Type of Approval (select one): ☒ **SAP** ☐ **Initiation of Programming SAP** ☐ **SAP Addendum**

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Fortrea Approval(s):

Lead Statistician

Approval Signature **Print Name** **Date**	PPD

Not applicable

Approval Signature **Print Name** **Date**	

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Immutep [redacted]

Approval Signature **Print Name** **Date**	[redacted]

Immutep [redacted]

Approval Signature **Print Name** **Date**	[redacted]

Immutep S.A.S.

STATISTICAL ANALYSIS PLAN

Protocol: TACTI-002 (IMP321-P015); Keynote-PN798

EUDRACT: 2018-001994-25

Treatment: eftilagimod alpha (efti, eftilagimod alfa, IMP321, LAG3-Ig)
pembrolizumab (Keytruda®; MK-3475)

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)

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Pages:	77

Contents

Abbreviations

AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ALK	Anaplastic Lymphoma Kinase
AR	All Randomized
AST	Aspartate Aminotransferase
BICR	Blinded Independent Central Reviewer
BMI	Body Mass Index
BOR	Best Overall response
BP	Blood Pressure
CPS	Combined positivity score
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CXCL-10	C-X-C motif chemokine 10
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DOR	Duration of Response
EAS	Evaluable Analysis Set
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
EOC	End of Combination
EOT	End of Treatment
FAS	Full Analysis set
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HIV	Human Immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
Hr	Hour
ICF	Informed Consent Form
i	Reference to iRECIST guideline
iCPD	Confirmed progressive disease
IEC	Independent Ethics Committees
IFN-γ	Interferon gamma
IMP	Investigational Medicinal Product
irAEs	Immune-Related Adverse Events
IRB	Institutional Review Boards
iUPD	Unconfirmed progressive disease
kg	Kilogram
L	Liter
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
Min	Minimum
mL	milliliter
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed cell death ligand 1
PFS	Progression free survival
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
RBC	Red Blood Corpuscle

RECIST	Response evaluation criteria in solid tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SD	Stable Disease
SMQ	Standardized MedDRA Queries
TPR	Timepoint to Response
TPS	Tumor proportion score
TTR	Time to response
WBC	White blood cell

1 Introduction

This document presents the statistical analysis plan (SAP) for Immutep, Protocol No. TACTI-002 (IMP321-P015); Keynote-PN798: 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 alfa (IMP321) in combination with pembrolizumab (PD-1 antagonist).

Version 1 of this analysis plan is based on the final protocol version 3.0 dated 28th July 2020 and electronic case report form (eCRF) version 5 dated 6th June 2019.

Version 2 of this analysis plan is based on the final protocol version 4.0 dated 30th April 2021 and electronic case report form (eCRF) version 6 dated 23rd March 2021.

Version 3 of this analysis plan is based on the final protocol version 5.0 dated 18th Aug 2023 and electronic case report form (eCRF) version 6 dated 23rd March 2021. This version is also updated to include additional analyzes and subgroup variables. Certain analyzes presented in Version 2 have been deleted in the list of outputs in section 5.

The SAP provides the description of every analysis including interim, primary and follow up analyzes.

2 Study Objectives

The primary objective of this study is:

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

The secondary objectives of this study are:

- 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.

The exploratory objective of this study is:

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

2.1 Primary Endpoints

The primary endpoint of this study is:

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

2.2 Secondary Endpoints

The secondary endpoints of this study are:

- 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 assessments.
- To assess time to response (TTR) and duration of response (DOR) according to iRECIST and RECIST 1.1.
- To assess ORR according to RECIST 1.1.
- To assess the disease control rate (DCR) 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 (Cmax), time to reach Cmax (tmax), systemic clearance (CL), elimination half-life (t1/2) and volume of distribution (VD) of eftilagimod alfa.

2.3 Exploratory Endpoints

The exploratory endpoints of this study are:

- To assess programmed cell death ligand 1 (PD-L1) expression assessed by central laboratory.
- CCI
- To assess Gene signature according to PanCancer Immune code set assessed by a central laboratory.
- To assess circulating level of Helper T Cells Type 1 (Th1) biomarkers [i.e., interferon gamma (IFN-γ), C-X-C motif chemokine 10 (CXCL-10)] assessed by a central laboratory.
- CCI

3 Study Design

3.1 Discussion of Study Design

The study was designed according to Simon's optimal two-stage design[1]. During the first stage of the study the number of N1 subjects were recruited for each indication into this multicenter, open label, phase II study. In case there were more responses than threshold r1 observed in subjects recruited in the initial stage (N1), additional subjects (N2) were to be recruited. Following the completion of the initial stage, the decision to recruit the additional subjects (N2) was 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 met a predefined threshold, an extension of this cohort could be set up to combine the patients of stages 1, 2, and newly enrolled patients 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, subjects must have had either:

Part A: Histologically- or cytologically-confirmed diagnosis of NSCLC stage IIIB not amenable to curative treatment (unresectable) or stage IV not amenable to Epidermal Growth Factor Receptor (EGFR)/ Anaplastic Lymphoma Kinase (ALK) based therapy, treatment naïve for advanced/metastatic disease.

Note: subjects 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, could be recruited provided that all other necessary requirements were 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, durvulumab, 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 discontinued PD-1/PD-L1 after being treated for at least 2 cycles for reasons other than progression, they could enroll in the study if initial progression occurred within 12 weeks after end of PD-1/PD-L1 therapy and progression was confirmed. Only patients receiving treatment in true second-line setting could be enrolled to Part B. Patients who 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 were not eligible for Part B.

Note: In Parts A and B subjects with neuroendocrine or sarcomatoid NSCLC tumor types were not eligible. Patients with undifferentiated lung carcinoma with certain neuroendocrine features could 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, and larynx that was considered incurable by local therapies after failure of prior platinum-based therapy.

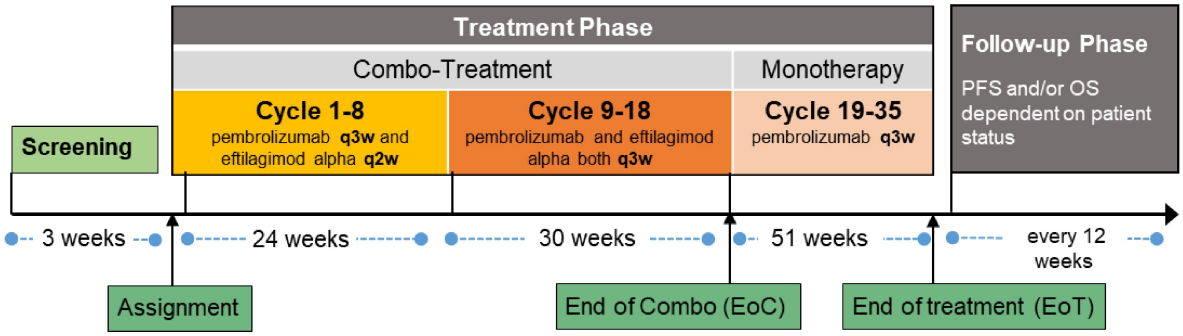
Note: in all three parts subjects would be enrolled regardless of their PD-L1 expression.

3.2 Study Treatment

Part A+B+C:

Subjects received pembrolizumab and eftilagimod alfa starting from cycle 1 day 1 as follows:

- 200 mg pembrolizumab every 3 weeks intravenously (IV) (30 min) for up to 35 cycles; 1 cycle = 3 weeks;
- 30 mg of eftilagimod alfa (efti, IMP321) every 2 weeks subcutaneously (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.



Legend: 1 cycle = 3 weeks; q2w = every 2 weeks; q3w = every 3 weeks.

Figure 1: Study flow chart for Part A, B and C.

Screening of subjects for eligibility to enter this study was done in the three weeks prior to cycle 1 day 1. Subjects were enrolled in parallel except for the first three subjects in each part who were enrolled at least 1 week apart. A subject stayed 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 end of the combination therapy (cycle 18) end of combination (EOC) therapy assessments were to be performed. Three (3) weeks after end of any study treatment (cycle 35) an end of treatment (EOT) visit was to be performed. Upon start of study treatment, subjects will be followed for PFS and OS. PFS will be radiologically assessed at the study sites until 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 [partial response (iPR), complete response (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 unconfirmed progressive disease (iUPD). Subjects who have iUPD should stay on treatment (if clinically stable) until progression is confirmed (confirmed progressive disease (iCPD), provided they have met the conditions detailed in protocol Section 8.1.3.

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

Safety procedures are described in Section 9 of the protocol.

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.

The DMC reviewed available safety data of all subjects (part A-C) after 18 subjects completed at least two cycles (6 weeks) of therapy. In addition, the DMC reviewed the efficacy and safety data after the last subject N1 was enrolled or the minimum number of responses is reached for each part of the study, whatever was first. Subjects included in this decision needed at least one tumor imaging after treatment was initiated. The DMC gave a recommendation for each part of the study whether stage 2 could be opened. The 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 subjects, the sponsor will consult with appropriate regulatory authorities prior to early termination of the study based on any DMC recommendation.

The Sponsor could, 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 subjects, 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.

Subject 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.

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

3.3 Study Schedule

Subjects were screened for suitability for participation in the study within -21 to -1 days prior to the first administration of pembrolizumab and eftilagimod alfa (Visit 1: Day 1 of Cycle 1).

