binds to Major Histocompatibility Complex (MHC) class II molecules on the surface of antigen presenting cells (APC) and promotes the activation, maturation and chemokine secretion of APC (29-35). Efti is a first-in-class APC activator.

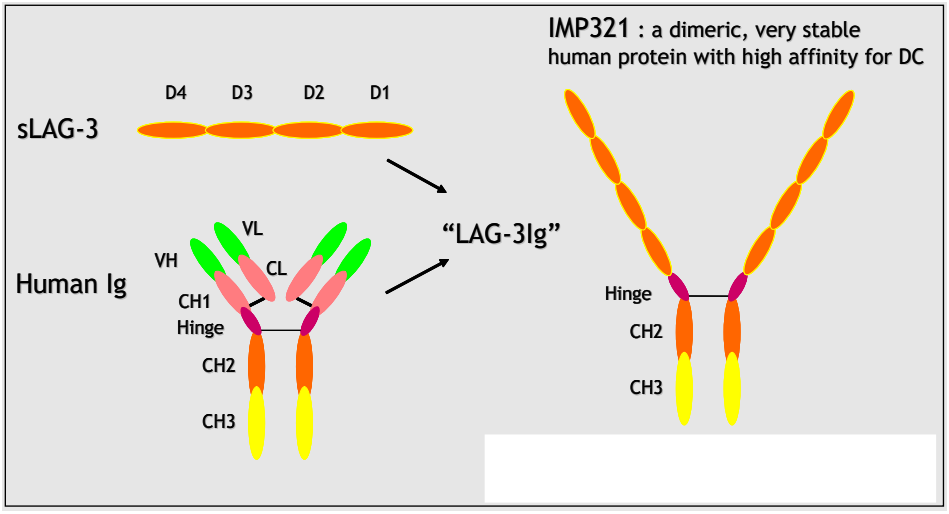

Figure 2: Diagrammatic structure of efti (IMP321), a first-in-class APC activator

APC such as dendritic cells (DC) and monocytes/ macrophages form a network in tissues. Following a "danger signal" (e.g., local infection/ tumor) DC capture non-self-microbial/ oncogenic proteins, digest these proteins into immunogenic peptides, migrate to the draining lymph nodes a few centimeters away and present these peptides to CD4 and CD8 T-lymphocytes. The binding of efti to MHC class II leads to APC activation/ expansion with enhanced presentation of tumor antigens to T-cells. As a result, strong and sustained anti-tumor cytotoxic T-cell responses are obtained. This natural process is made even more effective when efti is given the day after chemotherapy at a time when APC are fully loaded by tumor cell antigenic debris from the dying tumor cells.

3.2.1. Non-clinical Data

As already mentioned above, LAG-3 is a membrane protein associated with the T-cell receptor on the surface of activated T cells, which binds to MHC class II molecules on the surface of APC (28, 34, 36-38) and promotes the activation, maturation and chemokine secretion of human DC (31-33). In addition, a natural soluble form of the LAG-3 molecule (sLAG-3), is found in normal sera and has been shown to be a good prognostic factor as a Th1 marker in tuberculosis and breast cancer.

Immune checkpoint pathways strongly downregulate T-cell activation with the intent of keeping nascent T-cell responses in check and reducing the likelihood of an immune attack against normal tissues. During tumorigenesis, however, cancer cells may exploit these inhibitory pathways to resist detection or avoid elimination by the adaptive immune system. PD-1 is a critical checkpoint molecule that is expressed by T cells upon activation. The PD-1 pathway blockers display a remarkable success in anti-tumor response but with heterogeneous efficacy depending on patients and cancer types.

Exploiting these two aspects of immune system regulation by combining efti as APC activator with checkpoint blockers is therefore an attractive way to increase the response level and number of responsive patients. The benefit of combining these two agents is supported by in vitro and in vivo experiments. In culture, primary human blood cells stimulated with sub-optimal dose of antigen, incubated with low dose of efti or low dose of anti-PD-1 or PD-L1 blocking antibody produced Type-1 cytokines and T cell expressed activation markers. When combining low dose of both reagents, a synergy is observed inducing more cytokines secretion and more T cells to express activation markers compared to the response observed even at concentration of PD-1 pathway blockers that was 30 or 100-fold higher. It was concluded from these results that the *ex vivo* type-1 response induced by PD-1 pathway antagonists is synergistically increased by efti.

In a mouse model of [redacted]. Further details can be found in the latest version of the Investigators Brochure.

3.2.2. Clinical Data

Based on the mechanism of action of efti as an APC activator, several options exist for the use of efti in the treatment of cancer:

- In combination with chemotherapy (**chemo-immunotherapy**) - amplifying the immune system response using the antigens released by dying tumor cells;
- In **combination with other active immunotherapies**, having a complementary mechanism of action as an immune checkpoint inhibitor (e.g. anti-PD-1/PD-L1, CTLA-4 mAb); and
- As an **adjuvant for cancer vaccines or after intra-tumoral injections (*in situ* immunization)** – locally boosting the immune response to specific tumor antigens.

Although efti was first tested as an adjuvant to cancer vaccines and later in combination with chemotherapy, this protocol is investigating the combination of efti with pembrolizumab, hence combining two active immunotherapies.

In total 234 cancer patients have received at least one dose of efti[2] (for details see *Table 2*). In all subjects, efti has been administered s.c. All patients had advanced/metastatic solid tumours, including 21 patients

[2] Thereof appr. 70 pts (50 % from 141) may have received placebo instead of IMP321.

with metastatic renal cell carcinoma, 189 with metastatic breast cancer and 24 with advanced metastatic melanoma. One-hundred-eighty-six (189) patients have received different dose levels of efti in combination with paclitaxel (80 mg/m^2 i.v. day 1, 8 and 15, every 4 weeks) and 24 patients have received efti in combination with pembrolizumab (2 mg/kg i.v. every 3 weeks). Of the 234 subjects 55 were treated with efti produced under the Henogen process and 180 with efti produced by Wuxi process (for details see respective IB).

Table 2: Overall exposure to efti (cut-off Oct 2018).

Parameter	Subjects with cancer (Henogen material)	Subjects with Cancer (Wuxi material)	Overall
Overall	54	180	234
mRCC (as monotherapy)	21	-	21
MBC (combination with paclitaxel)	33	156*	189
Met. Melanoma (combination with pembrolizumab)	0	24	24

A total of 234 subjects with advanced cancer were evaluated. No efti related death was reported in any of the trials. One subject within P011 had a fatal serious adverse event of Massive Pulmonary Embolism, which was considered unrelated to efti. 52 out of 234 (22.2 %) subjects experienced at least one SAE (in total 67 SAEs).

[redacted]

[redacted] and for both patient's treatment was permanently discontinued. Other SUSARs are most likely related to the underlying disease or the adjunctive chemotherapy and are described in detail in the IB.

Detailed analysis on adverse event level were performed for run.in phase of P011, P012 (part A) and P003 and P005 (n overall = 84). The majority of the adverse events reported were related to the underlying disease (late stage advanced, metastatic cancer), the adjunctive chemotherapy or to pembrolizumab.

Transient dose dependent [redacted] reported as shown in Table 3. These are likely related to the s.c. administration of efti.

[redacted] were the most common (≥10 %) adverse events related to the mechanism of action of efti.

Table 3: Overview TEAE related to the mechanism of action of efti and overall. n is the number of subjects. Total number of patients investigated [redacted].

Preferred *Term (> 10 % of pts)*	***Overall N (%)***
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

* - only includes FAS population for P005; # - incl. CCI

Repeated (every 2 weeks) subcutaneous injections of efti up to 30 mg alone or in combination with weekly paclitaxel or pembrolizumab as a treatment for advanced cancer are safe and well tolerated. At 30 mg one dose limiting toxicity (DLT) was observed (in combination with weekly paclitaxel), but the maximal tolerable dose was not reached in any of the clinical trials.

In the P012 (TACTI-mel) study 18 patients (17 male, 1 female) with advanced/metastatic melanoma and a median age of 67 years (range 48-85) were enrolled. Patients have been treated with the combination of pembrolizumab and efti (1, 6, and 30 mg) starting from cycle 5 of pembrolizumab. 6 patients have been treated at 30 mg level.

Table 4: Study P012 - adverse events by PT and worst severity. n= number of pts

Reported Term by frequency	Grade 1 n	Grade 1 %	Grade 2 n	Grade 2 %	Grade 3 n	Grade 3 %	Grade 4 n	Grade 4 %	Overall (N=18) n	Overall (N=18) %
Fatigue	CCI	CCI	CCI	CCI	CCI	CCI				
Rash#					CCI	CCI				
Diarrhoea					CCI	CCI				
Nausea										
Arthralgia										
Hyperglycaemia										
Altered liver function										
Anaemia of chronic disease										
Bilateral axillary dissection										
Decreased renal function										
Intestinal perforation							CCI	CCI		
Colitis										
Influenza A										
Intracranial Haemorrhage							CCI	CCI		
Hyponatraemia										
Pulmonary embolism										
Right sided chest pain										
Sepsis of unknown origin										
Shortness of breath										

Listed if occurred in ≥15 % or ≥ grade 3. # - including CCI

The data cut-off is Oct 2018. No treatment related death was reported. No treatment related death was reported. Seven SAEs in 6 subjects were reported. None of the SAEs were related to the study treatment.

One grade 4 intracranial haemorrhage was reported (not related) leading to death in one subject. Another subject permanently discontinued the treatment due to an anaemia of chronic disease grade 3 (not related to efti or pembrolizumab). No dose limiting toxicity at any dose was reported.

In summary efti given subcutaneously biweekly at a dose of 1, 6 or 30 mg in combination with 2 mg/kg IV pembrolizumab every 3 weeks was well tolerated without any DLT.

In total 133 AEs were reported in 18 subjects. The most frequently (>10 %) reported AEs were fatigue (44 %), rash (including maculo-papular rash) (39 %), diarrhea (28 %), nausea (28 %), arthralgia (17 %) and hyperglycemia (17 %).

One subject experienced not related a grade 4 AE (intracranial haemorrhage, 6 mg efti). Eighteen (18) AEs grade 3 were reported in eight subjects as listed. No adverse event grade 3 occurred twice except hyperglycemia.

Eighteen (18) AEs in 9 subjects were related to efti. One patient experienced grade 3 decreased renal function. All other AEs were grade 1 or 2.

The majority (78 %) of subjects had M1c stage disease. The ECOG status at screening was 0 in 14 (78 %) and 1 in 4 (22 %) subjects, respectively. Five (27.8 %) patients have received prior systemic therapy for metastatic disease. None of the patients had prior PD-1 or PD-L1 antibodies except the four cycles of pembrolizumab prior to study start. The majority of subjects had either an irSD (39 %) or irPD (28 %) as best response after the first 3 cycles of pembrolizumab monotherapy. Overall an ORR of 33.3 % was achieved incl. 1 subject (5.6 %) with a complete response as shown in Table 5. Besides six subjects with a tumor size decrease > 50 % compared to baseline including 2 subjects with complete disappearance of all target lesions, four subjects showed a decrease in target lesions between 45 and 49 %. In total ten subjects (55.6 %) had a target lesion decrease and disease control rate was 66.6 %.

Table 5: Study P012 – ORR acc to irRC.

Parameter acc. to irRC	**Total N=18**
Complete Response	1 (5.6 %)
Partial response	5 (16.7 %)
Stable disease	6 (33.3 %)
Progressive disease	6 (33.3 %)
Not evaluable#	0 (0.0 %)
Disease control rate (DCR)	11 (61.1 %)
Objective Response Rate (ORR)	6 (33.3 %)

There is little experience in large clinical studies in patients not responding well to pembrolizumab monotherapy and continuing on pembrolizumab. In treatment naïve melanoma patients with metastatic disease, pembrolizumab resulted in an ORR of 33-34 % (incl. 6-10 % complete responses) (39). In patients pre-treated with either BRAF/MEK inhibitors or ipilimumab pembrolizumab resulted in an ORR of 21-25 % with 2-3 % of complete responders (40, 41). Responses were assessed according to response evaluation criteria in solid tumors (RECIST) 1.1.

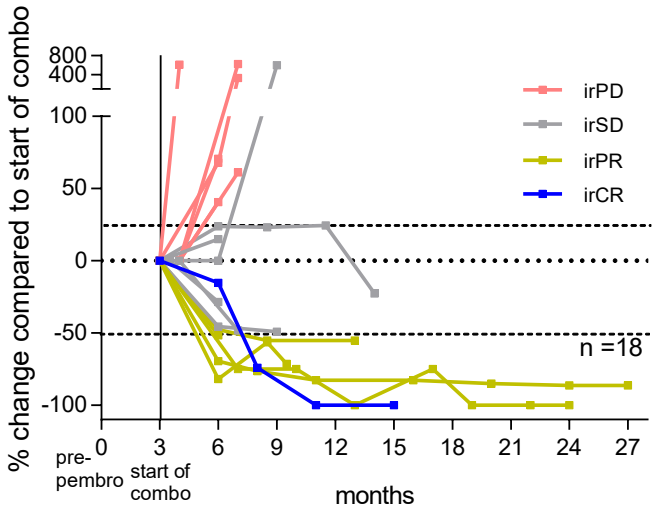

Figure 3: Trial P012 – Spiderplot (irRC) by subject. Data cut-off 15-Oct-2018.

In the P012 study 28 % have been pre-treated with either ipilimumab or a BRAF/MEK inhibitor and 28 % progressed on pembrolizumab monotherapy prior to study start. Responses were assessed according to irRC and not RECIST 1.1. Five partial and one complete response were observed leading to an ORR of 33.3 %. Although some of the patients initially had a progression on pembrolizumab monotherapy and others have been pre-treated the disease control rate and response rates observed so far are encouraging.

3.3. Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (i.v.) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

3.3.1. Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades . Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of $CD8^+$ effector T-cells/$FoxP3^+$ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and reinfused, inducing durable objective tumor responses in cancers such as melanoma (42).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (43).

The structure of murine PD-1 has been resolved. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (43, 44). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (45, 46). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in NSCLC and HNSCC.

3.3.2. Pre-clinical and Clinical Data

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (47-53). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia, and colorectal carcinoma (50, 52-55). In such studies, tumor infiltration by CD8+ T cells and increased interferon (IFN)-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* (52). Experiments have confirmed the *in vivo* efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

Efficacy data for the Merck-sponsored clinical trials used to support approvals in the US for the following indications: melanoma, NSCLC, HNSCC, cHL, UC, and MSI-H tumors.

The Reference Safety Database (RSD) is used to present the characterization of pembrolizumab's safety profile. [redacted]. Pembrolizumab is well tolerated in the approved indications, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs [redacted]%), discontinuations due to Aes ([redacted]%), and deaths due to drug-related Aes [redacted]%). Furthermore, the frequency of immune-mediated AEOSIs is low, and these events are readily managed in the clinical setting.

3.4. Study Rationale

Treatment of advanced solid tumors remains challenging despite the progress which has been made over the last years especially with targeted therapies like tyrosine kinase inhibitors, monoclonal antibodies and immunotherapies like PD-1/PD-L1 and CTLA-4 antagonists. Recently, immune therapies like anti CTLA-4 and anti PD-1 antagonist have been approved by the FDA in many different solid tumors. In general immune therapies as single agents achieved response rates between 12 % (ovarian cancer) and 40 % (melanoma, MSI-high) in a high number of solid tumors (i.e. NSCLC; small cell lung cancer , renal cell

cancer (RCC), HNSCC, triple negative breast cancer, hepatocellular cancer , gastroesophageal cancer and others) (1-6).

Understanding the reasons why a majority of patients does not respond to PD-1/PD-L1 blockade is key to develop new therapy combinations. On-treatment tumor biopsies have shown that non-responding patients have either little or no tumor-infiltrating lymphocytes (TILs) in the tumor bed or a non-functional immune response (i.e. no intratumoral IFNγ) with PD-1/PD-L1 negative TILs (7). Thus, immunogenic signals that induce tumor antigen-loaded DCs to escape peripheral tolerance and better prime and activate effector T cells are expected to reactivate the deficient early steps of the cancer-immunity cycle (8, 56).

In a mouse model of [redacted]

In clinical studies with efti it has been shown that efti as an APC activator at a dose of ≥ 1 mg/injection induced a sustained increase in monocyte and dendritic cells blood counts as well as a sustained activation of blood monocytes over 6 months. Moreover, this APC activation led to a sustained increase of activated CD8 T cells over 6 months and a sustained increase in serum IFNγ, a Th1 cytokine.

In the crosstalk between immune system and cancer, PD-1 antagonists like pembrolizumab address the immune escape (T cell downregulation). On the other hand, the capacity of the immune cells to recognize the tumor cells and prime an efficient effector response can be increased by an APC activator like efti.

In patients eligible to anti-PD-1 therapy, the addition of a well-tolerated APC activator like efti may help to activate the cellular immune response mechanisms to mediate tumor recognition and killing and thus may lead to higher frequency of durable responses compared to pembrolizumab monotherapy in different solid tumor without adding substantial toxicity.

3.5. Benefit and Risk Ratio

In toxicology studies in mice, efti was well tolerated with no sign of inflammation, either injected alone or as an adjuvant with strongly immunogenic antigens (57). [redacted].

The nonclinical toxicity studies for pembrolizumab consisted of [redacted]. These studies were supported by toxicokinetic evaluation of pembrolizumab. Additional evaluation included [redacted] There were no findings of toxicological significance in any of the conducted studies.