Screening assessments will include:

- Obtaining written informed consent prior to any study specific procedure (including screening procedures) being performed. *Note: Subject can be consented up to 35 days before cycle 1 day 1 to allow planning of fresh tumor biopsy and/or perform computed tomography (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-screening 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.

Each treatment cycle consisted of 3 weeks. After enrolment, each subject was to visit the hospital according to the schedule of assessments.

3.3.1 Screening (Day: -21 to -1)

- Confirmation of written informed consent form (ICF) of subject and Investigator (including ICF for PK sampling where applicable);
- Inclusion & exclusion criteria;
- Medical history & demographics;
- Physical examination including height and weight;
- Eastern Cooperative Oncology Group (ECOG) performance status;
- AEs;
- Prior Concomitant medications/procedures;
- 12- lead ECG (single);
- Vital signs;
- Laboratory testing
    - Hematology, biochemistry, coagulation and urinalysis;
    - Thyroid function test;
    - Pregnancy;
    - Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) (where applicable);
    - Gene expression profiling.
- Radiological assessment;

- Tumor tissue sample.

3.3.2 Day 1 of Cycles 1 to 8

Prior to pembrolizumab and eftilagimod alfa (efti, IMP321) administration:

- Confirmation of eligibility and assignment to treatment – ONLY cycle 1;
- Physical examination including weight;
- ECOG performance status;
- AEs;
- Concomitant medication/procedures;
- 12-lead ECG;
- Vital signs;
- Laboratory testing:
  - hematology, biochemistry, coagulation and urinalysis;
  - Thyroid function tests – ONLY Cycle 2, 4, 6 and 8;
  - Autoantibodies – ONLY pre-dose cycle 1;
  - Pregnancy testing (urine);
  - Anti-drug (efti) antibodies – ONLY pre-dose cycle 1 and 5;
  - Th1 biomarker – ONLY pre-dose Cycle 1 and 5;
  - Gene expression profile – ONLY pre-dose Cycle 5.
- Pembrolizumab infusion;
- For subjects who participate in the PK sampling please see Sections 3.3.6 and 3.3.7;
- Efti injection ≥ 30 minutes after pembrolizumab infusion was completed ONLY cycle 1, 3, 5 and 7.

  Subjects should remain in the ward for a minimum of 30 min after last study drug administration.

3.3.3 Day 8 of Cycles 2, 4, 6 and 8

Prior to eftilagimod alfa (efti, IMP321) administration:

- AEs;
- Concomitant medication/procedures;
- Vital signs;
- Laboratory testing:
  - Anti-drug (efti) antibodies – ONLY pre-dose Cycle 2.
- Efti administration.

  Subjects should remain in the ward for a minimum of 30 min after injection.

3.3.4 Day 15 of Cycles 1, 3, 5 and 7

Prior to eftilagimod alfa (efti, IMP321) administration:

- AEs;
- Concomitant Medication/procedures;
- Vital signs;
- Laboratory testing:
  - Anti-drug (efti) antibodies – ONLY pre-dose Cycle 3.
- Efti administration.

  Subjects should remain in the ward for a minimum of 30 min after injection.

3.3.5 Day 1 of Cycles 9 to 18

Prior to pembrolizumab and eftilagimod alfa (efti, IMP321) administration:

- Physical examination including weight;
- ECOG performance status;
- AEs;
- Concomitant medication/procedures;
- 12-lead ECG;
- Vital signs;
- Laboratory tests:
  - Hematology, biochemistry, coagulation and urinalysis;
  - Thyroid function test – ONLY cycle 10, 12, 14, 16 and 18;
  - Pregnancy testing (urine);
  - Autoantibodies – ONLY Cycle 9;
  - Anti-drug (efti) antibodies – ONLY pre-dose Cycle 9 and 13;
  - Th1 biomarkers – ONLY Cycle 9 and 13.
- Pembrolizumab infusion.
- For subjects who participate in the PK sampling please see Sections 3.3.6 and 3.3.7.
- Efti injection ≥30 minutes after pembrolizumab infusion was completed.

  Subjects should remain in the ward for a minimum of 30 min after last study drug administration.

3.3.6 Subjects Participating in PK Part Only - Day 1 of Cycles 1, 5 and 9

Prior to eftilagimod alfa (efti, IMP321) administration: blood sampling pre-dose.

After administration: blood sampling at 1, 2, 4 and 8h post-injection.

3.3.7 Subjects Participating in PK Part Only - Days 2, 3 4 and 5 of Cycles 1, 5 and 9

After administration: blood sampling at 24, 48, 72, 96 hours post-injection.

Adverse events and concomitant medications are to be recorded as well.

3.3.8 Cycle 19 to 35 Day 1 (Every 3 Weeks)

Prior to pembrolizumab administration:

- Physical examination including weight;
- ECOG performance status;
- AEs;
- Concomitant medication/procedures;
- 12-lead ECG;
- Vital signs;
- Laboratory tests:
    - Hematology, biochemistry, coagulation and urinalysis;
    - Pregnancy testing (urine);
    - Thyroid function test – ONLY cycle 20, 22, 24, 26, 28, 30, 32 and 34;
    - Autoantibodies – ONLY Cycle 19;
    - Anti-drug (efti) antibodies – ONLY Cycle 19;
    - Th1 biomarkers – ONLY Cycle 19.
- Pembrolizumab infusion.

3.3.9 End of Treatment Visit

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

The following assessments will be performed at the EOT visit:

- AEs;
- Concomitant medication/procedures;
- Physical examination including weight;
- ECOG performance status;
- 12-lead ECG;
- Vital signs;
- Laboratory tests:

- Hematology, biochemistry, coagulation and urinalysis;
- Pregnancy testing (urine);
- Thyroid function test;
- Autoantibodies;
- Anti-drug (efti) antibodies (ADA);
- Th1 biomarkers.

3.3.10 PFS - Follow-Up

Subjects 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 anti-cancer therapy, pregnancy, withdrawal of consent, loss to follow-up, death from any cause, or the end of the study (whichever occurs first).

For subjects 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 (the start of the treatment, Cycle 1 Day1) 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;
- ECOG performance status and body weight;
- AE follow-up.

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

3.3.11 OS - Follow-Up

After documented PD, or after start of any next line of anti-cancer therapy, the subject 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, subjects may be contacted occasionally outside of this follow up (FU) window.

Subjects who progress while on study treatment may receive any other next line of therapy, as clinically indicated, after performing the EOT visit. Subject 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 their duration/outcome will be recorded.

3.3.12 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.

3.4 Concomitant Medication

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 subject's primary physician. However, the decision to continue the subject on study treatment requires the mutual agreement of the investigator, the Sponsor and the subject.

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 Investigational Medicinal Product (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.

Subjects 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 subject'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:

- Subjects 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.
- Subjects 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 not 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 ECIs as defined in section 9.3 of the protocol.

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.

3.5 Study Analysis Populations

There are 4 analysis populations defined for this study:

3.5.1 Full Analysis Set

The Full Analysis Set (FAS) includes all assigned subjects 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 analyzes of efficacy endpoints, demographics and baseline characteristics.

3.5.2 Evaluable Analysis Set (EAS)

The Evaluable Analysis Set (EAS) is a subset of the FAS and includes all subjects who received at least one dose of trial drug and has at least one evaluable post-baseline tumor assessment.

Subjects with best overall response as "NE (Not Evaluable)" or "NA (Not applicable)" will be excluded from the EAS population. This population will be the secondary population for efficacy analyzes based on overall response e.g., for ORR and PFS.

3.5.3 Per-Protocol Population

The Per-protocol (PP) population includes subjects in the FAS without major violation criteria (see Section 4.17). This population will not be used for any analyzes.

3.5.4 Safety Population

The safety set is defined analogously to the FAS and includes all assigned subjects 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 analyzes of safety.

3.6 Withdrawn Subjects

Subjects should be withdrawn from the study if the subject:

- withdraws consent.
- is non-compliant with the study visits and procedures (refer to Section 7.4 of the protocol).
- becomes pregnant.

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

The reason for subject withdrawal will be noted on the eCRF. The Investigator should attempt to follow withdrawn subjects 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 subjects. Investigators shall make reasonable attempts to contact lost-to-follow-up subjects for evaluation of OS.

Subjects 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 subject has not progressed, otherwise OS follow-up) if:

- is non-compliant with the study treatments;
- the subject 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;
- subject has attained a confirmed complete response and has 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 subjects should then continue with PFS and/or OS follow-up as applicable.

The data collected until the withdrawal of the subject will be used in the analysis.

The number of patients to be included in the study may be increased 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 including iRECIST assessment, were to be replaced.

3.7 Randomization

Not applicable as study is not randomized; subjects were assigned to the single treatment arm according to the indication as assessed during screening.

3.8 Blinding

Not applicable as study is a single treatment arm, open-label study.

3.9 Sample Size

The null hypothesis that the true response rate is [p0] will be evaluated against a one-sided alternative. In the first stage, [n1] subjects will be accrued. If there are [r1] or fewer responses in these [n1] subjects, the study will be stopped. Otherwise, [n - n1] additional subjects will be accrued for a total of [n]. The null hypothesis will be rejected if [r2 + 1] or more responses are observed in [n] subjects. This design yields a type I error rate of CCI and power of CCI when the true response rate is [p1]. Calculations reveal that 17 subjects in the initial step and an additional 19 subjects, in total 36 subjects 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 (r_1/N_1 and r_2/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	r_2	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. For 2nd line NSCLC there are no available publications for pembrolizumab alone in PD-1/PD-L1 refractory subjects, 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. For HNSCC relevant publications from Keynote-012 and Keynote-040 were used for p_0.

Sample size calculations were performed using software R version 3.3.3 (2017-03-06), Package:

Kieser M, Wirths M, Englert S, Kunz CU and Rauch G (2017). "OneArmPhaseTwoStudy: An R Package for Planning, Conducting, and Analysing 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 was 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.

4 Statistical Methodology

4.1 Planned Analyzes

Baseline and demographic data will be summarized using the FAS population. Efficacy data will be summarized using the FAS and EAS populations (only final analysis). Safety data will be summarized using the safety population.

For continuous variables, data will be summarized by the number of subjects, mean, standard deviation, median, and minimum and maximum values. For categorical variables, data will be tabulated in frequency tables to display the number and percentage of subjects for each category.

Statistics will be displayed by part:

- Part A: NSCLC 1st line;
- Part B: NSCLC 2nd line;
- Part C: HNSCC 2nd line;

And by stage of inclusion. The stages will be derived as:

- Subjects include in Part A:
  - All subjects with Cycle 1 Day 1 (C1D1) date ≤ 30Jun19 should be included in stage 1.
  - All subjects with C1D1 date > 01Nov19 ≤ 30Sep20 should be included in stage 2.
  - All subjects with C1D1 date ≥ 01Oct20 should be included in stage 3 (extension).
- Subjects included in Part C:
  - All subject with C1D1 date ≤ 31Dec19 should be included in stage 1.
  - All subject with C1D1 date > 01Feb20 should be included in stage 2.
- Subjects included in Part B
  - All subject with C1D1 date ≤ 01Nov20 should be included in stage 1.
  - All subject with C1D1 date > 01Nov20 should be included in stage 2.

For some outputs overall (by stage for 1 part) or overall (all stages, all parts) will be generated.

Notes:

- Where a change from baseline is presented, if not specified in the footnote of the output, the results for baseline are defined as the last measurement obtained before the first dose of any study drug (efti or pembrolizumab, whichever occurs first); unscheduled assessment to be considered for determination of baseline only; the baseline is data collected at Cycle 1 Day 1 pre-dose for PK or TH1 biomarkers samples or at Screening for the gene expression.
- All data will be listed;
- The analyzes may be performed separately for each indication (dependent on availability of the results); if this is the case, only the column(s) for the relevant indication(s) will be included on tables;
- Separate clinical study reports (CSRs) may be written for each indication (dependent on availability of the results).

4.2 Timing of Analysis

Descriptive interim analyzes (including abbreviated reports, 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.

An initial descriptive interim analysis was performed with a data cut-off August 31, 2020. This interim analysis contained all subjects from stages who had completed enrolment (Part A and C). At least 90% of the subjects had a follow-up of ≥18 weeks (e.g. 2 post baseline tumor stagings) at data cut-off.

The primary analysis was conducted once all patients were enrolled and had a follow-up of ≥18 weeks (e.g., 2 post baseline tumor stagings) at data cut-off. The cut-off for the primary analysis was set July 1, 2022.

A follow up analysis (FU1) is planned to be conducted using the data cut-off date November 30, 2023. This analysis will have a minimum follow-up of 24 months, meaning that all subjects will have completed treatment.

CCI

This is an exploratory phase II umbrella trial. No formal hypothesis will be assessed.

Both DMC and the interim analysis do not affect the analysis of the primary endpoint. No adjustments for multiplicity are needed.

4.3 Disposition of Subjects

The number of subjects screened, assigned to treatment, in each analysis population, who completed/discontinued treatment and the reasons for any premature discontinuation from treatment will be presented by indication.

These analyzes will be produced in all screened subjects. Disposition will also be summarized by country and center.

4.4 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be summarized by indication. This will include:

- Demographics: country, age, sex, race, ethnicity, male sexual status, female reproductive status, height, weight, body mass index (BMI), ECOG performance status, smoking status, duration of smoking at screening and number of cigarettes per day.
- Medical/surgical history: past medical history and concomitant diseases summarized by system organ class and preferred term.
- Cancer history:
    - time since initial diagnosis (months), location (for HNSCC only), confirmed histological/cytological diagnosis, histology grade, tumor subtype, status of EGFR mutation (NSCLC only), status of ROS1 mutation (NSCLC only), status of BRAF mutation (NSCLC only), status of ALK translocation (NSCLC only), tumor stage at initial diagnosis, tumor stage at Screening; any metastatic disease (yes/no) and metastatic disease sites at screening (number and location of most frequent disease sites); brain metastases (Y/N); liver metastases (Y/N); HPV (HNSCC oropharyngeal only).

      PD-L1 central assessment_cat1 (by group: NSCLC: <1%, 1-49%, ≥50%, TPS, Not tested, Not evaluable; HNSCC: <1, 1-19, ≥20 CPS, Not Evaluable/Not Tested).

      PD-L1 – derived central or local_cat2 (by group: NSCLC: <1%, 1-49%, ≥50%, TPS, Not tested, Not evaluable; HNSCC: <1, 1-19, ≥20 CPS, Not Evaluable/Not Tested); priority for central PD-L1 and if not available take local data. HPV local assessment (Positive, Negative, and Not tested).
- History of HIV, HCV, HCV RNA, HBsAg.
- Active disease sites at baseline (any non-measurable lesions, Number of organs (site/location) affected by disease (target or non-target) and Site/Location.
- Other derived variables:
    - Descriptive statistics for absolute counts of lymphocytes, neutrophils and monocytes, NLR at baseline.
    - Lactate dehydrogenase (LDH) abnormality normal (≤250 U/L) or abnormality high (>250 U/L).
    - Primary or secondary resistance (Part B only) definition in Table 1:
    - Prior cetuximab (Prior Cetuximab, No Prior Cetuximab) Part C only.
    - Tumor Growth Kinetics Ratio – numeric and categorical
    - Overall ADA (Positive/Negative).
    - Prior therapy - Anti-PD-X

- Descriptive statistics of Maximum ALC Change from baseline up to and including Cycle 5 Day 1
- Maximum ALC Change from baseline up to and including Cycle 5 Day 1 lloq
- (<0.2/≥0.2 10^9/L)
- Baseline absolute lymphocyte count (<1.0/≥1.0 10^9/L).
- Baseline NLR (<4.0/≥4.0)
- NLR at Cycle 2 (<4.0/≥4.0)
- TH1 biomarker relative change at Cycle 5 Day 1 Pre-DOSE (PCHG < or ≥40%)

Table 1: Definitions of primary and secondary resistance in advanced disease setting (acc. to SITC) (3)

Resistance Type	Drug Exposure Requirement	Best Response
Primary	≥ 6 weeks	PD or SD for < 6 months
Secondary	≥ 6 months	CR, PR, SD for > 6 months

- Resistance is related to the last "Previous Systemic Anticancer Therapy Regimen" before efti and is related to the best response of their last therapy and how long they were on this treatment before progression.
  - Drug Exposure (months) = (Date of Progression - Start Date of last previous Systemic Anticancer Therapy) +1.
- As per SITC the resistance is to be calculated for patients who had prior immunotherapy.
- For SD, check the duration between (Start Date/Time of Clinical Event - Start Date/Time of last previous Systemic Anticancer Therapy.

- Active Disease site at baseline.

Notes:

- Age is recorded on the eCRF and will not be re-calculated.
- BMI will be calculated as weight (kg)/height^2 (m).
- Medical history is coded according to MedDRA version 21.1 or higher.
- Past medical history is defined as any medical/surgical history not marked as ongoing at time of screening.
- Concomitant diseases are medical/surgical history records marked as ongoing at the time of screening.
- Duration of Smoking at screening (Years) = (Years of stop date/Years of IC - Years of start date). (Years of IC for current smokers).
- NLR = Neutrophil Count/Lymphocyte Count at baseline.

  For Part A, the baseline characteristics are to be additionally presented by PD-L1 TPS (<1%, 1-49%, ≥50%, ≥1%). Note: this will be done for both central only and central or local.