In previous clinical studies, repeated s.c. doses of up to 30 mg efti alone (in metastatic RCC patients), in combination with paclitaxel (metastatic breast cancer (MBC) patients) and in combination with pembrolizumab (melanoma patients) were generally well tolerated and had an acceptable safety profile.

Efti is a soluble human recombinant protein with the potential risk of inducing an allergic reaction. Possible symptoms associated with an allergic reaction can include fever, chills, weakness, headache, nausea, vomiting, diarrhoea, swollen lips and neck, low blood pressure, respiratory symptoms and rashes.

CCI, CCI and CCI immediate systemic hypersensitivity reactions were reported in CCI trial subjects receiving 30 mg efti(/placebo) in combination with either paclitaxel or pembrolizumab. All CCI reactions show consistent time to onset from start of administration (i.e. within 30 minutes) and similar pattern of symptoms. All CCI cases occurred after multiple efti injections without any preceding signs/events suggesting systemic involvement and in all four cases the hypersensitivity symptoms resolved within one day.

As there is a risk of an CCI.

CCI.

In both dose finding trials (P011 – AIPAC, P012 – TACTI-mel) cytokine levels were closely monitored after the first and 12th injection of efti. No increase of CCI have been observed at any dose level up to 30 mg efti s.c.. Increase of CCI, CCI, CCI and CCI) have been reported from both trials at different dose levels (1-30 mg) of efti but these serum concentrations levels were too low to induce systemic reactions such as fever. Vital signs and other parameters are closely and frequently monitored during clinical trials with efti.

Transient injection site reactions (including skin changes e.g. erythema, pain and induration) of mild and moderate intensity have been reported from all trials.

Details on management of efti related adverse reaction are discussed in Section 6.7.1.

In studies P003 and P005, no ADAs were detected in the serum of patients even after 12 s.c. injections of efti over 6 months. However, confirmed ADAs against efti have been reported with low to intermediate titers in the studies P012 CCI patients tested post-treatment start) and P011 (CCI patients tested post-treatment start) and are further investigated. To evaluate this risk, the relationship between the therapeutic protein and endogenous LAG-3 (a co-inhibitory receptor expressed on activated T cells) should be considered. If ADAs are induced in metastatic breast cancer patients and if a significant fraction of these ADAs are neutralizing antibodies, the function of the endogenous LAG-3 receptor expressed on activated effector T cells and on Treg cells will be blocked. Consequently, the anti-tumor cellular responses of these patients would be increased due to immune checkpoint blockade. This could lead to additional clinical benefit for cancer patients which outweighs the risks of immune-related adverse events (irAEs).

Generally speaking, irAEs have been reported after the blocking of inhibitory receptors (CTLA-4, PD-1) expressed on T cells but not after stimulation of APCs (TLR8 or TLR9 agonists, anti-CD40 agonist mAb). So far, no irAEs have been observed. However, occurrence of irAEs cannot be excluded, especially when more patients are treated, potentially including patients predisposed to autoimmune reactions.

The rationale to combine pembrolizumab and efti comes from its complementary mechanism of action. Efti activates APCs and CCI to pembrolizumab.

In this study, efti will be combined with pembrolizumab. The CCI.

Based on the RSD, Pembrolizumab is well tolerated in the approved indications, as evidenced by a low rate of Grade 3 to 5 drug-related AEs (CCI %), discontinuations due to AEs CCI %), and deaths due to drug-related AEs CCI %). Furthermore, the frequency of immune-mediated adverse events of special interest is

low, and these events are readily managed in the clinical setting based on guidance provided to investigators on the management of immune and non-immune-mediated events of interest.

Pembrolizumab provided substantial, clinically meaningful benefits in terms of prolonged OS and PFS, and increased ORR in patients with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. In previously treated patients with PD-L1 expression ≥1 % and disease progression following platinum-containing chemotherapy, pembrolizumab provided a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy.

For patients with previously untreated metastatic NSCLC whose tumors expressed high (≥ 50 %) levels of PD-L1, pembrolizumab demonstrated significant improvements in PFS and OS over standard of care chemotherapy. For patients with previously untreated squamous or non-squamous NSCLC with ≥1 % PD-L1 expression pembrolizumab increased the overall survival significantly. Pembrolizumab in combination with pemetrexed/carboplatin for the first-line treatment of metastatic non-squamous NSCLC demonstrated both a statistically significant and clinically meaningful difference in ORR and a statistically significant benefit in PFS compared with pemetrexed/carboplatin alone.

In the treatment of advanced HNSCC after platinum based first line chemotherapy, pembrolizumab demonstrated a clinically meaningful ORR of ~15 % and a prolonged duration of response that was substantially distinct from what is expected with standard of care (i.e. methotrexate with ~ 8 % ORR) in previously treated patients with HNSCC. However, a treatment benefit of pembrolizumab over standard of care for overall survival has not been confirmed.

Efti has shown antitumor activity in combination with paclitaxel (P005 and P011) and in combination with pembrolizumab (P012) in MBC and metastatic melanoma patients with suboptimal response to pembrolizumab alone, respectively.

The principal aim of this study is to investigate the efficacy and safety of efti in combination with pembrolizumab in patients with: advanced/metastatic treatment naive NSCLC (1st line) (Part A), advanced recurrent PD-X refractory NSCLC after failure of 1st line PD-X containing therapy (Part B), and HNSCC after failure of prior platinum-containing 1st line therapy (Part C). The patients intended to be enrolled have no curative treatment options and especially for 2nd line NSCLC and 2nd line HNSCC there are only very limited treatment options (see section 3.1). Pembrolizumab monotherapy is approved for 1st line NSCLC patients with ≥50 % PD-L1 positivity and for ≥2nd line NSCLC patients progressing on (platinum containing) chemotherapy and with ≥1% PD-L1 positivity by EMA, FDA and TGA and for 2nd line HNSCC patients by the FDA and TGA. Efti injected s.c. every 2 weeks up to 30 mg has shown to be well tolerated in patients with advanced cancer in combination with chemotherapy or pembrolizumab. The dose finding was based on the preclinical and clinical data.

Furthermore, this trial will help to identify patients who may especially benefit from the combination of efti and pembrolizumab as different biomarkers (PD-L1 expression, gene expression profile acc. to PanCancer Immune code, circulating level of Th1 biomarkers) will be assessed and analyzed under the current protocol.

The anticipated risks are based on efti and pembrolizumab non-clinical and clinical experience. Patients will be treated at well trained sites and with an emergency unit under the supervision of investigators experienced with the use of checkpoint therapies and experts in the treatment of NSCLC and HNSCC.

Despite the COVID-19 pandemic, due to the late-stage cancer disease of the subject populations under investigation, the risk benefit assessment does not change.

In summary it is considered that the combination of pembrolizumab and efti has an acceptable risk/benefit profile. The expected benefit outweighs the expected risks for the patients.

3.5.1. Management of Risks

To minimize the risk to patients and maximize safety, the following factors have been incorporated into the study design:

- Detailed safety and laboratory assessments will be performed as outlined in section 8.5 of this protocol.
- All clinical observations will be evaluated by the investigator on an ongoing basis.
- The DMC will review the safety and efficacy data of all patients (part A-C) on a regular basis as specified in the DMC charter.
- Each patient must stay on site for at least 30 minutes after the last study drug administration on each treatment day
- The inclusion and exclusion criteria have been defined to exclude patients with unacceptable risks
- Special events of clinical interest have been defined which needs expedited reporting see section 9.3)

4 STUDY OBJECTIVES & ENDPOINTS

4.1. Primary Objectives

- To evaluate the response rate of eftilagimod alfa in combination with pembrolizumab in patients with advanced, metastatic, recurrent NSCLC and HNSCC

4.2. Secondary Objectives

- To evaluate the safety and tolerability of eftilagimod alfa when combined with pembrolizumab
- To further evaluate the antitumor activity of eftilagimod alfa when combined with pembrolizumab
- To assess the pharmacokinetic and immunogenic properties of eftilagimod alfa

4.3. Exploratory Objectives

- To identify and characterize relevant biomarkers
- To further characterize the antitumor activity of eftilagimod alfa in combination with pembrolizumab

4.4. Endpoints

4.4.1. Primary endpoint

- To determine the best overall response rate (ORR) according to iRECIST.

4.4.2. Secondary endpoints

- Safety profile in terms of frequency, severity, and duration of Adverse events (AEs), serious adverse events (SAEs) according to the current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5.0, events of clinical interest (ECI) and abnormalities in vital signs, physical examination, 12-lead electrocardiogram (ECG) and safety laboratory and urine assessments.
- To assess time to and duration of responses according to iRECIST and RECIST 1.1
- To assess the response rate according to RECIST 1.1
- To assess the disease control rate according to iRECIST and RECIST 1.1
- To assess progression free survival (PFS) and overall survival (OS)
- To assess occurrence and nature of anti-eftilagimod alfa-specific antibodies.
- To assess the plasma concentration time profile and derived PK parameters which may include but will be not limited to area under the curve (AUC), peak plasma concentration (C_{max}), time to reach C_{max} (t_{max}), systemic clearance (CL), elimination half-life (t1/2) and volume of distribution (VD) of eftilagimod alfa.

4.4.3. Exploratory endpoints

- To assess PD-L1 expression assessed by central laboratory.
- [redacted]
- To assess Gene signature acc. to PanCancer Immune code set assessed by a central laboratory.
- To assess circulating level of Th1 biomarkers (i.e. IFN-γ, CXCL10) assessed by a central laboratory.
- [redacted]

5 STUDY DESIGN

The study is designed according to Simon's optimal two-stage design (9). During the first stage of the study the number of N1 patients will be recruited for each indication into this multicenter, open label, phase II study. In case there are more responses than threshold r1 observed in patients recruited in the initial stage (N1), additional patients (N2) will be recruited. Following the completion of the initial stage, the decision to recruit the additional patients (N2) will be taken by the Data Monitoring Committee (DMC), as described later.

Indication	Threshold r1	Initial No of pts (N1)	Add. No. of pts (N2)	N total
NSCLC 1st line	4	17	19	36
NSCLC 2nd line	1	23	13	36
HNSCC	2	18	19	37

In case ORR in any part meets a predefined threshold an extension of this cohort may be set up to combine the patients of stages 1, 2, and newly enrolled patients in that respective part, to provide a reasonable basis in sample size considerations for further clinical studies. For sample size considerations in the extension phase please refer to the section "sample size calculations" in the synopsis and chapter 10 of the protocol.

To be eligible for participation, patients must have either:

Part A: Histologically- or cytologically-confirmed diagnosis of non-small cell lung cancer stage IIIB not amenable to curative treatment (unresectable) or stage IV not amenable to EGFR/ALK based therapy, treatment naïve for advanced/metastatic disease.

Note: Patients who received durvalumab or any other PD-1 or PD-L1 therapy as maintenance therapy to the adjuvant chemotherapy regimen and hence are not naïve to anti-PD-X agents, can be recruited provided that all other necessary requirements are met.

Part B: Histologically- or cytologically-confirmed diagnosis of NSCLC after failure of first-line treatment (for metastatic/advanced disease) with at least 2 cycles of any PD-1/PD-L1 therapy (e.g. nivolumab, pembrolizumab, avelumab, durvalumab, etc.) alone, or in combination with any other immunotherapeutic or chemotherapy given as part of first-line treatment

Note: Failure on therapy is defined as progress acc. to RECIST 1.1 and would require confirmation by a second assessment no less than four weeks from the first documented PD in the absence of rapid clinical progression. If patients discontinue PD-1/PD-L1 after being treated for at least 2 cycles for reasons other than progression, they may enroll in the study if initial progression occurs within 12 weeks after end of PD-1/PD-L1 therapy and progression is confirmed. Only patients to be receiving treatment in true second-line setting can be enrolled to Part B. Patients who have received durvalumab or any other PD-1 or PD-L1 therapy as part of their adjuvant therapy and no other PD-1/PD-L1 therapy in the first line treatment are not eligible for Part B.

Note: In Parts A and B patients with neuroendocrine or sarcomatoid NSCLC tumor types are not eligible. Patients with undifferentiated lung carcinoma with some neuroendocrine features can be recruited.

Part C: Histologically- or cytologically-confirmed recurrent disease not amenable to curative treatment with local or systemic therapy, or metastatic (disseminated) HNSCC of the oral cavity, oropharynx,

hypopharynx, or larynx that is considered incurable by local therapies after failure of prior platinum-based therapy.

Note: In all three parts patients will be enrolled regardless of their PD-L1 expression.

Part A+B+C:

Patients will receive pembrolizumab and efti starting from cycle 1 day 1 as follows:

- 200 mg pembrolizumab every 3 weeks IV (30 min) for up to 35 cycles; 1 cycle = 3 weeks
- 30 mg of efti every 2 weeks s.c. for the first six months (until including cycle 8) and shifted to every three weeks s.c. thereafter (cycle 9 to 18); 1 cycle = 3 weeks

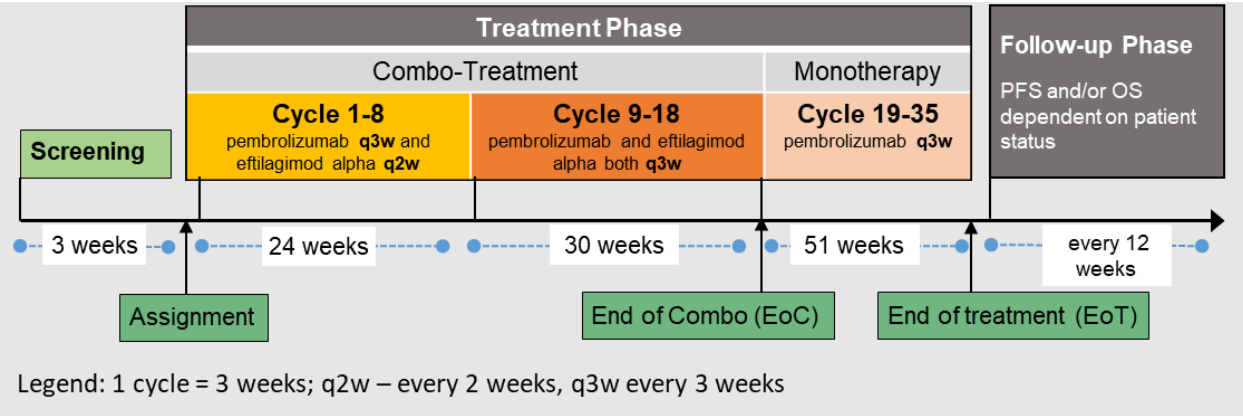

Figure 4: Study flow chart for part A, B and C.

Screening of patients for eligibility to enter this study will be done in the three weeks prior to cycle 1 day 1. Patients will be enrolled in parallel except for the first three patients in each part who are to be enrolled at least 1 week apart. A patient will stay on treatment until disease progression, unacceptable toxicity, completion of 35 cycles of pembrolizumab (~2 yrs.; completion of study treatment) or discontinuation for any other reason. Three (3) weeks after the end of the combination therapy (cycle 18) end of combination (EOC) therapy assessments will be performed. Three (3) weeks after end of any study treatment (cycle 35) an end of treatment (EOT) visit will be performed. Upon start of study treatment, patients will be followed for PFS and OS. PFS will be radiologically assessed at the study sites until progressive disease (PD), death, withdrawal of consent, loss to follow-up, or until the end of the study, whichever occurs first. Radiological assessment will be performed at intervals of 9 weeks until week 36 (week 9, 18, 27, 36) and every 12 weeks thereafter (after week 36). OS will be monitored until death, withdrawal of consent, loss to follow-up or until the end of the study, whichever occurs first. Measurability will be assessed according to iRECIST. Response to treatment and treatment decisions will be assessed according to iRECIST. Objective response (iPR, iCR) should be confirmed by a repeat imaging assessment at least 4 weeks after the first response is observed. Per iRECIST, disease progression should be confirmed 4 to 8 weeks after site-assessed first radiologic evidence of iUPD. Patients, who have unconfirmed disease progression (iUPD) should stay on treatment (if clinically stable) until progression is confirmed (iCPD), provided they have met the conditions detailed in Section 8.1.3.

Radiological scans and related information will be evaluated at the study sites for treatment decision and for primary objective and will be collected for potential later central evaluation by blinded independent radiologists.

Safety procedures are described in section 9.

The study agents must be administered in a clinical setting where emergency resuscitative equipment and personnel trained in the management of anaphylaxis are immediately available to treat systemic reactions under the direct supervision of the physician.

5.1. DMC Review

The DMC will review the available safety data of all patients (part A-C) after 18 patients have completed at least two cycles (6 weeks) of therapy. In addition, the DMC will review the efficacy and safety data after the last patient N1 has been enrolled or the minimum number of responses is reached for each part of the study, whatever is first. Patients included in this decision must have had at least one tumor imaging after treatment was initiated. The DMC will give a recommendation for each part of the study if stage 2 or an extension can be opened independently. Further details are described in the DMC charter.

Furthermore, the DMC will monitor safety and efficacy data at regular intervals and in accordance with the DMC charter. The DMC may recommend stopping/changing the study if at any time during the trial there are unacceptable adverse events or safety concerns. Unless immediate action is required to protect the safety and well-being of study patients, the sponsor will consult with appropriate regulatory authorities prior to early termination of the study based on any DMC recommendation.