4.5 Previous Anti-Cancer Therapy

- Any prior anti-cancer surgery (Y/N),
  [remark: from the eCRF 'Were there any prior cancer related surgeries = "Yes" and Intent of Surgery = "Palliative or Curative"]
- Any prior anticancer radiotherapy (Y/N);
- Any prior systemic anti-cancer therapy:
  - thereof chemotherapy (%)
    - thereof platinum (carboplatin, cisplatin or others) based therapy (%)
    - thereof targeting microtubules (e.g., paclitaxel, vinorelbine or others therapy (%)
    - thereof antimetabolites (5-FU, pemetrexed or others) therapy (%)
    - thereof DNA interacting (gemcitabine) therapy (%)
    - thereof other (%)
      - thereof drug name A
      - thereof drug name B
  - thereof targeted therapy (%)
    - thereof anti-EGFR therapy (cetuximab or others) (%)
    - thereof other (%)
      - thereof drug name A
      - thereof drug name B
  - thereof immune checkpoint inhibitors (%)
    - thereof CTLA-4 based therapy
    - thereof PD-1/PD-L1 therapy (%)
      - thereof PD-1 therapy
      - thereof PD-L1 therapy
    - thereof other (%)
      - thereof drug name A
      - thereof drug name B
  - any other systemic therapy (%)
    - thereof drug name A
    - thereof drug name B
- Any prior systemic therapy given with (neo-)adjuvant / curative intent;
  [remark: from the eCRF regimen name is not empty and Intention of therapy = "all except palliative"]
- Any prior systemic therapy given with palliative / symptomatic intent
  [remark: from the eCRF regimen name is not empty and Intention of therapy = "PALLIATIVE"]
- Last therapy prior to inclusion by intervention type:

  - radiotherapy alone
  - surgery alone
  - systemic therapy alone
  - combination of radiotherapy and/or surgery and/or systemic therapy

  [remark: Include all stop dates of radiotherapy, surgery and systemic therapy < inform consent date and select the last one;

- Last therapy prior to inclusion duration and best overall response
- Last therapy by intention of therapy:
  - adjuvant/neoadjuvant
  - curative
  - palliative/symptomatic
- In case palliative / symptomatic by BoR
  - PD, SD, PR, CR, unknown (The best response assessment linked to the last record in time is used.)
- In case last therapy contained systemic therapy split by:
  - Contained chemotherapy
  - Contained immune checkpoint inhibitor (ICI)
  - Contained targeted therapy
  - Single agent therapy
  - Combination therapy
- Duration between any last anticancer intervention (i.e., surgery and/or radiotherapy) until date of informed consent (days)
  [remark: inform consent date - last stop dates of radiotherapy, surgery+1]
- Duration between any last systemic anticancer therapy until date of informed consent (days)
  [remark: inform consent date - last stop dates of systemic anticancer therapy+1]
- Number of prior systemic therapies for underlying cancer (0;1;2;>2)

Notes:

- Number of prior systemic therapies for underlying cancer: Consecutive records will be regarded as 1 line of therapy unless the time interval between the records exceeds 30 days. The eCRF grouping variable Regimen Number is used to identify same treatments lines.

4.6 Concomitant Medication

Prior medications comprise all therapies that were stopped prior to cycle 1 day 1. Medications used at study entry are defined as medication that started prior to the treatment period (cycle 1 day 1) and still ongoing at 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). Any medications started more than 28 days after last dose of any treatment are defined as post-treatment.

Incidence of prior medications, medications used at study entry and concomitant medication will be presented by indication, ATC name and preferred drug name (using the FAS). ATC name will be the highest coded ATC name (i.e., ATC level 4 if the medication is coded to level 4) (using the safety set).

Post-treatment medications will be listed only.

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior, used at study entry, concomitant or post-treatment, it will be assumed that it is concomitant.

Notes:

- Medications are coded using WHO Drug dictionary, version SEP2018 or higher.

4.7 Concomitant Procedures

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 procedures will be summarized by system organ class and preferred term (using the safety set).

Notes:

- Procedures are coded according to MedDRA version 21.1 or higher.

4.8 Exposure and Compliance

For efti and pembrolizumab separately, exposure is defined as:

- Exposure (weeks) = (date of last dose – date of first dose + 1)/7.
- Follow-up time (months) = (date of last available information in the study – date of first dose + 1)/30.4375.

Note: Subjects who miss more than a total of 3 injections of efti or 2 infusions of pembrolizumab within the first 8 cycles or a total of more than 5 doses of efti or pembrolizumab until cycle end of combination treatment (end of cycle 18) will be regarded as treatment non-compliant. Subjects will need to end the treatment as per protocol.

For efti, the following summaries will be produced:

- Descriptive summary of exposure (weeks);
- Descriptive summary of exposure (months);
- Descriptive summary of the total number of doses received;
- Number and percentage of subjects with 1, 2 or > 2 treatment delay/interruptions and number and % of pts permanently discontinued
- Number and percentage of subjects with 1, 2, 3 or >3 missed doses within the first 8 cycles;

- Number and percentage of subjects with 1, 2, 3, 4, 5 or >5 missed doses during the whole combination treatment period;
- Number and percentage of compliant and non-compliant subjects as described above;
- Number and percentage of subjects withdrawn from treatment due to non-compliance.

For pembrolizumab, the following summaries will be produced:

- Descriptive summary of exposure (weeks);
- Descriptive summary of exposure (months);
- Descriptive summary of the total number of doses received;
- Number and percentage of subjects with 1, 2 or >2 treatment delay/interruptions and number and % of pts permanently discontinued
- Number and percentage of subjects with 1, 2 or >2 missed doses within the first 8 cycles;
- Number and percentage of subjects with 1, 2, 3, 4, 5 or >5 missed doses during the whole combination treatment period;
- Number and percentage of compliant and non-compliant subjects as described above;
- Number and percentage of subjects withdrawn from treatment due to non-compliance.

Exposure and compliance will also be described for efti and pembrolizumab combined, the definitions provided above will apply. First/last dose refers to efti or pembrolizumab whichever one come first.

In case there is a next visit treatment entered in row (i.e., no gap in numbering of visits), no matter how long after previous treatment, which should be regarded as delay/interruption and not missed dose.

4.9 Efficacy Analysis

iRECIST and RECIST 1.1 are used for the tumor evaluation see Section 8.1 of the protocol (efficacy assessment). iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs.

All efficacy analyzes are based on local Investigator assessments. The interim analysis, primary and FU1 analyzes have also been evaluated by a Blinded Independent Central Reviewer (BICR).

Efficacy analyzes will be performed for each part (A, B or C) of the study independently. It may be split by stage for ORR.

4.9.1 Primary Endpoint Analysis

4.9.1.1 Primary Efficacy Endpoint: iORR according to iRECIST

The primary endpoint, iORR, is defined as the proportion of subjects with a best objective response (iBOR) of complete response (iCR) or partial response (iPR) according to iRECIST.

The iBOR is the best response as determined by the Investigator (and BICR, if assessed) between the date of assignment and date of objective measurement of iUPD or iCPD by iRECIST, the date of subsequent therapy or date of lost to follow-up, whichever comes first.

The overall responses at each visit are used to determine the iBOR. iBOR will be assigned using the following categories (from best to worst responses): complete response (iCR), partial response (iPR), stable disease (iSD), unconfirmed disease progression (iUPD), confirmed disease progression (iCPD) or not evaluable (NE) at each timepoint.

iSD can only be assigned as iBOR if the patient has a best response of iSD that is at least 6 weeks after the date of treatment assignment (on or after study Day 43, 42 days after date of first dose of study treatment). If the patient had no subsequent post-baseline data, then the iBOR will be NE.

For BICR results iBOR of "Non-iCR/Non-iUPD" should be considered “iSD” for programming and will be included in the iDCR.

Unconfirmed iBOR:

Defined as the iBOR recorded during the observation period defined in Section 4.9.1.1.

Confirmed iBOR:

Applicable only for subjects with an iBOR of iCR or iPR, a response may be considered confirmed if observed at subsequent radiological assessments at least 4 weeks apart and there are no assessments with an overall response of iSD or iUPD between the 2 assessments. Alternatively, an iBOR of iCR that does not meet the criteria for confirmed iCR may still meet the criteria of confirmed iPR if there is a response of iPR that is confirmed with an overall response of iCR at least 4 weeks apart and there are no assessments with an overall response of iSD or iUPD between the 2 assessments. An iBOR of iPR meets the criteria of confirmed iPR if the overall response of iPR is confirmed with an overall response of iPR at least 4 weeks apart and there are no assessments with an overall response of iSD or iUPD between the 2 assessments.

See Table 2 below for the derivation of confirmed iBOR when iCR or iPR is believed to be the iBOR.

Table 2: iBOR when confirmation of iCR and iPR is required

Response: First Time Point	Subsequent Time Point	BOR	Also Requires
iCR	iCR	iCR	Normalization of tumor markers. All tumor nodes <10 mm.
iCR	iPR	iSD, iUPD or iPR (see comment*)	
iCR	iSD	iSD provided minimum criteria for iSD duration met, otherwise, iUPD	
iCR	iUPD	iSD provided minimum criteria for iSD duration met, otherwise, iUPD	
iCR	NE	iSD provided minimum criteria for iSD duration met, otherwise NE	
iPR	iCR	iPR	
iPR	iPR	iPR	
iPR	iSD	iSD	
iPR	iUPD	iSD provided minimum criteria for iSD duration met, otherwise, iUPD	
iPR	NE	iSD provided minimum criteria for iSD duration met, otherwise NE	
NE	NE	NE	
* If iCR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting iPR criteria relative to baseline, makes the disease iUPD at that point (since disease must have reappeared after iCR). Best response would depend on whether minimum duration (at least 6 weeks after start of treatment) for iSD was met.			

For each part (and stage dependent on the time of analysis) separately and for both the FAS and EAS populations, iORR will be summarized by binomial response rate with two-sided 95% exact confidence intervals (CIs) using the Clopper-Pearson method.

4.9.2 Secondary Endpoints Analyzes

All secondary analyzes will be performed descriptively and based on local assessments and BICR, if assessed.

4.9.2.1 Secondary Efficacy Endpoint: ORR According to RECIST 1.1

ORR follows the same definition used by iRECIST in Section 4.9.1.1, using however the RECIST 1.1 criteria to assess responses (4).
ORR, per RECIST 1.1, is defined as the proportion of subjects with a best objective response (BOR) of complete response (CR) or partial response (PR).

The overall responses at each visit are used to determine the BOR. BOR will be assigned using the following categories (best to worst): CR, PR, SD, PD and NE.

The principles of unconfirmed and confirmed responses (for BOR PR or CR) are as previously described per iRECIST. Similar analyzes will be conducted for ORR as described for the primary endpoint iORR.

4.9.2.2 Secondary Efficacy Endpoint: Disease Control Rate (DCR) According to iRECIST and RECIST 1.1

iDCR is defined as the percentage of subjects achieving an unconfirmed iCR, iPR or iSD (iSD duration from C1D1 lasts at least 6 weeks) as iBOR.
iDCR will be analyzed using the same methods specified for iORR.
DCR (per RECIST 1.1) will be analyzed using the same methods specified for iDCR.

4.9.2.3 Secondary Efficacy Endpoint: Progression Free Survival (PFS) According to iRECIST and RECIST 1.1

iPFS is defined as the time from the date of first treatment (C1D1) to the date of first documentation of disease progression per iRECIST (iUPD, except when there is a subsequent timepoint with iSD, iPR or iCR and no iCPD in between) or date of death due to any cause, whichever occurs first:

$$PFS\ (months) = \frac{Date\ of\ First\ Documented\ Progression/Death/Censoring\ Date - Date\ of\ start\ of\ treatment\ (C1D1) + 1}{30.4375}$$

For subjects without progression or death, iPFS will be censored as described in Table 3.

The iPFS rate at 3, 6, 12, 18, 24, 36 and 48 months and corresponding 95% CIs will be estimated using the Kaplan-Meier method. The total number of patients who experienced the event and number of patients censored will also be reported. iPFS will also be displayed graphically using a Kaplan-Meier plot.

As per iRECIST guidelines, disease progression can be confirmed by the site 4–8 weeks from the scan showing iUPD if the subject is clinically stable. 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. Subjects who have unconfirmed disease progression and are clinically stable can continue treatment until progression is confirmed.

PFS will be summarized similarly to iPFS based on RECIST 1.1.

Table 3: Censoring Rules for PFS for RECIST and iRECIST

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 first treatment	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

Situation	Date of Progression or Censoring	Outcome
Death or progression after two or more consecutive missed radiological assessments	Date of last radiological assessment visit without documentation of disease progression that is before the missed visit	Censored
Two consecutive missed, scheduled radiological assessment (+ windows)	Date of last radiological assessment	Censored
Alive and without documentation of disease progression	Date of last radiological assessment	Censored
Additional censoring rules specific for iRECIST handling of PD assessments		
If progression = iUPD and iUPD is identified as the last iRECIST assessment (not confirmed)	Date of the first radiological assessment of iUPD in sequence leading to a final iUPD result[2]	Progressed
If progression = iCPD and the iUPD then iCPD are consecutively confirmed	Date of the first radiological assessment of iUPD in sequence leading to a final iCPD result[2]	Progressed
If progression = iUPD* but neither confirmed nor identified as PD for subsequently performed iRECIST assessments	Date of last radiological assessment	Censored[2]
[1] May be only one or multiple, consisting of a pattern of repeated iUPD tumor assessment results. [2] Censoring may also be required per rules above.		

Table 4 below describes examples of censoring rules for iPFS using iRECIST Guidelines.

Table 4: Example of censoring rules for iPFS using iRECIST

Date 1	Outcome 1	Date 2	Outcome 2	Date 3	Outcome 3	Used for PFS per iRECIST
01.01.2020	iUPD	15.03.2020	iPR	Pt left study	NA	No event → censored with 15.03.2020
01.01.2020	iUPD	pt left study	NA	NA	NA	PD event 01.01.2020
01.01.2020	iUPD	15.03.2020	iPR	25.06.2020	iUPD	PD event 25.06.2020
01.01.2020	iUPD	15.03.2020	iCPD			PD event 01.01.2020

4.9.2.4 Secondary Efficacy Endpoint: Duration of Response (DoR) according to iRECIST and RECIST 1.1

The response will be further evaluated by iDoR based on iRECIST. iDoR is calculated only for subjects with a confirmed iBOR of iCR or iPR up to an objective documentation of progression or death, whichever occurs first.

$$iDoR\ (months) = \frac{Date\ of\ First\ Disease\ Progression/Death/Censoring\ \ date\ -\ Date\ of\ First\ iCR\ or\ iPR\ +1}{30.4375}$$

Progression and censoring dates for iDoR are determined the same way as iPFS (see Table 3).

For subjects who receive subsequent anticancer therapy prior to objective disease progression, iDoR will be censored at the date of the last tumor assessment date prior to the date of subsequent therapy.

For each indication separately and for the FAS population, iDoR will be summarized using the Kaplan-Meier method. The median time to event will be calculated along with 95% CIs using the Kaplan-Meier method. Mean (SD), 25th and 75th percentiles and minimum and maximum values will also be presented. In addition, the proportion of responders still in response at 3, 6, 9, 12, 18 and 24 months will be presented.

iDOR will also be displayed graphically using a Kaplan-Meier plot.

DoR will be presented in the same way as iDoR based on RECIST 1.1.

4.9.2.5 Secondary Efficacy Endpoint: Time to Response (TTR) According to iRECIST and RECIST 1.1

iTTR will be evaluated for the subset of patients categorized as confirmed responders for the assessment of iORR.

iTTR is defined as the time from start of treatment (C1D1) to first iCR or iPR response.

$$iTTR\ (months) = \frac{Date\ of\ First\ iCR\ or\ iPR\ -Date\ of\ start\ of\ treatment\ (C1D1)\ +1}{30.4375}$$

For each indication separately and for the FAS population, iTTR will be summarized using descriptive statistics including mean (SD).

TTR will be presented in the same way as iTTR based on RECIST 1.1.

4.9.2.6 Overal1 Survival (OS)

All subjects in the trial will be followed up for survival until death, end of the trial, withdrawal of consent, or loss to follow-up, whichever of these occurs first.

OS is defined as the time from the start of the treatment (C1D1) to the date of death due to any cause. For subjects still alive at the time of analysis, OS will be censored at the date the subject was last known to be alive.

$$OS\ (months) = \frac{Date\ of\ Death/Last\ Known\ to\ be\ Alive\ -Date\ of\ Start\ of\ Treatment\ (C1D1)\ +1}{30.4375}$$

Date of Last Known to be Alive is the last date with available information for a subject in the study.

For each separate indication, using the FAS population, 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. Mean (SD), 25th and 75th percentiles and minimum and maximum values will also be presented. The OS rate at 3, 6, 12, 18, 24, 36 and 48 months and corresponding 95% CIs will also be estimated using the Kaplan-Meier method.

OS will also be displayed graphically using a Kaplan-Meier plot.

4.9.3 Exploratory Efficacy Endpoint Analyzes

4.9.3.1 Exploratory Efficacy Endpoint: Circulating biomarkers

Plasma samples will be collected prior to dosing on Day 1 of Cycles 1, 5, 9, 13, end of combination (EOC) therapy and at EOT to assess for Th1 biomarkers (IFN-γ, CXCL10/IP10, CXCL11/iTAC) at the central laboratory (Charles River Laboratories). Results with < LLOQ or > ULOQ are set at the LoQ value for analysis purposes and can be identified in the listing.

In the subset of subjects with PK assessment, Th1 biomarkers may be additionally assessed in samples collected at selected time points after dosing with efti at cycle 1, cycle 5 and cycle 9.

Available results for each circulating TH1 biomarker of interest will be listed and summarized by indication, visit and time point (if applicable) using the FAS. Descriptive statistics (including quartiles) will be reported for absolute values and absolute and percentage change from baseline calculated as follows,

Percentage Change = 100* (Value at the visit – Value at Baseline)/Baseline value

4.9.3.2 Exploratory Efficacy Endpoint: Gene Expression Profiling

Whole blood samples were collected in PaxGene tubes for gene expression profile (GEP) analysis at the central laboratory (Covance/Labcorp, Indianapolis) prior to dosing at screening and cycle 5 day 1.
GEP analysis was done separately and is not part of this SAP.
A separate analysis report will be developed and will be included as appendix to the CSR.

4.9.3.3 Exploratory Efficacy Endpoint: CCI

CCI

CCI

CCI

CCI

CCI analyzed on FAS and EAS population.

4.9.4 Other Exploratory Endpoints

4.9.4.1 Exploratory Endpoint: Tumor PD-L1 Expression

Archival tumor material or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated was provided by subjects on a mandatory basis. PD-L1 expression was centrally analyzed by Covance, Geneva. Results will be displayed with an overall score CPS (HNSCC, Part C) and TPS (NSCLC, Parts A and B). Available locally obtained results will also be included.

PD-L1 expression status in tumor tissue will be provided as by subject including subject ID, stage and part of the trial, score and type of score (TPS/CPS) for centrally and locally obtained results. A pre-defined cutoff will be used to determine PD-L1 expression status (see Section 4.4).