5.2. Study Stopping Rules

The Sponsor may after careful evaluation decide to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites or at all sites at any time for reasons including but not limited to, incidence or severity of AEs in this study that indicate a potential health hazard to study patients, unacceptable safety concerns, unfavorable risk/benefit ratio, ethical issues, inaccurate or incomplete data recording, noncompliance or unsatisfactory enrolment with respect to quality or quantity and decision by the Sponsor to suspend or discontinue testing, evaluation, or development of the product.

Patient safety will be monitored at study level (within the DMC) and on substance level (Immutep safety monitoring board). The recommendation of the above committees will be taken into consideration in such decisions of the Sponsor. The Investigators will be notified by the sponsor if the study is terminated or placed on hold. The relevant Independent Ethics Committees (IEC) / Institutional Review Boards (IRB) and health authorities will also be informed according to applicable regulatory requirements.

5.3. End of Study

The end of study is defined 36 months after last patient first visit.

5.4. Justification for Dose of eftilagimod alfa

Efti dose selection is based upon previous experience in studies P003, P005, P011 and P012.

As efti is an agonist binding to MHC class II receptors injected subcutaneously, Pharmacokinetics (PK) and Pharmacodynamic (PD) parameters were considered for guiding the correct dosing of efti. Deep s.c. injections in the thigh means that efti as a large molecule (MW of 160 kDa) is primarily (> 80 %) being absorbed by convection through the lymphatic vessels and not directly through the blood venules (58). It will have to pass through the inguinal nodes and then migrate to the lymph duct to reach the subclavicular vein and the blood stream. In between, the product migrates directly from the lymphatics vessels to the

tissues to reach their MHC class II expressing target cells (i.e. monocytes and dendritic cells). This explains, in part, why only CCI ng/ml (and not µg/ml) concentrations of efti are measured in the plasma as maximum (or peak) serum concentration (C_{max}) and CCI after s.c. administration of CCI mg efti. The CCI and CCI can be CCI. Therefore, dosing was primarily based on pharmacodynamic parameters CCI measured directly ex vivo in fresh PBMCs of patients treated with efti.

Dose levels of 0.25 to 30 mg efti injected s.c. biweekly either alone, in combination with weekly paclitaxel (80 mg/m2 IV D1, 8, 15 in a 4-week schedule) in MBC patients or in combination with pembrolizumab (2 mg/kg i.v. every 3 weeks) in melanoma patients were safe and well tolerated with one DLT (isolated gamma-GT increase grade 3 for > 7 days) and CCI mg. Various types of local injection site reactions up to grade 2 are the most common adverse event associated with efti. The number of patients affected and the frequency per patient, but not the severity increased with increasing dose levels of efti.

Table 6: Exposure of efti over time at CCI and CCI mg

Dose efti [mg/treatment]	**C_{max} > CCI ng/ml**	**CCI ng/ml at CCI hours**	**CCI ng/ml at CCI hours**
CCI	CCI (CCI %)	CCI (CCI %)	CCI (CCI %)
CCI	CCI (CCI %)	CCI CCI %)	CCI (CCI %)

Efti showed CCI from 1 to 30 mg. After CCI mg s.c. injection C_{max} is higher and concentrations above CCI ng/ml (a preclinically active concentration *in vitro*) were found in the majority of patients compared to CCI mg dose as shown in Table 6. At dose level below CCI mg PK parameters could not be established reliably in all patients due to the Lower Limit of Quantitation (LLOQ).

Dose levels of CCI mg (CCI mg and CCI mg) were found to be pharmacodynamically active with dose dependent effects on secondary target cells (increase in activated CD8 T cells) after 3 months. In the P005 study number of monocytes, dendritic cells, natural killer (NK) cells and activated CD8 T cells were increased after injection of either 0.25, 1.25 or 6.25 mg efti s.c. biweekly in conjunction with weekly paclitaxel (80 mg/m^2 D1,8 and 15 in a 4-week cycle). CCI. The number CCI. In the P011 study, number of primary (monocytes and dendritic cells) and secondary target cells (NK and CD8 T cells) as well as circulating cytotoxic T lymphocyte (CTL) immune response biomarkers like interferon gamma (IFN-γ) and C-X-C motif chemokine 10 (CXCL-10) were measured after injection of 6 and 30 mg efti s.c. biweekly in conjunction with weekly paclitaxel (80 mg/m^2 D1,8 and 15 in a 4-week cycle). Immuno-monitoring of circulating blood cells after three and six months showed an increase in the number of all primary and secondary target cells. The CCI, and therefore of a good systemic CTL immune response. It can be concluded that biweekly s.c. injections of ≥ 1 mg efti induced a sustained (i.e. observed 13 days after efti injection) increase in primary target cell (monocyte and dendritic cells) numbers and activation markers throughout the treatment. Moreover, this APC activation led to a sustained increase of

activated CD8 T cells (secondary target cells) over 6 months and a sustained increase in serum IFN-γ and CXCL-10, specially for the 30 mg dose.

The [redacted]. In all three studies, pharmacodynamic evaluations were made directly prior to the next dosing of efti, 13 or 14 days after the last administration. Hence, the pharmacodynamic effects described above correspond to the minimal residual effect of efti two weeks after administration. Since efti is then injected again, this observed minimal residual effect is said to be sustainable for months as long as efti continues to be injected every 2 weeks.

Thus, efti should be injected s.c. at a dose level of 30 mg.

5.5. Justification for Dose of pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK (PBPK) analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 patients were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other patient covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that

fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

5.6. Selection of Patients

5.6.1. Inclusion Criteria

Patients may be enrolled if they meet all of the following criteria at screening:

1. Willing to give written informed consent and to comply with the protocol.

2.2 Part A (1st line, PD-X naïve in metastatic setting NSCLC): histologically- or cytologically-confirmed diagnosis of non-small cell lung carcinoma stage IIIB not amenable to curative treatment or stage IV not amenable to EGFR/ALK based therapy, treatment naïve for systemic therapy given for advanced/metastatic disease (previous palliative radiotherapy for advanced/metastatic disease acceptable).

Note: Patients who received durvalumab or any other PD-1 or PD-L1 therapy as maintenance therapy to the adjuvant chemotherapy regimen and hence are not naïve to anti-PD-X agents, can be recruited provided that all other necessary requirements are met.

Part B (2nd line, PD-X refractory NSCLC): Histologically- or cytologically-confirmed diagnosis of NSCLC after failure of first-line treatment (for metastatic/advanced disease) with at least 2 cycles of any PD-1/PD-L1 containing based therapy (e.g. nivolumab, pembrolizumab, avelumab, durvalumab, etc.) alone, or in combination with any other immunotherapeutic or chemotherapy given as part of first-line treatment.

Note: Failure on therapy is defined as progress acc. to RECIST 1.1 and would require confirmation by a second assessment no less than four weeks from the first documented PD in the absence of rapid clinical progression. If patients discontinue PD-1/PD-L1 after being treated for at least 2 cycles for reasons other than progression, they may enroll in the study if initial progression occurs within 12 weeks after end of PD-1/PD-L1 therapy and progression is confirmed. Only patients to be receiving treatment in true second-line setting can be enrolled to Part B. Patients who have received durvalumab or any other PD-1 or PD-L1 therapy as part of their adjuvant therapy and no other PD-1/PD-L1 therapy in the first line treatment are not eligible for Part B.

Note: In Parts A and B patients with neuroendocrine or sarcomatoid NSCLC tumor types are not eligible. Patients with undifferentiated lung carcinoma with some neuroendocrine features can be recruited.

Part C (2nd line PD-X naive HNSCC): Histologically- or cytologically-confirmed recurrent disease not amenable to curative treatment with local or systemic therapy, or metastatic (disseminated) head and HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx that is considered incurable by local therapies after failure of prior platinum-based therapy.

3.1 Availability of formalin-fixed diagnostic tumor tissue (in the case of participants having received adjuvant therapy, the tissue should be taken after completion of this therapy).

4. Female or male ≥18 years of age on the day of signing the informed consent.

5. All female patients of childbearing potential must have a negative highly sensitive pregnancy test at screening (within 72 hours prior to cycle 1 day 1); all patients of reproductive potential must agree to use highly effective method for contraception from study entry until at least 4 months after the last administration of any study treatment.

A woman must either be,

- not of childbearing potential: postmenopausal (≥ 60 years of age, or < 60 years of age and amenorrhoeic for 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression with follicle-stimulating hormone (FSH) above 40 U/L and estradiol below 30 ng/L, or if taking tamoxifen or toremifene, and age < 60 years, then FSH and estradiol in the postmenopausal range), permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy), or otherwise incapable of pregnancy
- of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: e.g., established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; male partner sterilization (the vasectomized partner should be the sole partner for that subject).

6. A man who is sexually active and has not had a vasectomy must agree to use a barrier method of birth control e.g., either condom or partner with occlusive cap (diaphragm or cervical/vault caps) from study entry until at least 4 months after the last administration of study treatment. All men must also not donate sperm from time of study entry until at least 4 months after the last administration of study treatment.
7. ECOG performance status 0-1.
8. Expected survival > 3 months.
9. Evidence of measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 modified for immune-based therapeutics (iRECIST). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
10. Laboratory criteria: (collected ≤ 10 days prior to cycle 1 day 1):
    - Absolute neutrophil count > 1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
    - Hemoglobin ≥ 9 g/dL or 5.58 mmol/L[3]
    - Serum creatinine ≤ 1.5 × ULN, or if > 1.5 ULN with a clearance of ≥ 50 mL/min acc to. Gault-Cockcroft formula
    - Total bilirubin ≤ 1.5 x ULN or direct bilirubin ≤ ULN for patients with total bilirubin > 1.5 x ULN
    - AST (=SGOT) and ALT (=SGPT) ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases are present.
    - International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN unless patient is receiving anticoagulant therapy as long as PT or activated partial thromboplastin time (aPTT) is within therapeutic range of intended use of anticoagulants.

5.6.2. Exclusion Criteria

Patients are to be excluded from the study at the time of screening for any of the following reasons:

[3] Must be met without erythropoietin dependency and without packed red blood cell transfusion within the last 2 weeks prior to screening.

1.2 For part A (1st line, PD-X naïve in metastatic setting NSCLC):

- The NSCLC can be treated with curative intent with either surgical resection and/or chemoradiation and/or radiation.
- Has received systemic therapy for the treatment of their stage IV NSCLC. Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.
- Epidermal growth factor receptor (EGFR)-sensitizing mutation and/or is echinoderm microtubule-associated protein-like 4(EML4) gene/anaplastic lymphoma kinase (ALK) gene fusion positive (ALK translocation).
- Has received radiation therapy to the lung that is >30Gy within 6 months of the first dose of trial treatment.

For Part B (2nd line, PD-X refractory NSCLC):

- Symptomatic ascites or pleural effusion.
- >1 line of any systemic anticancer therapy for advanced or metastatic disease.
- Has received radiation therapy to the lung that is >30Gy within 6 months of the first dose of trial treatment.

For Part C (2nd line PD-X naive HNSCC):

- Disease is suitable for local therapy administered with curative intent.
- Previously treated with > 1 systemic regimen for recurrent and/or metastatic disease.

2. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) **(Part A and C only)**.

3. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher irAE **(Part B only**).

4. No tumor specimen evaluable for PD-L1 expression by the central study laboratory.

5.1 Prior anti LAG-3 therapy (e.g. anti-LAG-3 antibodies).

6. Prior high-dose chemotherapy requiring hematopoietic stem cell rescue.

7. Prior targeted small molecule therapy (i.e. kinase inhibitors), or radiation therapy within 2 weeks prior to cycle 1 day 1.

Note: Patients must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Patients with ≤Grade 2 neuropathy, alopecia and elevated transaminases in case of liver metastases may be eligible. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation to non-CNs disease

8.1 Has received prior chemotherapy, anti-cancer monoclonal antibody, major surgery, another systemic cancer therapy or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to cycle 1 day 1.

Note: Patients must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Patients with ≤Grade 2 neuropathy, alopecia and elevated transaminases in case of liver metastases may be eligible. If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment. Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Note: Wash-out period for pembrolizumab is not applicable to patients having received pembrolizumab and are to be enrolled into Part B. These patients are allowed to enter as long as the last pembrolizumab dose is ≥ 2 weeks prior to cycle 1 day 1 and they fulfill all other requirements in terms of adverse events.

9.1 Known active central nervous system metastasis and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable: i.e. without evidence of progression for at least 4 weeks documented by repeat imaging performed after therapy completed for CNS metastasis and with at least 4 weeks difference, clinically stable and without requirement for steroid treatment for at least 14 days prior to cycle 1 day 1.

10. Women who are pregnant or lactating. A woman of child-bearing potential who has a positive serum pregnancy test (within 72 hours) prior to cycle 1 day 1.

11. Serious intercurrent infection within 4 weeks prior to cycle 1 day 1 or active acute or chronic infection.

12.1 Evidence of severe or uncontrolled cardiac disease within 6 months prior to first dose of study treatment including: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 5.0 Grade ≥ 2, atrial fibrillation > grade 2 not controlled by a pacemaker, coronary/peripheral artery bypass graft, symptomatic congestive heart failure (NYHA III-IV), cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

13. Has interstitial lung disease or history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

14. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

15. Has a known history of human immunodeficiency virus (HIV) infection.

Note: No HIV testing is required unless mandated by local health authority.

16.1 Has a known history of Hepatitis B ((defined as a known Hepatitis B surface antigen [HBsAg] positive result) or known active Hepatitis C virus (defined as a known positive anti-Hepatitis C antibody result and known detectable level of HCV RNA [qualitative] on PCR)) infection.

Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority. No treatment with antiviral therapy allowed.

17. Has a life-threatening illness unrelated to cancer.

18.1 Has previous malignancies within the last three years other than described in inclusion criterion 2, except successfully treated basal or squamous cell carcinoma of the skin, superficial bladder cancer, ductal carcinoma in situ of the breast, and in situ carcinoma of the cervix.

19. Receives continuous systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days prior to cycle 1 day 1. Inhaled or topical steroids and physiological replacement doses of up to 10 mg daily prednisone equivalents are permitted in the absence of active auto-immune disease.

20.1 Has a hypersensitivity to efti and/or pembrolizumab and/or any of its excipients.

21. Live vaccine within 30 days of planned cycle 1 day 1. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

23. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the study.

6 STUDY TREATMENTS

6.1. Identity of Investigational Medicinal Products

6.1.1. Eftilagimod alfa

The efti drug product is a single-use, preservative-free, sterile solution of efti for subcutaneous injections at a concentration of 25 CCI CCI mg/mL in CCI [redacted]. The drug product is filled into [redacted] mL glass vials with an extractable fill volume of CCI mL.

6.1.2. Pembrolizumab

Pembrolizumab Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab. The product is preservative-free, latex free solution which is essentially free of extraneous particulates.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

6.2. Packaging, Labelling, and Shipping

Efti will be provided free of charge by the Sponsor. Efti has been manufactured by WuXi Biologics (formerly WuXi AppTec) (Wuxi, China) according to EU and US GMP guidelines (EU GMP: Volume 4 of "The rules governing medicinal products in the European Union"; US GMP: US Codes of Federal Regulations 21 CFR Part 210/211 and 21 CFR Part 11) and released by a European qualified person according to respective GMP guidelines.

Pembrolizumab will be provided free of charge by the sponsor. Pembrolizumab has been manufactured using facilities and practices under Good Manufacturing Practice (GMP) requirements.

Vials of the two study treatments will be packaged to maintain cooled CCI [redacted]) temperature and shipped by courier to the clinical site as per instructions in the IMP Handling Manual. Each vial will contain a label that conforms to Annex 13 EU-GMP guideline as well as to Code of Federal Regulations Title 21 and the appropriate local regulations. Full details of product packaging, labelling, storage and shipping are provided in the IMP Handling Manual.

6.3. Storage

Efti must be stored at CCI [redacted] and CCI [redacted] as described in the IMP Handling Manual. Pembrolizumab must be stored at 2°C to 8°C (36°F to 46°F) and protected from light as described in the IMP Handling Manual. Upon receipt of efti or pembrolizumab shipper container, the site pharmacists or designated personnel should record the receipt, date and time. The temperature loggers need to be read out. Any efti or pembrolizumab that arrives with a temperature recording out of the predefined temperature range needs to be handled as described in the IMP Handling Manual.

6.4. Dose Regimen, preparation and administration of study treatments

Pembrolizumab will be administered as intravenous infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. Pembrolizumab will be given on day 1 from cycle 1 to cycle 35. Pembrolizumab will be administered at a dose of 200 mg using a 30-minute i.v. infusion.

Withdraw the required volume from the vial(s) of pembrolizumab from the 100 mg/4 mL vial solution for infusion and transfer into an i.v. bag containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL. Store the diluted solution:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the i.v. bag, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution (96 hours is acceptable dependent upon country approved commercial Keytruda label). If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min).

Efti will be injected every 2 weeks until end of cycle 8 (12 doses). Thereafter efti will be administered every 3 weeks starting cycle 9 until end of cycle 18 (10 doses). Efti will be administered as subcutaneous injection (single anatomical site) anterior face of the thigh (it is recommended to rotate the injections site every injection). The injection should be performed slowly to avoid discomfort at the site of injection.

CCI). Syringes should be CCI and until administration of the product. Efti should be administered immediately after preparation.

Full details of efti and pembrolizumab preparation and handling are provided in the IMP Handling Manual for each study treatment.

All doses of study treatment must be administered by the Investigator or designated study personnel. The exact times of dosing must be recorded in the source and entered into the electronic CRF.

The combined immunotherapy of pembrolizumab and efti requires on several occasions that both treatments will be given on the same day. Efti is always administered at least 30 minutes after pembrolizumab infusions has been completed.

CCI

CCI

CCI

A patient will stay on treatment until disease progression, unacceptable toxicity, completion of 35 cycles of pembrolizumab (~2 yrs.; completion of study treatment) or discontinuation for any other reason whatever occurs first.

6.5. Methods of Assigning Patients

In the initial stage, patients will be recruited to according to their temporal availability, which can be characterized as a 'first comes, first chosen' approach. Therefore, the recruitment of patients for part A, B, C will be influenced neither by the study personnel nor by any characteristics of the patients, but only by temporal availability. The same applies for the additional recruitment (N2 and any extensions), if applicable.

Screening and enrolment number will be assigned to each patient prior to the first pembrolizumab or efti administration on cycle 1 day 1. Once an enrolment number has been assigned, it cannot be reassigned to any other patient.

6.6. Blinding and Procedure for Unblinding

This trial will be conducted in an open label fashion, hence no procedure for unblinding is in place.

6.7. Dose Modifications and treatment delays

6.7.1. Eftilagimod alfa (efti)

No dose modifications for efti are allowed.

On days pembrolizumab and efti are given the same day (e.g. cycle 1 day 1), in case there is an adverse event after pembrolizumab administration which necessitates delay of efti administration, efti administration can be delayed up to 72 hours after end of pembrolizumab infusion. If the recovery (as described below) occurs more than 72 hours after end of pembrolizumab administration, then the efti administration will be omitted. Next treatment of efti will then occur at the next planned injection of efti in case adverse events improved as described in the next paragraph.

On days efti is given alone, in case during the study there is an adverse event which necessitates delay (but not discontinuation) of efti administration, then the medical monitor should be informed, and efti should be delayed until the patient has recovered to ≤ grade 1, except for isolated laboratory values abnormalities which should recover to ≤ grade 2 or baseline. Please contact your medical monitor in such cases. All grade 3 adverse events related to efti need to be discussed individually with the medical monitor to assess potential treatment delay or discontinuation. Exceptions to this rule are any ≥3 grade systemic immediate or delayed hypersensitivity reactions) related to efti, after which the patient must be permanently discontinued from any further study treatment. Grade 4 adverse events related to efti will result in discontinuation of efti treatment. Treatment decision for grade 4 laboratory abnormalities related to efti may be discussed with the medical monitor. In case efti needs to be discontinued due to safety reasons, patients who have completed at least 2 cycles are allowed to switch to pembrolizumab treatment only. Investigator must ask the medical monitor beforehand.

Table 7: Toxicity Management and Discontinuation Guidelines for local injection site reactions and systemic hypersensitivity reactions related to eftilagimod

Type of AE	Toxicity grade or conditions	Action taken to eftilagimod	AE management	Monitor and follow-up
Local injection site reactions	Grade 1, 2	Treatment may continue or delayed at the discretion of the investigator	In case of local pain: NSAIDs (e.g. ibuprofen 3 x 200 mg PO) o If treatment continues then for subsequent cycles: NSAID starting on day of administration few hours prior to injection o Continue for 2-3 days In case of local itching: topical steroid. Oral antihistamine may also be considered.	Monitor patients for signs and symptoms until resolution.
	Grade 3	To be discussed with study medical monitor if treatment needs to be delayed or discontinued permanently		
	Grade 4	Permanently discontinue		
Immediate (occurring within 30 minutes of injection) or delayed (occurring after 30 minutes of injection) hypersensitivity reactions	Grade 1, 2	Treatment may continue only after consultation with, and agreement by study medical monitor	As clinically indicated.	Additional blood samples may be required, based on discussion with study medical monitor. Monitor patients for signs and symptoms until resolution.
	Grade ≥3	Permanently discontinue	See summary and Figure 5 below.	

Management of trial subjects developing severe, immediate hypersensitivity reaction, beyond standard measures of emergency medical care (i.e. provision if intravenous access, assessment of breathing, circulation and vital signs, oxygen support on demand) should include administration of epinephrine i.m., antihistamine i.v. and corticosteroid i.v., in line with the state-of-the-art good medical practice and applicable professional guidelines (59, 60). Figure 5 below outlines a study tailored management of hypersensitivity reactions. 6.7.1

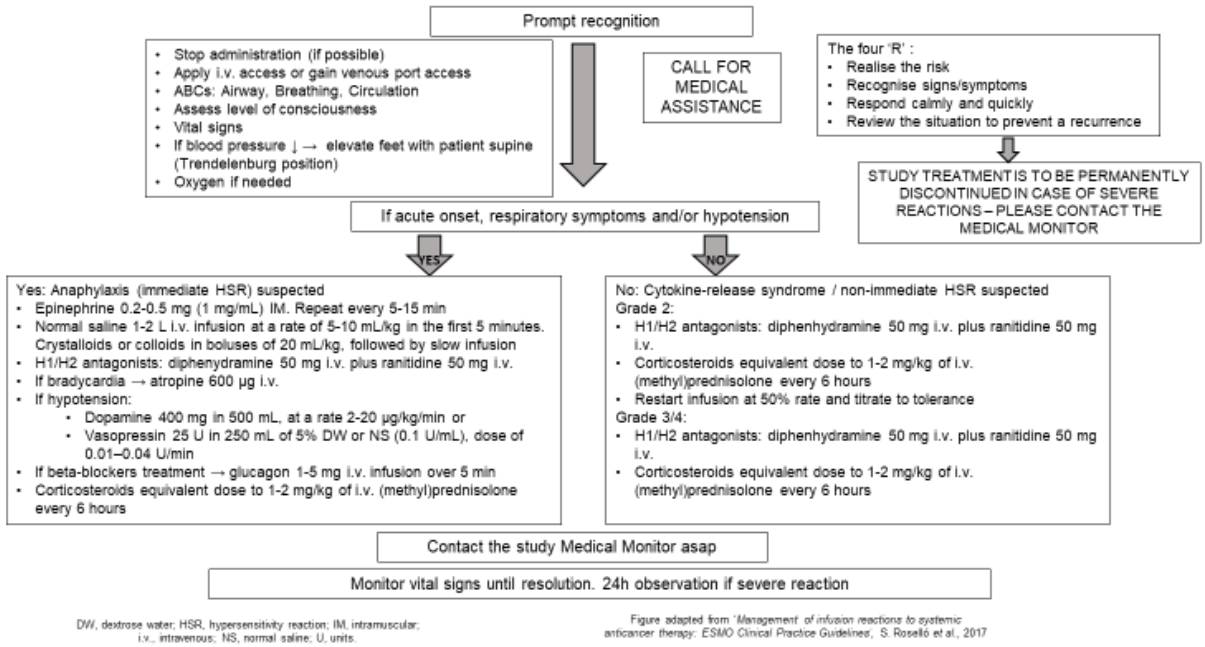

Figure 5 Management of hypersensitivity reactions, adapted from (59)

The number of doses of efti allowed to miss are described in section 6.11.

6.7.2. Pembrolizumab

Dose modification and toxicity management for immune-related AEs

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table **8**.

In case pembrolizumab needs to be discontinued due to safety reasons, patients who have completed at least four infusions of pembrolizumab are allowed to switch to efti treatment only. Investigator must ask the medical monitor beforehand.

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 8 and Table 9.

Table 8: Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab

General instructions: • Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks. • For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks. • For severe and life-threatening irAEs, i.v. corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.				
Immune-related AEs	Toxicity grade or conditions	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor patients for signs and symptoms of pneumonitis; Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment; Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor patients for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie. peritoneal signs and ileus). Patients with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Patients with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via i.v. infusion.
	Grade 4, or recurrent Grade 3	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2[a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3[b] or 4[c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	Initiate insulin replacement therapy for patients with T1DM Administer antihyperglycemic in patients with hyperglycemia	Monitor patients for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes

	Confirmed SJS, TEN or DRESS	Permanently discontinue		
Other irAEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event.[e]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

a) AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

b) AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

c) AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal;
bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

1- d) The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

NOTE: For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

2- e) Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

Table 9: Pembrolizumab Infusion Reaction Dose modifications and Treatment guidelines

NCI CTCAE Grade	Treatment	Premedication subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • i.v. fluids; Antihistamines; NSAIDs; Acetaminophen; Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise, dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine**; i.v. fluids; Antihistamines; NSAIDs; Acetaminophen; Narcotics; Oxygen; Pressors; Corticosteroids Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Patient is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.		

6.8. Other allowed dose interruption for study treatment

Pembrolizumab and/or efti may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons (e.g. COVID-19) not related to study therapy. Medical Monitor must be consulted prior to the event to discuss the best option for each patient. Patients should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Medical Monitor. The reason for interruption and missed doses should be documented in the patient's study record. The maximum number of interruptions and missed doses per patient before non-compliance is reached is described in section 6.11.

6.9. Rescue Medications & Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section above. Where appropriate, these guidelines include the use of oral or i.v. treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab and/or efti.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab and/or efti, the investigator does not need to follow the treatment guidance.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.10. Prior and Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria (including the timeframe mentioned there) are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Medical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study treatment requires the mutual agreement of the investigator, the Sponsor and the patient.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and/or efti
- Radiation therapy Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator’s discretion.
- Live vaccines within 30 days prior to the first dose of study treatment, while participating in the study and four months after the last dose of IMP. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and

typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than (1) to modulate symptoms from an AE that is suspected to have an immunologic etiology or (2) to treat an AE of not immunologic etiology, only for a short course (i.e. no longer than 10 days) and if that is in line with the site's SOC. Inhaled or topical steroids and physiological replacement doses of up to 10 mg daily prednisone equivalents are permitted in the absence of active auto-immune disease. In case of doubt, the study Medical Monitor should be contacted.

Patients who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study treatment.

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Acceptable concomitant therapy is defined as follows:

- Patients may receive supportive care including but not limited to antibiotics, analgesics, transfusion of blood products, anti-diarrheal medication or laxatives according to local clinical practice and the approved pembrolizumab label.
- Growth factors (such as filgrastim) are allowed a minimum of 2 days after efti or pembrolizumab administration
- Vaccination (e.g. influenza, COVID-19) with any non-live vaccine (e.g. Vector based, mRNA based) is allowed if it takes place more than 3 days prior to or after any efti or pembrolizumab administration. Live attenuated vaccines cannot be used.
- Bisphosphonates and RANK-targeted therapy as clinically indicated.
- Patients receiving opiates will be given preventive treatment for constipation and followed carefully.
- Inhaled or topical steroids.
- Acute surgery or elective (pre-planned) surgical procedures with non-oncological intent.

All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC) products, herbal supplements, and i.v. medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

Prior chemotherapy (neoadjuvant or adjuvant, first line), targeted small molecule, anti-cancer monoclonal antibody or other systemic investigational drug therapy to treat the cancer disease including but not limited to are allowed in respective time windows defined in the inclusion and exclusion criteria and is to be recorded in the eCRF.

Prior high-dose chemotherapy requiring hematopoietic stem cell rescue or chemotherapy for metastatic disease is <u>not</u> permitted.

All concomitant medications received within 28 days prior to the first dose of study treatment and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in section 9.3.

The medical monitor should always be contacted to clarify and discuss the use of any concomitant therapies/procedures beforehand if not in line with the protocol.

6.11. Treatment Compliance

Patients are expected to receive both intravenous pembrolizumab infusion and subcutaneous injections of efti as per protocol schedule within the allowable time window (see section 6.7).

In the event a patient misses a dose, the Investigator must contact the Medical Monitor to determine whether to dose the patient out of window or to miss the dose. Any subsequent dose should then be given according to the previous schedule as outlined in section 6.7.

Patients who miss more than a total of 3 (2) injections of efti (pembrolizumab) within the first 8 cycles or a total of more than 5 (5) doses of efti (pembrolizumab) in total until cycle end of combo treatment (end of cycle 18) will be regarded as treatment non-compliant. Patients will need to end the treatment. An end of treatment (EOT) visit will be performed. The patients should then continue with PFS (if not progressed) or OS follow-up (if progressed or receiving another therapy).

6.12. Drug accountability

Investigators must maintain accurate records regarding the receipt, dispensing, and return or destruction of pembrolizumab and efti for each patient in the study. Any used vials, as well as any unused vials or unused portions of vials, must be maintained until accounted by the monitor. After accountability by the monitor and written approval from the Sponsor, all unused vials or medication not dispensed should be sent back to the Sponsor or a representative or is destroyed locally after prior approval by the sponsor (details are provided in the IMP Handling Manual). All used vials may be destroyed locally, if the destruction is fully documented, and following the site's SOP for destruction of biological waste.

6.13. Contraception Methods

Efti and Pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab and/or efti have transient adverse effects on the CCI .

Patient should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, patients of childbearing potential must adhere to the contraception requirement (from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 4 months after the last dose of the last study treatment. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

The following methods that can achieve a failure rate of less than 1 % per year when used consistently and correctly are considered as highly effective birth control methods. Highly effective birth control methods include:

- intrauterine device
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence
- hormonal contraceptives as clinically allowed

Notes: abstinence is only acceptable as true abstinence when it is in line with the preferred and usual lifestyle of the patient, periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and

withdrawal are not acceptable methods.

6.14. Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab or efti, the patient will be immediately discontinued from study treatment. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of patient`s pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. Details are described in section 9.2.

7 INVESTIGATIONAL PLAN

7.1. Study visits and procedures

Patients will be screened for suitability for participation in the study within -21 to -1 days prior to the first administration of pembrolizumab and efti (VISIT 1: Day 1 of Cycle 1).

Screening assessments will include:

- Obtaining of written informed consent prior to any study specific procedure (including screening procedures) being performed. *Note: Patient can be consented up to 35 days before cycle 1 day 1 to allow planning of fresh tumor biopsy and/or perform CT scan for assessment of eligibility at screening (the latter for Part B only). All screening assessments including the biopsy or confirmatory tumor assessment for part B (to confirm progression) itself are still to be performed between -21 days and -1.*
- Check for every inclusion and exclusion criteria

Re-testing in the case of isolated out-of-range lab results during the screening period may be allowed on a case-by-case basis. The investigator must receive the approval from the Medical Monitor for each case beforehand A patient who failed screening due to an isolated out-of-range lab value may be allowed to be re-screened once, only on a case-by-case basis and only after approval by the MM.

Additional procedures (assessments) will be performed at screening and throughout the study. The following table provides a brief overview of the assessments and indicate references to specific chapters.

Table 10: Overview of study assessment specifications. All assessments are done locally if not otherwise indicated

Assessment	Specification
Physical examination (incl. Height & Weight)	Includes the following: head, eyes, ears, nose and throat; respiratory system/ chest; cardiovascular system/ heart; abdomen; skin, lymph nodes; extremities and (at the investigator's discretion) genitourinary system/ pelvis. For height and body weight measurements preferably, the same equipment should be used throughout the study. To obtain the actual body weight, patients must be weighed lightly clothed.
Medical History & Demographics	Each patient's medical history will be taken during screening. This includes patient demographics (date of birth or age whatever is allowed by local law, race and ethnicity if allowed by local law, sex) details of cancer onset, prior surgery, and past treatment including chemotherapy and/ or radiation therapy. Medical history should also include history of HIV, HCV and HBV exposure.
ECOG Status	The ECOG of each patient will be assessed regularly according to the ECOG scale. See appendix – section 19.1
Electrocardiogram (ECG)	Single 12-lead ECGs will be recorded according to local practice after the patients have rested for at least 10 min in a supine position. ECGs should preferably be performed prior to meals, vital sign measurements and any scheduled blood draws.
Vital Signs	Vital signs will be assessed and recorded (i.e. after a 10 min resting period and without any change of posture). Blood pressure and pulse rate should always be measured on the same arm. Parameters to be assessed are:

Assessment	Specification
	• Pulse rate • Systolic and diastolic blood pressure • Body temperature
Hematology	Parameters to be assessed: White Blood Cell (WBC) count with differential (absolute neutrophil count (ANC); absolute lymphocyte count, absolute monocyte count, absolute basophil count, absolute eosinophil count; neutrophil %, lymphocyte %, monocyte%, basophil %, eosinophil %); Red Blood Cells (RBCs); Platelet count; Hemoglobin; Hematocrit
Biochemistry	Parameters to be assessed: Creatinine, creatinine clearance according to Cockroft-Gault formula, random glucose, urea, alkaline phosphatase, alanine aminotransferase (ALT = GPT), aspartate aminotransferase (AST = GOT), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin (direct bilirubin in case total bilirubin >1.5 ULN), total protein, albumin/globulin ratio, sodium, potassium, chloride, calcium, phosphate, bicarbonates, uric acid, cholesterol, triglycerides, plasma amylase, CRP
Thyroid function testing	Parameters to be assessed: Triiodothyronine (T3) or Free Triiodothyronine (FT3); Thyroxine (T4) or Free thyroxine (FT4); Thyroid stimulating hormone (TSH)
Coagulation	Parameters to be assessed: Prothrombin time (PT), INR, activated partial thromboplastin time (APTT), APTT Ratio.
Pregnancy test	A serum pregnancy test will be performed at screening (<72 hours prior to cycle 1 day 1). On all other occasions, a negative urine test before any study treatment is administered is sufficient. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. For the assessment of childbearing potential, FSH and estradiol tests may be required at screening.
HIV, HBV*, HCV** tests	A serum test is to be performed at screening if applicable by local laws. * HBsAg; **anti-HCV antibodies and HCV RNA quantitative PCR (in case of positive anti-HCV antibodies)
Autoantibodies	Autoantibodies (i.e. anti-mitochondrial antibodies, rheumatoid factor, antithyroid [antithyroglobulin] antibodies and antinuclear antibodies) are to be assessed
Anti-drug (efti) antibodies (central lab)	Anti-drug (efti) antibodies (ADA) are to be assessed
Urinalysis	Parameters to be assessed: dipstick, *or* standard urinalysis (UA) with reflex microscopy and culture if clinically indicated. Gross urine examination (dipstick) and other tests,

Assessment	Specification
	should include visual inspection, pH, protein, ketones, glucose, bilirubin, nitrite, urobilinogen, occult blood, WBCs
ECIs	Events of clinical interest as described in section 9.3 are to be assessed as described in section 9
(S)AEs	To be assessed according to the current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v5.0) – see section 9
Concomitant medications/procedures	Each concomitant medication or procedure is to be recorded
Radiological Scans	Radiological scans will be performed throughout the study to assess the tumor response to study treatment. Modalities and frequencies are described in section 8.1 Tumor response will be evaluated according to RECIST and iRECIST. For details please see section 8.1 and section 19.2.
Color digital photography	In case of superficial clinical lesion (e.g., skin nodule) they must be measured in at least one dimension (longest diameter in the plane of measurement will be recorded) with a minimum size of the longest axis being ≥ 10 mm as imaged with scale in color photography. Details are described in section 8.1.
Gene expression profile (central lab)	Gene expression profile analyses will be performed (i.e. acc. to PanCancer Immune Code)
Pharmacokinetics (central lab)	The plasma concentration time profile of efti and derived PK parameters will be assessed (selected sites in UK/ES) for patients in subset of 20 patients in Stage 1 and an additional subset of at least 10 patients in Stage 2.
Tumor tissue (Central lab)	Tumor tissue samples will be obtained from every patient to assess certain biomarker (e.g. PD-L1 expression, HPV status (for HNSSC only, if applicable). (Note: regardless of the above, if the patient has known results of HPV (for HNSCC) or PD-L1 expression status from previous records that should be documented in the designated form in the eCRF.)
Th1 biomarker (central laboratory)	The plasma concentration of Th1 biomarkers (e.g. IFN-γ , CXCL-10) will be assessed.