Centrally assessed PD-L1 results (from Covance lab) should be primarily used. For subjects whose PD-L1 result was found not evaluable by the central lab, the PD-L1 result assessed in the local laboratory will be used. Two different populations will be used for efficacy analysis:

1. Central only
2. Central or local (meaning that for each patient where central was not available but local the local result will be used)

The data for local PD-L1 is collected in the eCRF as numerical and as categorical. It may happen that the numerical value is empty when the categorical value is negative, i.e., <1% for TPS. For the analysis and consistency, the derived categorical data which contains the items "<1% ; 1-49% and ≥50%, will be created by considering these data in the item the category "<1%". If numerical value is empty and categorial is "negative" then the derived variables will take a value "<1%" for categorial and 0 for numerical.

4.9.4.2 Exploratory Endpoint: Immunogenicity

Autoantibodies such as 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.

The formation of anti-drug antibodies (ADA) against efti and their neutralizing capacity (Neutralizing Antidrug Antibody, Nab) will be assessed at the central laboratory (Charles River Laboratories) 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.

Results for each immunogenicity parameters will be summarized by indication and per visit (including C1D1) as % positive, negative or non-tested samples (using the FAS) and as descriptive statistics for ADA-titer and Nab-titer (including quartiles). For ADA and Nab,

overall results will also be presented by considering the results of all post-baseline visits, for the categorical variable (i.e., ADA positive/negative or Nab positive/negative), if at least one post baseline timepoint (visit) is positive then subject need to be reported as positive; for the numeric values, the maximum value of all post-baseline visits will be considered for overall (peak ADA-titer or peak Nab-titer).

4.10 Pharmacokinetic Analysis

Pharmacokinetics analysis will be provided to Immutep by PhinC development according to analytical plan using the plasma concentration of LAG-3 results generated by Charles River Laboratories Saint Nazaire.
PK analysis was done separately and not part of this SAP.
A PK analysis report will be developed by PhinC and included as appendix to the CSR.

4.11 Subgroup Analysis

The subgroups listed below will be analyzed for ORR, PFS (per iRECIST and RECIST 1.1) and OS. DOR (per iRECIST and RECIST 1.1 is required for selected subgroups, defined in Table 5. All subgroup analysis will be done based on investigator assessment for the FAS population. The details for each subgroup and part are listed in Table 5.

The following subgroups will be analyzed:

- PD-L1 status (central only and central or local):
  - PD-L1 NSCLC (Part A)
    - Negative (<1% TPS); TPS 1-49%; TPS ≥50% and Positive (≥1% TPS).
  - PD-L1 NSCLC (Part B)
    - Negative (<1% TPS); TPS 1-49%; TPS <50%; TPS ≥50% and Positive (≥1% TPS).
  - PD-L1 HNSCC (Part C)
    - Negative (<1 CPS); 1-19 CPS; ≥20 CPS; <20 CPS and Positive (≥1 CPS).
- Sex:
  - Male
  - Female
- Smoking Status:
  - Never
  - Former
  - Current
  - Former + current
- Age:
  - <65 years
  - ≥65 years
- ECOG Performance Status at screening:
  - 0
  - 1
- Overall ADA (see Section 4.9.4.2):

  - Positive
  - Negative
- Region:
  - Spain
  - Non-Spain
- Tumor Type (Part A only):
  - Squamous
  - Non-Squamous

  [remark: this information will be derived from the eCRF 'Cancer History Log Form', subject with tumor type or sub-type "Squamous Cell Carcinoma" will be included in the item Squamous]
- Resistance (Part B only):
  - Primary
  - Secondary
- Prior cetuximab (Part C only):
  - Prior cetuximab
  - No prior cetuximab
- HPV status (for Part C subjects with primary oropharyngeal tumors only):
  - Positive
  - Negative
  - Not Done/Not tested

  [Remark: this information will be derived from the eCRF ' Histology Cytology assessment details Log Form' HNSCC: Status of HPV item (Positive=yes, Negative=no, Not Done/Not tested].

  The subgroup analysis for this category will be performed only if at least 10 subjects are identified with positive HPV.
- Prior Therapy (Part B only; please see derivation rules provided in Appendix 5.6.2):
  - Anti-PD-X-based treatment + chemo
  - Anti-PD-X-based therapy alone or + ICI
- Maximum Absolute Lymphocyte count (ALC) change (all parts):
  - Max. ALC on treatment (any post study treatment initiation value till C5D1 versus baseline (C1D1 or Screening in case baseline is not applicable):
    1. <0.2 10^9/L;
    2. ≥0.2 10^9/L.

Table 5. Summary of required analyzes per subgroup (Investigator only)

Subgroup	Part A	Part B	Part C
PD-L1 central only			
<1% **1-49%** **≥50%** **≥1%** **<50%**	ORR, PFS, DoR, OS	NA	NA

<1 **1-19** **≥20** **>1** **<20**	NA	NA	ORR, PFS, DoR, OS
PD-L1 central or local			
<1% **1-49%** **≥50%** **≥1%**	ORR, PFS, DoR, OS	NA	NA
<1% **1-49%** **<50%** **≥1%** **≥50%**	NA	ORR, PFS, OS	NA
<1 **1-19** **≥20** **<20**	NA	NA	NA
Sex	ORR, PFS, OS	ORR, PFS, OS	ORR, PFS, OS
Smoking status			
Former or current **Never**	ORR, PFS, OS	ORR, PFS, OS	NA
Former **Current** **Never**	NA	NA	ORR, PFS, OS
Age	ORR, PFS, OS	ORR, PFS, OS	ORR, PFS, OS
ECOG	ORR, PFS, OS	ORR, PFS, OS	ORR, PFS, OS
Overall ADA	ORR, PFS, OS	ORR, PFS, OS	ORR, PFS, OS
Region	ORR, PFS, OS	ORR, PFS, OS	ORR, PFS, OS
Tumor type	ORR, PFS, DoR, OS	NA	NA
Resistance	NA	ORR, PFS, OS	NA
Prior cetuximab	NA	NA	ORR, PFS, OS
HPV status	NA	NA	ORR, PFS, OS
Prior therapy	NA	ORR, PFS, OS	NA
ALC change	ORR, PFS, OS	ORR, PFS, OS	ORR, PFS, OS
Note: ORR, PFS and DoR to be presented by both iRECIST and RECIST 1.1.			

4.11.1 Efficacy (Investigator only) by ALC change under therapy

KM for OS and PFS (iRECIST and RECIST 1.1) based on "Maximum ALC Change from baseline up to Cycle 5 Day 1– cat" will be presented in table and figure by part.

Boxplot of Max ALC Change will be displayed for confirmed iBOR (iCR + iPR vs Others) and iDCR (iCR+ iPR+ iSD vs Others) by part.

4.11.2 Overall Survival (OS) by Response (Investigator assessment only)

OS will be summarized by best overall response according to iRECIST per local assessment as described below and will be presented in a table and figures.

Part A:

- Confirmed iCR + iPR;
- Unconfirmed iPR + iSD;
- iUPD/iCPD + iNA/iNE

Part B:

- Confirmed iPR + iSD;
- iUPD/iCPD + iNA/iNE;

Part C:

- Confirmed iCR + iPR;
- Unconfirmed iPR + iSD + iUPD/iCPD + iNA/iNE.

4.12 Tumor Growth Kinetics

Tumor growth kinetics (TGK) are to be calculated for each subject in Part B whose identical target lesions have been tracked from pre- to post-baseline by local assessment and BICR.

Table 6. Example to determine which patients should be included for TGK analysis

Reference scan target tumor lesions	Post-baseline target tumor lesions	Patient to be included?
Lung (left lower lobe lung nodule)	Lung (left lower lobe lung nodule)	Yes
Lung (lower right lobe) Lymph node (right hilar)	Lung (lower right lobe) Suprarenal gland (left adrenal)	Yes- but only including measurements from lung (lower right lobe)
Lung (left upper lobe)	Lung (left supra clavicular node)	No

The list of patients and their lesions which should be part of tumor growth kinetics analysis in Part B are indicated in the appendix Section 5.6.1.

This calculation is based on a ratio comparing pre-treatment tumor behavior to the on-study tumor behavior (5). The following definitions are part of this calculation:

T1: date and time of confirmatory pre-baseline scan*

TPRE: date and time of reference scan

T0: date and time of baseline

TPOST: date and time of best post-baseline scan

S1: sum of the largest diameter of target lesions at confirmatory pre-baseline scan*

SPRE: sum of the largest diameter of target lesions at reference scan

S0: sum of the largest diameter of target lesions at baseline

SPOST: sum largest diameter of target lesions of best post-baseline scan (best post baseline = smallest post baseline value).

*If the confirmatory pre-baseline scan data is not available for any reason, then the initial progression pre-baseline scan may be used (ensuring that the same lesions are followed).