7.2. Overview of Study Assessment Schedule

Each treatment cycle consists of 3 weeks. After enrolment, each patient will need to visit the hospital according to the schedule of assessments (see Table 1).

The assessment procedures will be performed as already indicated in Table 10 and further details are provided in section 8 regarding imaging. The tables below provide detailed breakdown of assessment per visit and cycle/ day during screening (Table 11), combination treatment phase (Table 12, Table 13 and Table 14), monotherapy (Table 16) and EOT (Table 17). Details for patients participating in the PK part are described in Table 15.

The order in which assessments should be performed is also indicated.

Information on concurrent illness/ therapy is to be collected during each patient visit.

Important Note: Radiological assessment will be determined based on the treatment assignment date. All details are described in section 8.1.

Table 11: Overview of assessments at Screening

All assessments to be performed on the day of the screening visit **(Day: -21 to -1)**
1) Confirmation of written inform consent form[4] of patient and Investigator (including PK consent for 20 patients in Stage 1 and at least additional 10 patients in Stage 2) 2) Inclusion & Exclusion criteria 3) Medical history & demographics 4) Physical examination including height and weight 5) ECOG performance status 6) Adverse events 7) Prior Concomitant medications/procedures 8) 12- lead ECG (single) 9) Vital signs 10) Laboratory testing a. hematology, biochemistry, coagulation and urinalysis b. thyroid function test c. Pregnancy d. HIV, HBV and HCV in case applicable e. Gene expression profiling 11) Radiological assessment (as described in section 8.1.1) 12) Tumor tissue sample

Table 12: Overview of Assessments during combination treatment Cycle 1 to 8

Day 1 of Cycles 1 to 8
Prior to pembrolizumab and efti administration 1) Confirmation of eligibility and assignment to treatment – ONLY cycle 1 2) Physical examination including weight 3) ECOG performance status 4) Adverse events 5) Concomitant medication/procedures 6) 12-lead ECG 7) Vital signs 8) Laboratory testing: a. hematology, biochemistry, coagulation and urinalysis b. Thyroid function tests – ONLY Cycle 2, 4, 6 and 8 c. Autoantibodies – ONLY pre-dose cycle 1 d. Pregnancy testing (urine) e. Anti-drug (efti) antibodies – ONLY pre-dose cycle 1 and 5

[4] *Note: Patients in Part B can be consented up to 35 days before cycle 1 day 1 to allow planning of fresh tumor biopsy and/or perform CT scan for assessment of eligibility at screening (the latter for Part B only). All screening assessments including the biopsy or confirmatory tumor assessment for part B (to confirm progression) itself are still to be performed between -21 days and -1.*

f. Th1 biomarker – ONLY pre-dose Cycle 1 and 5
g. Gene expression profile – ONLY pre-dose Cycle 5

9) **Pembrolizumab infusion**
10) **For patients who participate in the PK sampling please refer to Table 15**
11) **Efti injection ≥ 30 minutes after pembrolizumab infusion was completed ONLY cycle 1, 3, 5 and 7**
Patients should remain in the ward for a minimum of 30 min after last study drug administration

Table 13: Overview of Assessments on Day 8 of each even cycle and Day 15 each odd cycle

Day 15 of Cycles 1, 3, 5, 7
Prior to efti administration 1) Adverse Event 2) Concomitant Medication/procedures 3) Vital signs 4) Laboratory testing: a. Anti-drug (efti) antibodies – ONLY pre-dose Cycle 3 5) **Efti administration** Patients should remain in the ward for a minimum of 30 min after injection
Day 8 of Cycles 2, 4, 6, 8
Prior to efti administration 1) Adverse Events 2) Concomitant medication/procedures 3) Vital signs 4) Laboratory testing: a. Anti-drug (efti) antibodies – ONLY pre-dose Cycle 2 5) **Efti administration** Patients should remain in the ward for a minimum of 30 min after injection

Table 14: Overview of assessments during day 1 of cycles 9 to 18

Day 1 of Cycles 9 to 18
Prior to Pembrolizumab and efti administration 1) Physical examination including weight 2) ECOG performance status 3) Adverse Events 4) Concomitant medication/procedures 5) 12-lead ECG 6) Vital signs 7) Laboratory tests: a. hematology, biochemistry, coagulation and urinalysis

b. Thyroid function test – ONLY cycle 10, 12, 14, 16 and 18
c. Pregnancy testing(urine)
d. Autoantibodies – ONLY Cycle 9
e. Anti-drug (efti) antibodies (ADA) – ONLY pre-dose Cycle 9 and 13
f. Th1 biomarkers – ONLY Cycle 9 and 13

8) **Pembrolizumab infusion**
9) *For patients who participate in the PK sampling please refer to Table **15***
10) **Efti injection ≥ 30 minutes after pembrolizumab infusion was completed**
Patients should remain in the ward for a minimum of 30 min after last study drug administration

Table 15: Assessments for subset of patients who participate in the PK part

Day 1 of Cycles 1, 5 and 9 (in subset of 20 patients in Stage 1 and additional 10 patients in Stage 2, at selected sites)
Prior to efti administration: blood sampling pre-dose After administration: blood sampling at 1, 2, 4 and 8h post-injection
Days 2, 3, 4 & 5 of Cycle 1, 5 and 9 (in subset of 20 patients at selected sites)
After administration: blood sampling at 24, 48, 72, 96 hours post-injection Adverse events and concomitant medications are to be recorded as well.

Table 16: Overview of Assessments during Cycle 19 until 35 (Pembrolizumab monotherapy). Cycle 19 may also be end of combination treatment

Cycle 19 until Cycle 35 Day 1 (every 3 weeks)
Prior to Pembrolizumab administration 1) Physical examination including weight 2) ECOG performance status 3) Adverse Events 4) Concomitant medication/procedures 5) 12-lead ECG 6) Vital signs 7) Laboratory testing: a. hematology, biochemistry, coagulation and urinalysis b. Pregnancy testing (urine) c. Thyroid function test ONLY at Cycle 20, 22, 24, 26, 28, 30, 32, 34 d. Autoantibodies – ONLY Cycle 19 e. Anti-drug (efti) antibodies (ADA) – ONLY Cycle 19 f. Th1 biomarkers – ONLY Cycle 19 ➢ **Administration Pembrolizumab**

7.2.1. End of Treatment Visit

All patients are scheduled to receive 8 cycles of combined pembrolizumab every 3 weeks and efti every 2 weeks followed by further 10 cycles of pembrolizumab and efti every 3 weeks. Thereafter pembrolizumab will be given every 3 weeks (cycle 19 till cycle 35) unless any of the reasons as specified in section 7.3 occur. An End of Treatment (EOT) visit will be performed 3 weeks (± 7 days) after the last dose of any study treatment. The patients should then continue with PFS follow-up or OS follow-up dependent on the status of their disease.

Table 17: Overview of Assessments at the End of Treatment

All assessments to be performed at **EOT visit**
1) Adverse Events 2) Concomitant medication/procedures 3) Physical examination including weight 4) ECOG performance status 5) 12-lead ECG 6) Vital signs 7) Laboratory testing: a. hematology, biochemistry, coagulation and urinalysis b. Pregnancy testing (urine) c. Thyroid function test d. Autoantibodies e. Anti-drug (efti) antibodies (ADA) f. Th1 biomarkers

7.2.2. Progression Free Survival (PFS) - Follow-Up

Patients who complete all study Treatment Visits without documented PD will attend PFS Follow-Up Visits every 12 weeks (± 9 days) until PD, start of next anticancer therapy, pregnancy, withdrawal of consent, loss to follow-up, death from any cause, or the end of the study (whichever occurs first).

For patients who prematurely discontinue treatment for any reason except PD and do not receive any other anti-cancer therapy or any other investigational therapy, PFS Follow-Up Visits will occur every 9 weeks until week 36 after treatment assignment and every 12 weeks after week 36 dependent on the most recent radiological assessment prior to discontinuation.

At each PFS Follow-Up Visit, the following will be performed:

- Radiological assessment as described in section 8.1
- Eastern Cooperative Oncology Group (ECOG) performance status and body weight
- Adverse event follow-up

Note: Once a patient starts new line of anti-cancer therapy, the patient will be followed up for OS. Details on the next anti-cancer therapies will be recorded.

7.2.3. Overall Survival (OS) - Follow-Up

After documented PD, or after start of any next line of anti-cancer therapy, the patient will be followed up for survival every 12 weeks (± 4 weeks) until end of study, lost to follow-up, withdrawal of consent or death whatever occurs first. The first overall survival visit will take place 12 weeks after the last visit of the treatment phase (EOC, EOT) or PFS follow up whatever was last. The visit can be performed via a telephone call. If necessary, patients may be contacted occasionally outside of this follow up (FU) window.

Patients who progress while on study treatment may receive any other next line of therapy, as clinically indicated, after performing the EOT visit. Patient who do not progress and complete the study treatment period (i.e. reach the end of cycle 35 without progression) may receive any other next line of therapy, as clinically indicated, after performing the EOT visit. In both cases this is to be recorded during overall survival follow-up. Additionally, any details on the next anti-cancer therapies and its duration/outcome will be recorded.

7.2.4. Unscheduled Visits

Additional unscheduled visits may be conducted to assess adverse events or to evaluate disease status or for any other reason according to the Investigator's clinical judgment. These visits will be documented in the eCRF.

7.3. Withdrawal, Discontinuation and Replacement of Patients

7.3.1. Patient Withdrawal

Patients should be withdrawn from the study, if patient:

- withdraws consent
- is non-compliant with the study visits and procedures (refer to section 7.4)
- becomes pregnant

It is recommended that the Investigator attempts to perform an EOT visit evaluations if a patient withdraws consent during the treatment period.

The reason for patient withdrawal will be noted on the eCRF. The Investigator should attempt to follow withdrawn patients until resolution of any adverse events, or at least 30 days after the last dose of study agent, or until completion of pregnancy whichever takes longer.

Upon withdrawal, no further dosing, or follow-up visits should be performed for these patients. Investigators shall make reasonable attempts to contact lost-to-follow-up patients for evaluation of OS.

7.3.2. Early Treatment Discontinuation for individual patients

Patients may discontinue treatment other than for death, end of study, withdrawal of consent, lost to follow-up or (confirmed) progression, but remain on the study (e.g. PFS follow-up in case the patient has not progressed, otherwise OS follow-up) if:

- is non-compliant with the study treatments (refer to section 7.4)
- the patient has clinically significant lab abnormalities or AEs (i.e. recurrent pneumonitis grade 2) that, in the Investigator's judgment, would preclude continued treatment
- any other reason except withdrawal of consent

- patient has attained a confirmed complete response and have been treated for at least 8 cycles receiving at least 2 cycles of pembrolizumab after the iCR was first declared.

The reason for treatment discontinuation will be noted and an end of treatment visit will be performed. The patients should then continue with PFS and/or OS follow-up as applicable.

7.3.3. Replacement of Patients

The number of patients to be included in the study may be increased in order to achieve the expected number of patients with evaluable data for the primary objective analysis. Therefore, patients discontinued from study treatment due to SARS-CoV-2 infection before their on treatment radiological assessments incl. iRECIST assessment, are to be replaced. Details on the analysis will be described in the SAP.

7.4. Protocol Compliance

Patients are expected to have all visits and procedures done within the allowable time window as indicated in Table 1. Discontinuation due to safety reasons is described in the respective section.

In the event a patient misses a scheduled radiology scan, this should be rescheduled for the earliest possible date. Subsequent scans will then be performed every 6 weeks from the original scheduled scan date until week 12, every 9 weeks until week 30 and every 12 weeks thereafter. Patients who are persistently noncompliant may be withdrawn from the study at the Investigator's or the Sponsor's discretion.

8 STUDY ASSESSMENTS

8.1. Efficacy Assessments

8.1.1. Radiological Scans and color digital photography

A computed tomography (CT) scan with contrast of the chest, abdomen and pelvis is required for each patient at each timepoint. For patients in part C (HNSCC) a head and neck CT scan is required at each timepoint in addition. Tumor imaging is strongly preferred to be acquired by CT with contrast enhancement. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. For the chest, a non-contrast CT of the chest is recommended to evaluate the lung parenchyma. If brain imaging is performed to document the stability of existing metastases, MRI is the strongly preferred modality (not mandatory for patients without evidence of brain disease). The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a patient throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

The machines (CT or MRI) to be used are described in the imaging manual. The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM).

All scheduled images for all study patients from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the central imaging vendor.

The Imaging Central Laboratory will receive all information that is relevant (e.g., previous radiation, bisphosphonate therapy, etc.). Specific methodological details for all radiological assessments will be provided in the Imaging Review Charter.

All treatment decisions will be based on the investigator`s read.

A lesion identified at follow-up in an anatomical location that was not scanned at screening is considered a new lesion and will be handled accordingly. An example of this is when a patient has visceral disease at screening and while on study requires a CT or MRI scan of the brain which reveals metastases. The patient's brain metastases are considered new lesions even if there was no brain imaging conducted at screening.

Imaging will be performed independently to the treatment schedule according to the following schedule:

- Screening: ≤ 21 days prior to initiation of therapy, historical images (obtained within a window of ≤ 28 days prior to the start of study treatment) can be used for assessment of patient eligibility for part A and C, if they are in line with the imaging protocol. For part B a confirmatory scan needs to be performed to confirm initial progression if patient was on PD-1 therapy at the time of consenting as detailed in the respective inclusion criterion.
- 9-weekly (± 6 days) intervals starting from date of assignment to treatment until week 36, meaning week 9, 18, 27 and 36
- 12 weekly (± 9 days) intervals thereafter, meaning week 48, 60, 72, etc.

Please Note: Actions taken with the study treatment /study agent (e.g. drug withdrawn or delayed) do not affect the imaging schedule. The imaging schedule shall remain as determined from date of assignment.

Skin (Clinical) lesions if present at screening will be assessed in the same intervals as described above.

Clinical Lesions: Clinical lesions detected by physical examination will only be considered measurable if they are superficial and ≥ 10 mm in diameter as measured with calipers (for example skin nodules). If skin

lesions are present at screening the documentation of these visible lesions (e.g. index tumor lesion and/or new skin lesions) by color photography including a centimeter ruler to estimate the size of the lesion is recommended. All photographs will maintain the anonymity of the patient and will be labelled using the patient's study identifier and photograph date. Detailed photography instructions will be provided in the Imaging Manual.

If skin lesions can be evaluated by both, clinical examination and imaging, imaging evaluation should be undertaken since it provides a more objective evaluation.

Superficial clinical lesion (e.g., skin nodule) must be measured in at least one dimension (longest diameter in the plane of measurement will be recorded) with a minimum size of the longest axis being ≥ 10 mm as imaged with scale in color photography per RECIST 1.1.

If a patient has clinically-indicated skin lesion(s), the investigator site will perform color digital photography of all skin lesions using a ruler held flush to the skin next to the longest diameter of the lesion to indicate the size of the lesion at every time point scheduled for radiological scans that a lesion is present. Once a lesion(s) is documented, the target area should be documented at every subsequent time point for the duration of the study.

8.1.2. Tumor Response acc. to iRECIST

Only patients with measurable disease at screening will be included in this study. When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be assessed at baseline and specified time points throughout the study. Initial tumor response and treatment decisions will be done according to iRECIST. iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression and make treatment decisions. When clinically stable (see section 8.1.3), patients should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in section 8.1.3. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some patients can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Tumor response for target lesions will be evaluated at each timepoint according to the iRECIST.

- Complete Response (iCR): disappearance of all target and non-target lesions
- Partial Response (iPR): at least 30 % decrease from baseline in the sum of the longest diameters (longest axis for non-nodal lesions, short axis for nodal regions) of target lesions
- Unconfirmed progressive Disease (iUPD): at least 20 % increase (≥ 5 mm) in the sum of the longest diameters (longest axis for non-nodal lesions, short axis for nodal regions) of target lesions, taking as a reference the smallest sum on study
- Confirmed progressive Disease (iCPD): a further increase of at least ≥ 5 mm in the sum of the longest diameters (longest axis for non-nodal lesions, short axis for nodal regions) of target lesions, taking as a reference the last iUPD assessment on study
- Stable Disease (iSD): small changes that do not qualify for the above criteria

For target lesions iCR, iPR and iSD can all be assigned after iUPD (unconfirmed progress).

All other lesions (or sites of disease) should be identified as non-target lesions and will also be assessed at baseline and specified time points throughout the study. Tumor response for the group of non-target lesions will be evaluated according to the iRECIST:

- iCR: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
- iNon-CR/ iNon-PD: Persistence of one or more non-target lesion(s).
- iUPD: Unequivocal progression of existing non-target lesions.
- iCPD: Further increase of non-target lesions taking as a reference the last iUPD assessment on study.

New lesions are assessed and classified as non-measurable or measurable (if ≥ 10 mm; ≥ 15 mm for nodal lesions as per RECIST 1.1). From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target. First occurrence of new lesions leads to iUPD.

The Medical Monitor is to be contacted within due time after a patient is assessed as having iUPD. Confirmation in clinically stable patients as described in section 8.1.3 is necessary. Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to the latest prior iUPD time point
    - For non-target lesions, worsening is any significant growth in lesions overall, compared to the latest prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - an increase in the new lesion sum of diameters by ≥5 mm from the latest prior iUPD time point
        - visible growth of new non-target lesions
        - the appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

The reason why iUPD cannot be confirmed (e.g. patient clinically not stable, treatment stopped but patient not reassessed/imaging not performed due to patient refusal, protocol noncompliance or patient death) should be recorded.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

At each specified time point, the overall response will be determined as described below. For each patient the best overall response rate will be evaluated according to 19.2.

Table 18: Assessment of overall response at a specific timepoint (61).

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category*
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same. *Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.

8.1.3. Confirmation of Progressive Disease acc. to iRECIST

Efti and pembrolizumab are expected to produce their anti-tumor effects by inducing a cancer-specific immune response. This may result in a clinical response pattern different to cytotoxic agents characterized by an initial increase in tumor burden including the appearance of new lesions due to either continued tumor growth until a sufficient immune response develops or transient immune-cell infiltrates.

In order to account for the expected delayed onset of action a confirmation of progression is required. Per iRECIST (section 19.2), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable patients. Patients, who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided the patient is clinically stable. Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the patient may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later (i.e. earlier than originally scheduled according to the protocol but not earlier than 4 weeks after the previous one) to confirm PD by iRECIST, per Investigator assessment.

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule (e.g., in the combo-treatment phase scans were to be done at week 9, 18, 27, 36, and a scan was done at week 13 to confirm progression, then the next scans should be done at week 18, 27 and 36, as planned). Patients who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable.

If however PD is confirmed (iCPD) as defined in Appendix 1, patients should be discontinued from study treatment. Nevertheless, if a patient with confirmed radiographic progression (iCPD) is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 13 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in section 19.2, with additional details in the iRECIST publication (61). A summary of imaging and treatment requirements after first radiologic evidence of progression is provided and illustrated as a flowchart in the figure below:

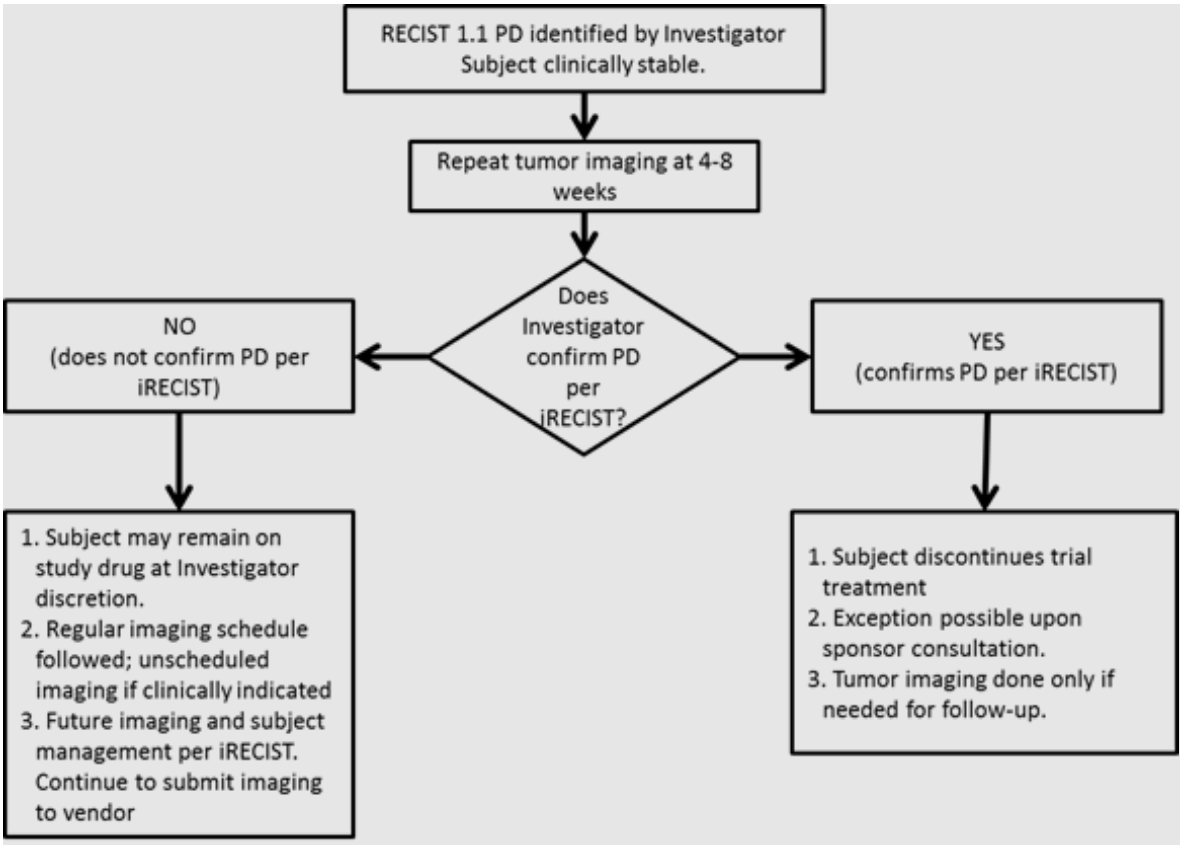

Figure 6: Imaging and Treatment for Clinically Stable Patients Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Investigator

Confirmation of objective response by repeat imaging assessment is required as well. As opposed to the rules in place for confirmation of iUPD, confirmation of iPR and iCR can be done within 4 to 9 weeks until week 36 and within 4 to 12 weeks thereafter, respectively. In other words, the radiological confirmation of the response can be done earlier but also as per the original radiological assessment schedule, at the discretion of the Investigator.

Patients who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable.

8.1.4. Tumor Response acc. to RECIST 1.1

Only patients with measurable disease at screening will be included in this study. When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be assessed at baseline and specified time points throughout the study. Tumor response for target lesions will be evaluated according to the RECIST version 1.1:

- Complete Response (CR): disappearance of all target lesions

- Partial Response (PR): at least 30 % decrease from baseline in the sum of the longest diameters (longest axis for non-nodal lesions, short axis for nodal regions) of target lesions
- Progressive Disease (PD): at least 20 % increase in the sum of the longest diameters (longest axis for non-nodal lesions, short axis for nodal regions) of target lesions, taking as a reference the smallest sum on study
- Stable Disease (SD): small changes that do not qualify for the above criteria

All other lesions (or sites of disease) should be identified as non-target lesions and will also be assessed at baseline and specified time points throughout the study. Tumor response for the group of non-target lesions will be evaluated according to the RECIST version 1.1:

- CR: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/ Non-PD: Persistence of one or more non-target lesion(s).
- PD: Unequivocal progression of existing non-target lesions.

At each protocol-specified time point, the overall response will be determined as shown below:

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

8.1.5. Progression-Free Survival

PFS is defined as the number of days between the date of treatment assignment and the earliest date of documented disease progression or death without prior progression. The date of disease progression or censoring for PFS will be determined according to the conventions listed below. These conventions are based on the May 2018 FDA Guidance for Industry, '*Clinical Study Endpoints for the Approval of Cancer Drugs and Biologics*' (https://www.fda.gov/media/71195/download) and on the Apr 2015 FDA Guidance for the Industry, 'Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics' (https://www.fda.gov/media/116860/download).

Table 19: Censoring rules for PFS.

Situation	Date of Progression or Censoring	Outcome
Death or disease progression between planned radiological assessments	Date of death or first radiological assessment showing disease progression, whichever occurs first	Progressed
Death before first radiological assessment	Date of death	Progressed
No baseline or post-baseline radiological assessments	Start date of treatment with the study drug	Censored
New anticancer treatment started before documentation of disease progression or death	Date of last radiological assessment prior to the start of non-protocol anticancer treatment	Censored
Death or progression after one missed radiological assessment	Date of missed radiological assessment visit	Progressed
Death or progression after more than one missed radiological assessment	Date of last radiological assessment visit without documentation of disease progression that is before the missed visit	Censored
Alive and without documentation of disease progression	Date of last radiological assessment	Censored

8.1.6. Overall Survival

Overall survival (OS) is defined as the time between the date of treatment assignment and the date of death. For patients without documentation of death, OS will be censored on the last date the patient was known to be alive. OS will be followed continuously while patients are on the study treatment and during OS follow-up via in-person or phone contact after patients discontinue the study treatment. If necessary, patients may be contacted occasionally outside of this FU window.

8.2. Pharmacokinetics

At each time point a single blood sample collected will be sufficient for all test to be performed for PK analysis purposes.

In the subpopulations of 20 patients in Stage 1 and at least additional 10 patients in Stage 2, samples will be collected in EDTA tubes on day 1 of cycle 1, 5 and 9 before and after the efti injections (pre-dose and then at 1, 2, 4, 8, 24, 48, 72 and 96 hours after dosing). PK sampling will be done at selected sites in ES and UK.

Plasma, prepared from the blood samples, will be stored at -80°C (-112 F). Details on handling of blood samples will be described in detail in the Laboratory Manual.

Note: The following windows are permitted on the assessment time points for PK sampling:

- up to 1 hour for the pre-dose assessment

- ±5 minutes for the 1-hour assessment
- ±15 minutes for the 2 hour and 4-hour assessments
- ±30 minutes for the 8-hour assessment
- ±2 hours for the 24 and 48-hour assessment,
- - 4 hours and up to +48 hours for the 72 and 96-hour assessments

8.3. Biomarkers

Details on biomarker collection and shipment will be described in the Laboratory Manual.

8.3.1. Th1 Biomarkers

All patients are expected to have Th1 biomarkers assessments.

Plasma samples will be collected in EDTA tubes to assess for Th1 biomarkers (e.g. IFN-γ, CXCL10) pre-dose on Day 1 Cycle 1, 5, 9, 13, EOC and EOT. Plasma, prepared from the blood samples, will be stored at -80°C (-112 F) and shipped in batches to the central laboratory.

In the subsets of patients with PK assessment, Th1 biomarkers will be additionally assessed in samples collected at selected timepoints after dosing with efti at cycle 1, cycle 5 and cycle 9. No additional blood samples will be taken. The PK samples available at these timepoints will be sufficient.

8.3.2. Tumor tissue sample

Archival tumor material or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated will be provided by patients on a mandatory basis. Samples will be shipped in batches to the central laboratory.

It will be analyzed in order to identify potential biomarkers of response (i.e. PD-L1 expression). These analyses will involve histopathological (e.g., immunohistochemistry) and/or molecular (e.g., protein sequencing, MS-based proteomics[5]) and/or genetic (e.g. gene expression profile analysis) assay technologies. Other potential biomarkers may also be assessed depending on emerging scientific data. Specific methodological details for all tumor tissue assessments will be provided in the Tumor Tissue Manual.

8.3.3. Gene expression profile analyses

Whole blood will be collected at screening and pre-dose cycle 5 from each patient for gene expression profile analyses (acc to PanCancer Immune Code). Blood samples will be shipped to the central laboratory according to the instructions on the Laboratory Manual.

8.4. Immunogenicity

Autoantibodies (i.e. antimitochondrial antibodies, rheumatoid factor, antithyroid (antithyroglobulin) antibodies, and antinuclear antibodies) will be evaluated at the local laboratory at cycle 1 day 1, cycle 9 day 1, EOC and EOT.

[5] No DNA analysis or genotyping will be performed.

The formation of anti-drug antibodies (ADA) against efti will be assessed at the central laboratory in blood samples collected at cycle 1 day 1, cycle 2 day 8, cycle 3 day 15, cycle 5 day 1, cycle 9 day 1, cycle 13 day 1, EOC prior to dosing and at the EOT visit.

Blood samples for ADA will be collected in a tube without any anticoagulant to prepare serum. These samples will be stored at -80°C (-112 F). ADA samples will be shipped in batches to the central laboratory. Details on handling of all blood samples will be described in detail in the Laboratory Manual.

8.5. Safety Assessments

Details for all safety assessments will be recorded in both the eCRF and the patient's source documents.

8.5.1. Laboratory Tests

All laboratory test results fulfilling one or more criteria defined in section 9.1 are to be recorded as AE. Pregnancy is an exclusion criterion. Any positive pregnancy test must be reported immediately using a pregnancy form (see section 9.5) and further study treatment must be discontinued. Patients must be followed throughout the duration of the pregnancy. Abnormal pregnancy outcomes are considered SAEs and must be reported using the SAE form.

Routine safety laboratory assessment, including hematology, biochemistry, coagulation, thyroid function test and urinalysis values will be performed as specified in Table 9 in Section 7.1.

8.5.2. 12-Lead ECGs

ECGs will be evaluated by the Investigator or a designee according to the usual site procedures. All patients will have single ECG recordings at screening on day 1 of each cycle, EOC and at EOT. Patients must be supine for approximately 10 minutes before ECG collection and remain supine but awake during ECG collection. For all patient ECG should be performed prior to meals.

For the purpose of immediate patient safety at the site, a qualified physician (the Investigator or qualified designee) will be responsible for interpreting the ECGs. If a clinically significant quantitative or qualitative change from baseline is identified after enrolment, the Investigator will assess the patient for symptoms to determine whether the patient can continue in the study. The Investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation. The following variables will be measured or calculated for each ECG: QRS duration and axis; PR interval; Heart rate and RR interval and QT interval.

8.5.3. Vital Signs Assessments

Vital signs will be assessed at regular intervals as indicated in the schedule of assessments. Vital signs will be recorded after a 10 minute resting (supine position) period. The following variables will be measured:

- Systolic and diastolic blood pressure (mm/Hg)
- Pulse rate (beats per minute)
- Body temperature (Celsius or Fahrenheit)
- Body weight
- Height (at screening only)

All blood pressure measurements should be made using the same type of device on the same arm, using a completely automated device. Manual techniques will be used only if an automated device is not available. Body temperature will be measured in a consistent manner throughout the study.

8.5.4. Adverse Events

AEs will be collected, categorized and reported as described in section 9.

8.6. Medical History

Each patient's medical history will be taken during screening. This includes in particular patient demographics, smoking history, details of cancer onset, cancer history including prior PD-L1 status, prior surgery, and past treatment including chemotherapy and/ or radiation therapy and for HNSCC prior HPV status. Medical history should also include history of HIV, HCV and HBV exposure.

8.7. Concomitant Therapy and Concomitant Procedures Assessment

Prior medications comprise all therapies that were stopped prior to cycle 1 day 1. Concomitant medications are defined as medications that were started on or after cycle 1 day 1 until 28 days after end of treatment (last dose of any study drug). Acceptable concomitant therapy is described in section 6.10. Concomitant procedures will be assessed, starting from cycle 1 day 1 until 28 days after end of treatment (last dose of any study drug). Concomitant therapy and concomitant procedures need to be assessed at every visit.

9 ADVERSE & SERIOUS ADVERSE EVENTS

9.1. Adverse Events

An AE is any untoward medical occurrence (which does not necessarily have to have a causal relationship with this treatment). An AE can be any unfavorable and unintended sign (including abnormal laboratory findings as described below), symptom, or disease, whether or not related to any study drug. This includes any occurrence that was new in onset or aggravated in severity or frequency from the baseline condition.

All AEs, regardless of severity or causality, will be documented for type of adverse event, date and time of onset, date of resolution, duration, severity grade according to the current CTCAE version 5.0 where applicable, relationship (unrelated, possibly related, or related) to each of the study drugs separately (efti or pembrolizumab), remedial actions taken, and outcome (see section 19.5).