Using the above definitions, TGKPRE is calculated as the difference of the sum of the largest diameters of the target lesions (according to iRECIST or RECIST 1.1) per unit of time (months) between pre-baseline and baseline imaging:

$$TGKPRE = (S1\text{-}SPRE) / (T1\text{-}TPRE).$$

$$TGKPOST(=(SPOST\text{-}S0) / (TPOST\text{-}T0).$$

The final calculation of TGK ratio (TGKR) is defined as the ratio,

$$TGK\ ratio\ (TGKR) = (TGKPOST/\ TGKPRE)$$

Shrinkage= TGKR<0
Deceleration= 0<TGKR<1
Acceleration=TGKR≥1

To present a figure on tumor dynamics, each applicable patient is to have three points:

1. Reference scan: Months from baseline (x-axis), % change from baseline (y-axis)
2. Baseline: Months from baseline (x-axis), % change from baseline (y-axis), i.e. (0.0)
3. Best post-baseline scan: Months from baseline (x-axis), % change from baseline (y-axis)

These 3 points are to be joined by a line that is color coded by the patient's TGKR.
Shrinkage= green
Deceleration= orange
Acceleration= red

TGK ratio will be derived and summarized as numeric and categorical parameter as described above. The corresponding figure will also be presented.

Tumor growth kinetics will also be analyzed using the data from BICR. Same tabulation and figure as described above will also be repeated using BICR data.

4.13 Safety Analysis

The safety endpoints of this study are the frequency, severity and duration of AEs, SAEs, ECIs and abnormalities in vital signs, physical examination, 12-lead ECG and safety laboratory and urine assessments.

4.13.1 Adverse Events

An 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, ECIs, TEAEs related to efti, TEAEs related to pembrolizumab, fatal TEAEs (i.e. AE grade 5 and/or AE outcome death), TEAEs leading to temporary and permanent discontinuation of treatment (each treatment separately) and discontinuation from study treatment, TEAEs according to worst severity and combinations of previously mentioned type of AEs. For each parameters causality information will be shown as specified below.

The number and percentage of subjects with at least 1 TEAE will be tabulated by preferred term and system organ class. For these tabulations, the number of subjects (i.e., subjects 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. For severity tabulations highest grades will be shown. Similar tables will be produced for serious TEAEs, fatal TEAEs, TEAEs leading to permanent discontinuation of treatment, discontinuation from study and events of clinical interest. The previously mentioned type of TEAEs might also be presented in combination with treatment-relatedness.

AEs will also be tabulated by severity and relationship to each study drug. At each level of tabulation, the event with the highest level of severity or strongest drug relationship will be presented. Possibly related and Related assessment in the clinical database translates to Related in the outputs. Causality information will be shown as (1) related to efti, (2) related to pembro, (3) related to trial treatment (i.e., efti and/or pembro) and (4) regardless of relationship (as applicable).

All AEs will be listed. In addition, detailed listings will be provided for subjects 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 of pembro and efti, respectively. Events with a time of onset within 24 hours from time of most recent efti injection will be flagged (using the flag: 24-hr) if the event time is missing and event date is the same as date of efti injection the event will be flagged.

Non-treatment emergent events (starting prior to exposure to study treatment) will be included in the subject listings and flagged but will not be included in the above summaries. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

AEs with a coded PT meeting the broad Standardized MedDRA Query (SMQ) “Hypersensitivity” will be listed. AEs occurring within 24 hours from most recent efti injection will be flagged.

AEs with a coded preferred term meeting the broad MedDRA SMQ “Extravasation events (injections, infusions and implants)” and including PT “Injection site reaction”, at least possibly related to efti and/or adverse events with indication “local injection site reaction in the clinical database will be listed.

Patients with a recurrent adverse reaction (i.e., adverse reactions at least possible related to efti) indicating systemic inflammatory response with onset date within 24 hours after efti injection will be listed.

Patients with adverse reaction indicating immune-related adverse event will be listed.

Non-treatment emergent events (starting prior to exposure to study treatment) will be included in the subject listings and flagged but will not be included in the above summaries. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

Systemic inflammatory response will be summarized and listed. Terms to be used for selection include chills, cytokine release syndrome, feeling cold, feeling hot, influenza like illness, malaise, myalgia, post-procedural complication, pyrexia.

Based on the selection above,

- ✓ A listing will be created with all events which are within 24 hrs from efti intake and are a matching term even if unrelated to efti, and even if only one event per patient.
- ✓ A table who include only the patients who have at least two such of events and both are related to efti, and both have start date 24 hrs from the intake of efti OR one matching term the verbatim of which includes "intermittent" (or variation thereof) and is related to efti and start is w/in 24 hrs from intake of efti

Patients with adverse reaction indicating immune-related adverse event will be listed.

Immune-Related Adverse Events (irAEs) will be summarized per groups term and pertaining PTs and per severity grades and listed. Grouping (in bold) and preferred MedDRA terms to be used for selection are listed in the Table 7:

Table 7: irAEs (Adverse reactions – at least possibly related to either pembro and/or efti)

irAEs (adverse reactions – at least possibly related to either pembro and/or efti)	
	Preferred Terms
Hypothyroidism	CCI
Hyperthyroidism	
Pneumonitis	
Infusion Reactions	

irAEs (adverse reactions – at least possibly related to either pembro and/or efti)
Preferred Terms
CCI
Colitis
CCI
Severe Skin Reactions (i.e., ≥gr 3)
CCI
Hepatitis
CCI
Thyroiditis
CCI
Adrenal Insufficiency
CCI

irAEs (adverse reactions – at least possibly related to either pembro and/or efti)
Preferred Terms
CCI
Hypophysitis
CCI
Nephritis
CCI
Myositis
CCI
Pancreatitis
CCI
Type 1 Diabetes Mellitus
CCI
Uveitis
CCI

irAEs (adverse reactions – at least possibly related to either pembro and/or efti)	
Preferred Terms	
CCI	
Sarcoidosis	
CCI	
Myocarditis	
CCI	
Encephalitis	
CCI	
Guillain-Barre Syndrome	
CCI	
Myasthenic Syndrome	
CCI	
Vasculitis	
CCI	
Myelitis	
CCI	
Meningitis	
CCI	
Rash	
CCI	
Pruritus	
CCI	
Vitiligo	
CCI	
Lichenoid keratosis	
CCI	
Musculoskeletal pain	
CCI	
Arthritis	
CCI	
Tendosynovitis	
CCI	

irAEs (adverse reactions – at least possibly related to either pembro and/or efti)
Preferred Terms
Oedema
CCI

Notes:

- Tables presented will contain both counts of subjects and events. Subjects who have multiple events in the same system organ class and preferred term will be counted only once in the subject counts.
- AEs coded using MedDRA version 21.1 or higher.
- Treatment-emergent principle All adverse events starting on or after first dosing are considered treatment-emergent adverse events (TEAE). All adverse events emerging during the screening period will only be listed, not presented in any of the tables. These events are no TEAEs. All tables will present TEAEs only.
- Treatment relatedness Following ICH-E3, the drug relatedness will be dichotomized as follows: Drug related: at least possibly drug related, OR with missing drug relatedness (= worst-case) Not drug related: not related. In tabulations this dichotomized parameter will be used, but in the listings the original parameter will be presented.
- Worst-case principle When cross-tabulating AE preferred terms versus an AE attribute (e.g., severity), the worst-case is always applied within each analysis period. I.e., when a subject has two times the same AE preferred term in the same analysis period, then the subject is reported only once: only with the worst severity. If this happens in two different analysis periods, the AE is reported twice: once in each analysis period. In the analysis the worst-case will be defined.

4.13.2 Laboratory Findings

Results (values and change from baseline) from the following laboratory parameters, recorded at screening and pre-dose on day 1 of each cycle except thyroid function tests which are performed at screening and every 2nd cycle starting with cycle 2, will be summarized by indication and visit.

Hematology:

Leukocytes/White blood cell (WBC) count with differential including absolute neutrophil count (ANC), absolute lymphocyte count, NLR ratio (absolute neutrophil count/ absolute lymphocyte count) absolute monocyte count, absolute eosinophil count, absolute basophil count; Erythrocytes/red blood cells (RBC) count, platelet count, hemoglobin and hematocrit.

Biochemistry:

Creatinine, random glucose, urea, alkaline phosphatase, alanine aminotransferase (ALT = GPT), aspartate aminotransferase (AST = GOT), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), total bilirubin, total protein, albumin/globulin ratio, sodium, potassium, chloride, calcium, phosphate, bicarbonates, uric acid, cholesterol, triglycerides, plasma amylase and c-reactive protein (CRP).

Hepatic toxicity will be assessed based on the following Liver Function Tests (LFTs): Albumin, ALT, AST, ALP and Total Bilirubin (TBL). For these parameters, NCI-CTCAE grades are defined.

Tabulation of liver function parameters for Hy's law interpretations will be generated presenting frequencies of subjects with post- C1D1 parameters:

- Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) >3, >5, >10 and >20 times upper limit of the normal range (ULN), Bilirubin (BILI) >2x ULN;
- Simultaneous occurrence of ALT or AST >3x ULN and BILI >2.0x ULN;
- Simultaneous occurrence of ALT or AST >3x ULN and BILI >2.0x ULN subcategorized by ALP <2x ULN and >2x ULN.

Post-baseline potential Hy's Law cases will be identified using the following definition:

- either AST or ALT > 3×ULN with concurrent ALP < 2 × ULN and concurrent total bilirubin ≥ 2×ULN.

Coagulation:

Prothrombin time (PT) and activated partial thromboplastin time (APTT).

Thyroid Function:

Triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH).

Urinalysis:

Dipstick, *or* standard urinalysis (UA) with reflex microscopy and culture if clinically indicated. Gross urine examination (dipstick) and other tests should include visual inspection, pH, protein, ketones, glucose, bilirubin, nitrite, urobilinogen, occult blood, WBCs.