If no common toxicity criteria (CTC) grading is available, the severity of an AE is graded as mild, moderate, severe, life-threatening or fatal. The respective translation in the gradings 1 to 5 is described in section 19.5.

It is the Investigator's responsibility to review all laboratory findings and vital sign measurements. Abnormal results of diagnostic procedures, including laboratory test abnormalities, are considered AEs if they result in any of the following:

- Discontinuation of study treatment
- Requirement for treatment or any other therapeutic intervention
- Necessity for further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Association with clinical signs or symptoms that may have a significant clinical impact, as determined by the Investigator.
- Clinically significant (as assessed by the investigator) changes of any laboratory parameter throughout the study (i.e. compared to the last assessment prior to any study treatment)
- Any abnormal laboratory parameter qualifying for any ≥ grade 3 NCI-CTC criteria

Note: If the abnormal result was already present at baseline with the same severity, it will be recorded as medical history. Only abnormal results of ≥ grade 3 that have changed in severity compared to baseline will be reported as AE, irrespective of clinical significance.

Patients should be encouraged to report AEs spontaneously or in response to general, non-directed questioning. The Investigator should question patients about AEs and changes in pre-existing illnesses since their last visit and must record the information in the patient's medical records. All AEs are to be recorded on the appropriate eCRFs and in detail on the source documents.

If it concerns a SAE, it must be reported to the Sponsor or its delegate within 24 hours of becoming aware of the event (for details see sections 9.2 and 9.5). Safety follow-up is to be performed.
Patients who experience AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. All AEs and laboratory abnormalities encountered during the study should be followed until resolution or stabilization of the event(s). Any action taken and follow-up results must be recorded in the patient's medical record. Follow-up laboratory results should be filed with the patient's source documentation and eCRF. Adverse events that are ongoing after the end of safety follow-up should be marked as ongoing.

For all AEs related to study treatment that require the patient to discontinue treatment, relevant clinical assessments and laboratory tests should be repeated on at least a monthly basis until final resolution or

stabilization of the event(s). These assessments should be captured in the source data, SAE forms and be entered in the eCRFs.

Observations of the same laboratory abnormality or vital sign abnormality from visit to visit should not be repeatedly recorded on the CRF, unless the etiology changes. The initial severity of the event should be recorded. If the severity or seriousness of the event changes, a new AE should be reported.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded. However, if the Investigator does not consider an observed or reported sign or symptom a component of a specific disease or syndrome, it should be recorded as a separate AE.

9.2. Serious Adverse Events

A SAE is generally any AE that results in one or more of the following:

- Death (not resulting due to disease progression).
- Is immediately life threatening (i.e. presents an immediate risk of death at the time of the AE, not an AE that hypothetically might have caused death if it were more severe).
- Requires or prolongs inpatient hospitalization.
- Causes persistent or significant disability/ incapacity.
- Is a congenital anomaly/ birth defect.
- Qualifies for ECIs as described in section 9.3.
- Other important medical events that may not be immediately life threatening or result in death or hospitalization, but based upon appropriate medical judgment, are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE

Elective pre-planned hospitalizations for treatment of an existing condition prior to entering the study or hospitalization due to social reasons or administration of study drug are not considered SAEs. Tumor progression and associated signs or symptoms are not considered SAEs, based upon investigators discretion.

The Investigator should consult with the Medical Monitor if there is any doubt regarding classification of a SAE.

Definition of Life-Threatening Adverse Events: An adverse event is life threatening if the patient was at immediate risk of death from the event as it occurred (i.e. it does not include a reaction that, had it occurred in a more serious form, might have caused death). For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis can be fatal.

Definition of Disabling/ Incapacitating Experience: An adverse experience is incapacitating or disabling if the experience results in a substantial and/ or permanent disruption of the patient's ability to carry out normal life functions.

9.3. Events of clinical interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor within 24 hours of awareness.

Events of clinical interest* for this trial include:

- an overdose of pembrolizumab or efti (For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥5 times the indicated dose and an overdose for efti will be defined as any dose of 150 mg or ≥5 times the indicated dose) – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

**Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Medical monitor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.*

9.4. Time period and frequency for collecting AEs, SAEs, pregnancy and ECIs

All AEs, SAEs and other reportable safety events (i.e. Pregnancy, ECIs) that occur after the consent form is signed but before treatment /allocation must be reported by the investigator. If an AE occurred after signing informed consent, the AE is to be recorded in the AE section of the eCRF.

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All AEs or ECIs (Events of Clinical Interest) from the time of treatment/ allocation through 30 days following cessation of study treatment must be reported by the investigator.

All AEs meeting serious criteria, from the time of treatment/ allocation through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.

All pregnancies and exposure during breastfeeding, from the time of treatment/ allocation through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

Safety follow-up is to be performed until resolution of AEs/ECIs/SAEs or for a minimum of 2 months after last study drug administration or until patients is receiving any other anti-cancer therapy or any other investigational therapy.

9.5. Expedited reporting of SAEs, ECIs or pregnancy

All AEs that meet the criteria for SAE require the completion of a study specific SAE Form (or Additional Safety Information (ASI) Form). This applies to all SAEs, whether or not they were considered to be related to the study treatment.

The Investigator must report all SAEs to the sponsor or its designee immediately, i.e. within 24 hours (by fax or e-mail) of learning of its occurrence. For this reporting, a SAE Form (provided in the Investigator

File) needs to be completed in English. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving the information. This follow-up data should ideally be provided on an updated SAE form.

If a SAE occurred after signing informed consent, but before study treatment and the patient continues on study, a SAE must also be entered on the relevant Medical History page of the CRF.

The SAE report should provide a detailed description of the AE and may include anonymized copies of hospital records and other relevant documents. Autopsy results, if applicable, should also be sent to the sponsor or its designee as soon as they become available. Copies of each report will be kept in the Investigator File.

All SAEs will need to be followed actively until resolution or stabilization (but for at least 2 months after last study drug administration). The above is also applicable to follow-up SAE information.

If a female patient becomes pregnant during the study, she will be removed from the study without receiving further study medication. Follow-up regarding the outcome of the pregnancy and any postnatal sequelae in the infant is required. Pregnancies are considered immediately reportable AEs (within 1 working day) and are to be documented in the eCRF. Furthermore, a Pregnancy Reporting Form (provided in the Investigator File) needs to be completed in English.

Suspected Unexpected Serious Adverse Reactions (SUSARs): SUSARs are SAEs that are at a minimum possibly related to any of the study agents or study treatment (efti or pembrolizumab) and are unexpected (i.e. not listed in the investigator brochure and/or SmPC). SUSARs will be collected and reported expeditiously to competent authorities and IECs)/IRBs according to regulations.

The reporting timelines are as follows:

- All fatal/ life-threatening SUSARs need to be reported within 7 calendar days of initial notification.
- All other SUSARs within 15 calendar days of initial notification.

Expectedness is determined by the sponsor according to the designated reference safety information.

Medical and scientific judgment is to be exercised in deciding whether expedited reporting is appropriate in other situations, such as for important medical events that are not immediately life threatening or do not result in death or hospitalization but jeopardize the patient or the patient population.

In addition to the expedited reporting of SUSARs, the Sponsor will submit, once a year throughout the clinical study, an aggregated safety report (Developmental Safety Update Report, DSUR) to the Regulatory Authorities and Ethics Committees of the participating sites in the concerned countries. This DSUR includes cumulative listings of all SAEs and SUSARs from the Sponsor’s clinical studies with efti during the reporting period.

10 STATISTICAL METHODS

A statistical analysis plan (SAP) will provide details on the methods of analysis to address all study objectives. The SAP may be amended during the study, but will be finalized before the cut-off date for any statistical analysis.

For continuous variables, data will be summarized with the number of patients, mean, standard deviation, median, and minimum and maximum values. For categorical variables, data will be tabulated in frequency tables to display the number and proportion of patients for each category. Baseline assessments for each outcome variable will be defined as the last measurement obtained before the first dose of study drug.

10.1. Sample Size Determination

The null hypothesis that the true response rate is [p0] will be tested against a one-sided alternative. In the first stage, [n1] patients will be accrued. If there are [r1] or fewer responses in these [n1] patients, the study will be stopped. Otherwise, [n - n1] additional patients will be accrued for a total of [n]. The null hypothesis will be rejected if [r2 + 1] or more responses are observed in [n] patients. This design yields a one-sided type I error rate of CCI and power of CCI % when the true response rate is [p1]. Calculations reveal that 17 patients in the initial step and an additional 19 subjects, in total 36 patients to be recruited into the study for the NSCLC first line and the other numbers as presented in the table below. Outcome of the calculation do not necessarily have to agree with the assumed proportions for the calculations (r1/N1 and $r2/N_{total}$ and p_1), especially for such small sample numbers.

Mini-max results of this calculation were used for this clinical trial.

Indication	response rate p_0	Alternative p_1	r_1	r2	Initial No of pts (n_1)	Add. No. of pts (n_2)	N total
NSCLC 1st line	23%	CCI %	4	CCI	17	19	36
NSCLC 2nd line	7 %	CCI %	1	CCI	23	13	36
HNSCC	15 %	CCI %	2	CCI	18	19	37

The "true response rates" for 1st line NSCLC were extracted from Keynote-024 and Keynote-042 under consideration that for PD-1 all comers response rate will be lower (10, 11). For 2nd line NSCLC there are no available publications for pembrolizumab alone in PD-1/PD-L1 refractory patients, but due to the confirmation of progression it (p_0) is considered close to 0 % for pembrolizumab alone. The alternative (p_1) of CCI % was considered clinically relevant especially in comparison to available standard chemotherapy[6]. For HNSCC relevant publications from Keynote 012 and Keynote-040 were used (2, 12) for p_0.

Sample size calculations were performed using the validated software R R version 3.3.3 (2017-03-06), Package:
Kieser M, Wirths M, Englert S, Kunz CU and Rauch G (2017). "One Arm Phase Two Study: An R Package

[6] Given the available treatment option in this patients population (mostly single agent chemo therapy) and its efficacy (about 20 % SD at 6 months; median OS 6-12 months), long-term stabilization of the disease (6+ months) are considered as a meaningful clinical benefit and will be counted equal to a response for the decision if stage 2 can be opened. Final decision is to be made by the DMC based on an updated risk benefit assessment.

for Planning, Conducting, and Analyzing Single-Arm Phase II Studies." _Journal of Statistical Software_, *81*(8), pp. 1-28. doi: 10.18637/jss.v081.i08 (URL: http://doi.org/10.18637/jss.v081.i08).

For part A an extension (Part A extension) is anticipated based on the ORR of efti in combination with pembrolizumab as test group in a single arm design. The true ORR of monotherapy pembrolizumab in NSCLC 1st line is expected to be 23%, whereas a rate of CCI % is expected for the test group (in case PD-L1 distribution is as expected from historical studies with ~70% <50% PD-L1expression). Using these assumptions with a power of CCI% and a one-sided level of significance of CCI% in this phase II trial, a sample size of 105 patients would be required for analysis. With a drop-out rate of 5%, a total of 110 patients need to be enrolled. With the 36 patients of stages 1 and 2, another 74 patients would be needed to be enrolled in total in this extension. This sample size is regarded sufficient to provide a reasonable precision for the estimate of ORR as basis for sample size considerations for further clinical studies.

Possible extensions of part B and C will be introduced via substantial amendments.

Calculations were performed using PASS 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

10.2. Assignment to treatment

Patients will be assigned to the single treatment arm according to the indication as assessed during screening.

10.3. Analysis Populations

Full Analysis Set

The Full Analysis Set (FAS) includes all assigned patients who received at least one dose of study drug (i.e. one dose of either pembrolizumab or efti). This population will be the primary population for the analyses of efficacy endpoints and baseline characteristics.

Per-protocol Population

In addition, a per protocol population analysis will be performed. Details are described in the SAP.

Safety Population

The safety set is defined analogously to the full analysis set and includes all assigned patients who received at least one dose of study drug (i.e. one dose of either pembrolizumab or efti). This population will be the primary population for the analyses of safety.

Pharmacokinetic population (PK population)

All patients of the subpopulations (20 in Stage 1 and additional 10 in Stage 2) will be taken into account who:

- received at least one dose of efti and
- have sufficient plasma concentration data to calculate reliable estimates of at least one PK parameter, and
- are without any protocol deviation that would interfere with the interpretation of PK results.

10.4. Handling of Missing Data

When tumor response (as defined by local image interpretation) based on target lesions is missing, it will be set to PD if the last non-missing observation is PD. No imputation will be used to handle any other patterns of missing data for tumor response (i.e., it will be censored in the efficacy analysis). Rules for handling of missing data for secondary endpoints including missing/ partial dates will be defined in the SAP.

10.5. Subgroup Analyses

Subgroup analyses (e.g. PD-L1 positivity) will be described in the SAP.

10.6. Interim Analyses

Descriptive interim analyses (incl. abbreviated report, if needed) may be performed e.g. for the DMC meetings or when one stage of one part of the study is completed, which do not affect the analysis of the primary endpoint. No adjustments for multiplicity are needed as no statistical test will be performed. Details will be described in the SAP.

10.7. Timing of analysis

The analyses (also interim analyses) may be performed separately for each indication (dependent on availability of the results) as described in the SAP. Separate clinical study reports (also interim analyses) may be written for each indication (dependent on availability of the results) as described in the SAP.

10.8. Baseline and Demographic Characteristics

Baseline characteristics and demographic information at baseline will be summarized with descriptive statistics for the FAS of each part A-C of the study. Medications will be coded using the most current version of the World Health Organization (WHO) Drug dictionary and will be summarized as treated for all patients in the safety population. Prior medications are defined as medications that were stopped prior to the treatment period/cycle 1 day 1. Medications used at study entry are defined as medication that started on or prior to the treatment period/cycle 1 day 1. Concomitant medications are defined as medications that were taken from cycle 1 day 1 until 28 days after end of treatment (last dose of any study drug).

10.9. Efficacy Analyses

Efficacy analyses will be performed for each part of the study independently.

For indications with an extension, the patients of stages 1 and 2 will be combined with the newly enrolled patients of the extension as combined dataset for analysis. Certain endpoints will in addition be analyzed in the subgroups "patients of stage 1+2" and "newly enrolled patients" to assess any effect of later enrollment on the outcome. All endpoints assessed in stages 1 and 2 will also be assessed for the extension as described above. Details will be given in the SAP.

10.9.1. Analysis of the primary endpoint

Primary endpoint is the objective response rate (ORR). The ORR is defined as the number of subjects with a best overall response (BOR) according to iRECIST as complete response (CR) or partial response (PR) divided by the number of subjects. The BOR is the best response as determined by the investigator between the date of assignment and date of objective measurement of progression by iRECIST or the date of subsequent therapy, whichever comes first. For patients with no documented progression or subsequent therapy, all available response assessments will be used to define BOR. In addition, analysis of confirmed responses will be described in the SAP.

The response will be further evaluated by the duration of response (DOR) based on iRECIST, calculated for all patients with CR or PR up to an objective documentation of progression or death, whichever occurs first. For patients with no documented progression or death, DOR will be censored at the date of last documentation of response.

DOR = Date of disease progression / death – Date of first partial or complete response + 1.

ORR will be summarized by binomial response rate with two-sided 95% exact confidence intervals using the Clopper-Pearson method.

The DOR will be summarized using the Kaplan-Meier product-limit method. The median time to event will be calculated along with 95% CIs using the Kaplan-Meier method. In addition, the proportion of responders still in response at different timepoints (3 and 6 months) will be assessed based on a Kaplan-Meier Plot.

As a sensitivity analysis ORR and DOR will be assessed based on RECIST 1.1 based on the investigator assessment. All efficacy analyses are based local investigator assessments. A central independent assessment may be conducted as specified in the SAP.

10.9.2. Analysis of the secondary and exploratory endpoints

All secondary analyses will be performed descriptively.

The time-to-event endpoints (PFS, CCI OS) will be summarized using the Kaplan-Meier product-limit method. The median time to event will be calculated along with 95% CIs using the Kaplan-Meier method. In addition, the proportion of responders still in response at different timepoints (3, 6 and 9 months) will be assessed based on a Kaplan-Meier Plot. The assessment of progression will be based on iRECIST (this does not apply to CCI).

PFS will be calculated as the time from the date of assignment into the study to the date of first documentation of disease progression or date of death due to any cause, whichever occurs first:

PFS = Date of disease progression/ death – Date of assignment into the study + 1.

The PFS rate at 6, 12, 18 and 24 months and corresponding 95% confidence intervals will be estimated using the Kaplan-Meier method.

The OS rate at 6, 12, 18, and 24 months and corresponding 95% confidence intervals will be estimated using the Kaplan-Meier method.

The overall survival (OS) will be calculated as the time from the date of assignment into the study treatment to the date of death from any cause:

OS = Date of death – Date of assignment into the study + 1.

CCI , will be estimated using the Kaplan-Meier method.

As a sensitivity analysis PFS will be assessed based on RECIST 1.1. All efficacy analyses are based on local investigator assessments. A central independent assessment will be conducted as specified in the SAP.

10.10. Pharmacokinetic Analyses

The plasma concentration time profile of efti will be summarized and PK parameters such as area under the curve (AUC), peak serum concentration (C_{max}), time to reach C_{max} (t_{max}), systemic clearance (CL), elimination half-life (t1/2) and volume of distribution (VD) will be calculated.

10.11. Immunogenicity analyses

The development of anti-efti antibodies will be evaluated and characterized. Autoantibodies will also be evaluated.

10.12. Biomarker Analyses

Tumor material or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated will be provided by patients on a mandatory basis. Blood sampling for potential biomarker will be conducted throughout the study. Exploratory analyses to assess correlations between biomarkers (PD-L1 expression, PancGen Score, TH-1 levels) and response endpoints will be done, depending on the available data.

10.13. Safety Analyses

Safety data will be summarized for the safety population. The baseline value for safety analysis is defined as the value collected at the time closest to and prior to the start of any study drug (pembrolizumab or efti whichever was first) administration (i.e. Day 1 of week 1 of cycle 1).

An adverse event (AE) summary table will include treatment-emergent adverse events (TEAE; i.e., AEs with onset dates on or after the first dose of study drug regardless of causality), serious TEAEs, TEAEs related to pembrolizumab and efti, fatal TEAEs, TEAEs leading to temporary and permanent stop, TEAEs according to worst severity and combinations of previously mentioned type of AEs.

The number and percentage of patients with at least 1 TEAE will be tabulated by preferred term and system organ class (i.e. from MedDRA). For these tabulations, the number of patients (i.e., patients with multiple events will be counted only once per preferred term) and the number of events (i.e. except for by severity tabulations) with that particular TEAE are presented. The AE tabulations including all TEAEs (by severity), serious TEAEs, fatal TEAEs, permanent stop of study agent TEAEs will be presented. The previously mentioned type of TEAEs might also be presented in combination with treatment-relatedness. AEs will also be tabulated by severity and/or relationship to study drug. At each level of tabulation, the event with the highest level of severity or strongest drug relationship will be presented. The tables will be described in detail in the SAP prior to any analysis.

All AEs will be listed. In addition, detailed listings will be provided for patients who die, experience a SAE, or discontinue the study because of an AE. These listings will include age, duration of follow up, number of doses received, and time since last dose.

Vital signs (blood pressure, temperature and pulse rate), body weight and derived body mass index, and laboratory parameters (e.g., hematology, biochemistry, coagulation, thyroid function testing, urinalysis, and ADA results) will be presented at each time point using descriptive statistics (number, arithmetic mean, standard error, standard deviation, 95% confidence interval of the mean, median, 1st and 3rd quartile, minimum, and maximum).

Cross-tabulations of hematology, biochemistry results, and other parameters as described in the SAP will be prepared to examine the worst CTCAE toxicity grade / abnormality versus the grade / abnormality at baseline. Cross-tabulations of vital sign results and categorical laboratory results will be prepared to

examine the result / abnormality per time point versus the result / abnormality at baseline. A tabulation of elevated liver function test will be presented and explained more in depth in the Statistical Analysis Plan.

All data from the 12-lead ECG will be analyzed descriptively.

For indications with an extension, the patients of stages 1 and 2 will be combined with the newly enrolled patients of the extension as combined dataset for analysis. Certain endpoints will in addition be analyzed in the subgroups "patients of stage 1+2" and "newly enrolled patients" to assess any effect of later enrollment on the outcome. All endpoints assessed in stages 1 and 2 will also be assessed for the extension as described above. Details will be given in the SAP.

11 DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms

All patient data generated in the study, and documented on the source documents on site, will be recorded in each patient's eCRFs. Data reported on the eCRFs that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. eCRFs will be considered complete when all missing and/ or incorrect data have been resolved and all safety data have been recorded.

11.2. Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

The Investigator and designees agree to maintain accurate eCRFs and source documentation as part of the case histories. Source documents are the originals of any documents used by the Investigator, sub-investigator, or hospital/ institution that will allow verification of the existence of the patient and substantiate the integrity of the data collected during the study.

eCRFs must be completed *only* by people designated by the Investigator. All data entered into the eCRF also must be available in the source documents. The Investigator will allow designated representatives of the Sponsor and regulatory bodies to have direct access to the source documents to verify the data reported in the eCRFs.

Each completed eCRF must be reviewed and digitally signed by the Investigator or designee in a timely manner. The completed eCRF will be reviewed by the Sponsor or its agents on a routine basis.

11.3. Record Retention

Study records and source documents need to be preserved for at least 15 years after the completion or discontinuation of/ withdrawal from the study, or 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region, whichever is the longest time period.

11.4. Drug Accountability

Each time study drug is dispensed to a patient this must be recorded on a drug dispensing/accountability log. Copies of this form will be supplied in the Investigator File.

At regular intervals the CRA(s) will perform a 'drug reconciliation visit', verifying if all study medication that has been shipped to the institute can be accounted for by records of receipt, dispensing and destruction.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed or returned stock. It is essential that all study treatment be accounted for by the Investigator or institute, and that any discrepancies are explained and documented.

After accountability by the monitor and written approval from the sponsor, all unused vials or medication not dispensed should be sent back to the sponsor or representative of the sponsor (details provided in the IMP Handling Manual). All used vials may be destroyed locally, if the destruction is fully documented, and following the site's SOP for destruction of biological waste. Unused vials might be destroyed locally only upon approval by the Sponsor.

12 MONITORING

In accordance with current applicable regulations, Good Clinical Practice (GCP), and applicable standard operating procedures, monitors will contact the site before the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Sponsor requirements.

When reviewing procedures for data collection, the discussion will include identification, agreement, and documentation of data items which will be recorded in each patient's eCRF.

The study will be monitored to ensure the following:

- Data are authentic, accurate, and complete.
- The safety and rights of patients are being protected.
- The study is being conducted in accordance with the currently approved protocol, any other study agreements, GCP, and all applicable regulatory requirements.

The exact extent of the monitoring procedures is described in a separate monitoring plan. All Investigators agree that the monitor regularly visits the clinical site and ensure that the monitor will receive appropriate support in their activities at the clinical site, as agreed in separate contracts with each clinical site. Under special circumstances, such as for example limitations caused by the COVID-19 (SARS-CoV-2 infection) pandemic and limitations for on-site visits, remote monitoring and remote source data verification (SDV) will be considered as per approval/guidelines from relevant regulatory authorities, ethics committees and sites and as per the clinical monitoring plan.

13 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor or its designee will perform the quality assurance and quality control activities of this study. However, responsibility for the accuracy, completeness and reliability of the study data presented to the sponsor lies with the Principal or qualified Investigator generating the data.

Quality control check (e.g. by monitoring, data management and medical review) of all key safety and efficacy data in the database will be made on an ongoing manner until the final database lock. By the conclusion of the study the occurrence of any Protocol violations will be determined.

14 PROTOCOL AMENDMENT AND PROTOCOL DEVIATION

14.1. Protocol Amendment

Administrative amendments to the protocol will be classified as amendments of typographical errors, clarifications of confusing wording, name changes, and minor modifications that have no impact on the safety of the patients or the science of the study. Administrative amendments will be submitted to the IRB/ IEC for information only. The Sponsor will ensure that acknowledgement of receipt is received and filed. Any other amendment will be classified as a substantial amendment and will be submitted to the appropriate regulatory authorities and the IRBs/IECs for approval.

14.2. Protocol Deviation

Important protocol deviations are any deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being.

This includes deviations related to patient eligibility, informed consent, IMP dosing errors or failing to perform assessments required to interpret the primary endpoint. Additional categories may be identified as deemed necessary by the Medical Monitor.

If a protocol deviation occurred due to COVID-19 crisis, this information should be captured clearly. All protocol deviations should be recorded by the monitor. The clinical team reviews all deviations recorded and determines whether a deviation is major or not. Deviations are reported to the Sponsor and Investigator as part of the regular reporting. Important protocol deviations will be summarized in the clinical study report. In accordance with applicable regulatory authority mandates, the investigator is responsible for reporting major protocol deviations to the IRB/ IEC as requested or deemed necessary.

15 ETHICAL CONSIDERATIONS

The study will be conducted according to current GCP, including any future revisions, all relevant local laws and regulations, as well as the principles of the Declaration of Helsinki and its amendments. IRB/ IEC committees will review and approve this protocol and informed consent. All patients must provide written informed consent before participation in the study. This study will be performed by qualified clinical investigators and in accordance with GCP. The study specifically incorporates *all* of the following features:

- Multicenter study design
- Prospectively stated objectives and analytical plan
- Accepted, pre-specified outcome measures for safety and efficacy
- Investigator meeting prior to study start and a detailed protocol to promote consistency across sites
- Compliance with current GCP, with assessment via regular monitoring
- Quality assurance procedures performed at study sites and during data management to ensure that safety and efficacy data are adequate and well documented.

15.1. Site Review

The Investigator will submit this Protocol, the site-specific informed consent form, and any required documents for review and approval as applicable by local law or regulation. All necessary approvals have to be in place prior to study start on site.

Prior to study start, the Investigator is required to sign a Protocol signature page confirming his/ her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this Protocol and to give access to all relevant data and records to CRAs, auditors, and regulatory authorities as required. Investigators ascertain they will apply due diligence to avoid Protocol deviations.

The Investigator will make appropriate reports on the progress of this study to CRO in accordance with applicable government regulations and their agreement with the CRO.

15.2. Informed Consent

Prior to obtaining informed consent, the purpose and nature of the study as well as possible adverse effects resulting from study drug administration must be explained to each patient. Written informed consent must be obtained in accordance with ICH-GCP guidelines using the approved informed consent form, before any

study specific procedures (including screening procedures) are performed. The process of obtaining informed consent should be documented in the patient source documents.

The Investigator shall provide a copy of the signed informed consent form to the patient and the signed original shall be maintained in the Investigator File. A copy of the signed informed consent form must be filed in the patient file. At any stage, the patient may withdraw their consent and such a decision will not affect any further treatment options.

16 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate clinical study agreement.

The Investigator/ institution is required to have adequate current insurance to cover claims for negligence and/ or malpractice according to applicable national regulations. The sponsor will provide insurance coverage for the clinical study as required by applicable national regulations.

Study patients will not be paid for their participation. Any study-related travel expenses made by the patient or the accompanying person will be reimbursed on the basis of actual cost as proven by original or copies of receipts, or an allowance per kilometer travelled.

17 PUBLICATION POLICY

Both the use of data and the publication policy are detailed within the clinical study agreement.

The Investigator should be aware that intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be patient to the terms of a clinical study agreement that will be agreed upon between the institution and the Sponsor or designee. With respect to such rights, the Sponsor or designee will solely own all rights and interest in any materials, data, and intellectual property rights developed by any party performing the clinical study described in this protocol, patient to the terms of any such agreement. In order to facilitate such ownership, the relevant party will be required to assign all such inventions either to the relevant institution or directly to the sponsor or their designee, as will be set forth in the clinical study agreement.

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19 APPENDICES

19.1. ECOG Performance Status

The ECOG performance status is in the public domain and therefore available for public use (Oken M, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP: Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55).

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

19.2. iRECIST: Guidelines for response criteria for use in trials testing Immunotherapeutics

The iRECIST guideline can be assessed using the following link:

http://recist.eortc.org/irecist/

19.3. Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1

The RECIST guideline, version 1.1, can be accessed using the following link:

https://recist.eortc.org/recist-1-1-2/

19.4. Imaging Protocols

CT Imaging Protocol: The specific parameters of the CT imaging protocol are shown in Table 20, below.

CT scan with contrast of the thorax, abdomen and pelvis is the recommended modality. If there are brain metastases/tumors, an MRI scan of the head must also be performed. Patients with HNSCC will perform a head and neck CT.

Intravenous contrast on CT and MRI exams is recommended when not medically contraindicated.

Patients who have a contraindication to i.v. contrast may have MRI exams performed instead, except for exams of the chest. In these cases, a non-contrast CT of the chest is recommended to evaluate the lung parenchyma.

Note: The anatomical coverage must be complete at baseline and all follow-up visits. Scans lacking complete anatomical coverage will be considered non-readable data and will exclude patients at screening.

- MRI without and with i.v. contrast is the preferred modality for brain imaging. If there is a contraindication to MRI, then CT of the brain without and with i.v. contrast is a second choice.
- It is recommended that CT scans be performed with i.v. contrast. However, scans should be performed according to local site imaging protocols based on the clinical status of the patient.

MRI Imaging Protocol: MRI examinations should be performed with the recommended 1.5T or 3T MRI system. It is preferable that repeat MRI examinations are performed on the same type of T system. The specific parameters of the MRI imaging protocol will be provided in an imaging manual.

Bone Scan Imaging Protocol: Radionuclide bone scans should only be performed when clinically indicated. If bone scans were clinically indicated and positive at baseline, they should be repeated at the time of confirmation of response either if these lesions are not assessable on CT, or to confirm CR. The choice of radionuclide scanning, bone scan (i.e. Technetium-99m bone scintigraphy (Tc-99m bone scans)) should be based on site standard of care. The specific parameters will be provided in an imaging manual.

Color Digital Photography: Superficial clinical lesion (e.g., skin nodule) must be measured in at least one dimension (longest diameter in the plane of measurement will be recorded) with a minimum size of the longest axis being ≥ 10 mm as imaged with scale in color photography per RECIST 1.1.

If a patient has clinically-indicated skin lesion(s), the investigator site will perform color digital photography of all skin lesions using a ruler held flush to the skin next to the longest diameter of the lesion to indicate the size of the lesion at every time point scheduled for radiological scans that a lesion is present. Once a lesion(s) is documented, the target area should be documented at every subsequent time point for the duration of the study. The imaging manual will include more detailed instructions for the site to follow during image capture.

Table 20: CT Imaging Protocol

Type of scan	Spiral CT
Patient orientation	Supine, head first, arms above the head
Anatomy	Chest-abdomen-pelvis (from lung apices to the pubic symphysis)
Breathing instructions	Suspended inspiration
kV/mAs	Use the normal dose, but not low dose settings
Detector collimation	Use vendor specification
Filter	Standard and High-resolution reconstruction algorithm (lung window) for lungs Soft tissue filter for abdomen and pelvis
Slice thickness	3 mm recommended (acceptable range is 2.5-5 mm), continuous slices

Gap (slice spacing)	None
i.v. contrast	100 ml Omnipaque 350 or equivalent non-ionic contrast medium at a concentration of 350mgl/ml
Injection rate	3ml/sec + 50ml saline flush
Scan delay	Given 3ml/sec, start delay optimized for venous portal phase during abdominal scanning (routinely 70 seconds). If done locally, biphasic neck injection can be used.
Contrast enhancement	The portal phase implies that the contrast reached the liver and portal venous system. The liver parenchyma enhances through blood supply by the portal vein and hepatic veins should already enhance.

19.5. Definitions for Clinical and Laboratory AEs

All AEs (clinical and laboratory) will be rated AEs and SAEs, according to the current National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v5.0)

The applicable National Cancer Institute CTCAE, can be accessed using the following link: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs will also be categorized in terms of a) severity, b) causal relationship, c) action taken regarding to study treatment and d) outcome to date, as follows:

a) Severity (Clinical Events Only) if not listed in the CTCAE v5.0

Severities of clinical events are to be graded as follows:

Code	Descriptor	Definition
1	Mild	An event that may be associated with the awareness of a sign or symptom and is easily tolerated or discomfort noted, but no disruption of normal daily activity
2	Moderate	An event that causes discomfort enough to cause interference with usual activity or discomfort sufficient to reduce or affect normal daily activity
3	Severe	An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity
4	Life threatening or disabling	An event that is life threatening or disabling
5	Fatal	An event that is fatal

b) Causal Relationship

The Investigator should use medical judgment to determine whether there is a reasonable causal relationship, including all relevant factors such as temporal course and latency, results from de-challenge or re-challenge, pattern of the reaction, known pharmacological properties of the product, and alternative explanations (e.g., other drugs, medical history, concomitant diseases). The expression "reasonable causal relationship" means to convey in general that there is evidence or argument to suggest a causal relationship. Causality assessment will be documented on the AE and SAE form.

No reasonable possibility of causal relationship:

- *Unrelated:*
    - There is no reasonable causal relationship between the investigational medicinal product and the event.

Reasonable possibility of causal relationship:

- *Possibly related:*
    - Event or laboratory test abnormality, with reasonable time relationship to drug intake.
    - Could also be explained by disease or other drugs.
    - Information on drug withdrawal may be lacking or unclear.
- *Related:*

There is a reasonable causal relationship between the investigational medicinal product and the event.

For CIOMS forms a binary form of causality assessment will be used as outlined in the safety handling manual:

- **Yes:** There is a reasonable causal relationship between the investigational medicinal product and the AE
- **No:** There is no reasonable causal relationship between the investigational medicinal product and the AE

c) Action Taken Regarding any study treatment

The investigators are to record the action taken regarding treatment agent using the following 4 categories:

Code	Descriptor	Definition
1	None	No change in study treatment was made
2	Discontinued	The study treatment was permanently stopped
3	Delayed/ Interrupted	Study treatment/study agent was delayed or was temporarily stopped
4	Partial/ Incomplete Dose	The complete Study treatment dosage was not given

d) Outcome to Date

The investigators are to record the outcome to date using the following 5 categories:

Code	Descriptor	Definition
1	Recovered	The patient fully recovered from the AE with no residual effect observable
2	Recovered with sequelae	AE resolved, but residual effect(s) are present. Residual effects of the AE are still present and observable
3	Ongoing	The AE itself is still present and observable
4	Death	Death
5	Unknown	