Changes from baseline will also be summarized where applicable.

Where applicable, CTCAE grades will be assigned to laboratory parameters. Certain parameters may have both high and low CTC grades assigned and where this occurs, high and low grades will be summarized separately. Shift tables comparing the worst post-baseline grade against the baseline grade will be prepared and will be provided for final analysis.

If possible, CTCAE Grade will be calculated for following parameters,

- Hematology parameters (all on two directions Low and High).
  - Leukocytes/White blood cell (WBC) count with differential including absolute neutrophil count (ANC), absolute lymphocyte count, ratio (absolute neutrophil count/ absolute lymphocyte count), absolute monocyte count, absolute eosinophil count, absolute basophil count; Erythrocytes/red blood cells (RBC) count, platelet count, hemoglobin and hematocrit.
- Biochemistry:
  - On two directions (Low and High): Creatinine, random glucose and urea;

  - On one direction (High): alkaline phosphatase, alanine aminotransferase (ALT = GPT), aspartate aminotransferase (AST = GOT), triglycerides and plasma amylase.
- Thyroid Function (all on two directions Low and High): Triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH).

Categorical laboratory parameters will be summarized by shift tables comparing the result/abnormality at each visit against the result/abnormality at baseline.

Serology results at Screening are described in Section 4.4.

Pregnancy test results will be listed only.

Notes:

- All results outside predefined normal ranges will be flagged in the data listings;
- Repeat laboratory results within a visit will not be used in any summary calculations; Unscheduled and repeat results will be listed only;
- Any other laboratory results will be listed only;
- CTCAE Grade version 4.03 will be used for derivation of the laboratory parameters;

4.13.3 Vital Signs

Results for systolic and diastolic blood pressure, temperature, pulse rate, body weight and derived BMI will be summarized by indication and visit. Changes from baseline will also be summarized.

4.13.4 ECG Results

The quantitative ECG assessments (heart rate, PR interval, RR interval, QRS duration and QT interval) will be summarized by indication and visit. Changes from baseline will also be summarized.

Investigator interpretation is collected for each parameter individually will be derived to create an overall investigator interpretation at each visit as,

- in case any of the parameters for the given ECG assessment is marked as “abnormal, clinically significant”, the whole test should be considered as “abnormal, clinically significant”;
- if none of the parameters are “abnormal, clinically significant” but at least one is indicated as “abnormal, not clinically significant”, the whole ECG assessment should be considered as “abnormal, not clinically significant”;
- if all the parameters are “normal”, then the whole ECG assessment should be considered “normal”;

The overall investigator interpretation will be listed.

4.13.5 ECOG Performance Status

The number and percentage of subjects with each ECOG PS response at each visit will be presented. In addition, the number and percentage of subjects who have improved, deteriorated and stayed the same compared to baseline will be presented at each post-baseline visit.

4.13.6 Physical Examination

Data collected from the physical examination will be listed only.

4.14 Adjustment for Covariates

There is no statistical analysis planned and hence no adjustment for covariates.

4.14.1 Center Effects

This study will be conducted at approximately 12 centers. Subjects from all centers will be pooled. No adjustment for centers will be conducted.

4.15 Protocol Violations or Deviations

A protocol deviation (PD) list is created at beginning of the study to collect all PD identified on site and/data issue. The PD list is reviewed on an ongoing basis by sponsor and Fortrea team. During this review, the deviations are classified as important and non-important.

Important deviations will be tabulated and listed.

4.16 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 manage any other patterns of missing data for tumor response (i.e., it will be censored in the efficacy analysis).

Partial dates will be imputed only to allow classification of medications as prior, used at study entry, concomitant or post-treatment and AEs as treatment-emergent or not. The following rules will apply:

- Medications:
  - Start Dates:
    - Missing day will be imputed by 1st day of the month; if same month and year than the date of first dose then the date of first dose will be used.
    - Missing month will be imputed by January; if same year as first dose, then the date the date of first dose will be used.
    - For completely missing date, then date of first dose will be used.
  - End Dates:
    - Missing day will be imputed by last day of the month; if same month and year than date of the last intake of study drug then the date of last dose will be used.
    - Missing month will be imputed by last month of the year; if same year as date of the last intake of study drug, then the date of last dose will be used.
    - For completely missing date then no substitution (i.e., treatment considered as still ongoing)

If (partially) missing dates do not allow to allocate the therapy as the last prior to inclusion, then the therapy is assumed before therapy with non-missing date information. Therapy 30 days before last therapy record prior to inclusion (date of date of first dose) is also considered

as last therapy. In case there is more than one therapy with the same end date all are considered as last therapy prior to inclusion. For best overall response assessment recorded on the last therapy record prior to inclusion, only prior anticancer systemic regimens will be considered.

After the imputation of missing partial start date by date of first intake, if the start date is after the end date of medication, then the start data = end date;

- AEs:
  - When AE start date time is missing, the AE will be allocated to the first treatment period in the study.
  - Start Dates:
    - missing day will be imputed by 1st day of the month; if same month and year than the date of first dose then the date of first dose will be used.
    - missing month will be imputed by January; if same year as first dose, then the date the date of first dose will be used.
    - if date is completely missing the date of first dose will be used.
    - This approach will ensure that AEs with partial dates are assigned as treatment-emergent if the partial date is ambiguous.
  - End Dates:
    - missing day will be imputed by last day of the month; If same month and year than last visit date, then last visit date will be used;
    - missing month will be imputed by December; if same year than last visit date then the date last visit will be used.
    - if date is completely missing the date of last visit will be used.
  - Missing time will not be imputed.
  - Date of last visit is the date of last visit as recorded in eCRF.

Imputed dates will not be listed and will not be used to calculate any durations.

4.17 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final CSR.

4.18 Changes in Conduct or Planned Analyzes from the Protocol

4.18.1 Confirmatory Pre-Baseline RECIST 1.1

A note to file was created to correct the following inconsistency in the eCRF.

On form “Confirmatory Pre-Baseline RECIST 1.1 Response Assessment" (form only applicable for Part B subjects) the following issues were noticed:

1. the lower header of the form “Confirmatory Pre-Baseline RECIST 1.1 Response Assessment" includes a typo “iRECIST 1.1” instead of “RECIST 1.1”
2. for target and non-target lesion evaluation the options in the drop-down menus are given as per iRECIST and not as per RECIST 1.1

Both issues could only be solved with an eCRF update and migration, but sponsor confirmed that they do not want a migration to solve that issues at this time. The following solutions have been discussed and agreed:

Issue #1: The typo in the header can be accepted without any changes.

Issue #2: The inconsistent drop-down menus will remain as they are, and Statistics will hard code the information as following:

***Folder*: Confirmatory Pre-Baseline Radiological Assessments** ***Form*: Confirmatory Pre-Baseline RECIST 1.1** ***Form header*: CONFIRMATORY PRE-BASELINE iRECIST 1.1 RESPONSE ASSESSMENT** ***Item*: Evaluation of Target Lesions [CCPIR.CONFEVLTL]**	
***eCRF drop down menu options*:**	**to be hard coded to:**
(iCR) COMPLETE RESPONSE	(CR) COMPLETE RESPONSE
(iPR) PARTIAL RESPONSE	(PR) PARTIAL RESPONSE
(iUPD) UNCONFIRMED PROGRESSIVE DISEASE	(PD) PROGRESSIVE DISEASE
(iCPD) CONFIRMED PROGRESSIVE DISEASE	(PD) PROGRESSIVE DISEASE
(iSD) STABLE DISEASE	(SD) STABLE DISEASE
(NE) NOT EVALUABLE	(NE) NOT EVALUABLE
iNON-CR/iNON-PD	NON-CR/iNON-PD

***Folder:* Confirmatory Pre-Baseline Radiological Assessments** ***Form:* Confirmatory Pre-Baseline RECIST 1.1** ***Form header*: CONFIRMATORY PRE-BASELINE iRECIST 1.1 RESPONSE ASSESSMENT** ***Item*: Evaluation of Non-Target Lesions [CCPIR.CONFEVLNTL]**	
***eCRF drop down menu options*:**	**to be hard coded to:**
(iCR) COMPLETE RESPONSE	(CR) COMPLETE RESPONSE
iNON-CR/iNON-PD	NON-CR/NON-PD
(iUPD) UNCONFIRMED PROGRESSIVE DISEASE	(PD) PROGRESSIVE DISEASE
(iCPD) CONFIRMED PROGRESSIVE DISEASE	(PD) PROGRESSIVE DISEASE
(NE) NOT EVALUABLE	(NE) NOT EVALUABLE

4.18.2 Per Protocol Analysis

The analysis for efficacy endpoints will not be repeated for per-protocol analysis population. Another population of analysis was derived, the Evaluable Analysis Set (EAS) is a subset of the FAS and includes all subjects who received at least one dose of trial drug and has at least one evaluable post-baseline tumor assessment. The analysis initially planned to be run in per protocol population will be run on the EAS, e.g. for ORR, DCR, TTR, DoR, PFS and OS.

4.18.3 Non-CR/Non-PD in BICR

For BICR data patients with BOR of "Non-CR/Non-PD" are included in stable disease category, so, considered as part of the Disease Control Rate for both RECIST 1.1 and iRECIST Guidelines.

4.19 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**

PROC UNIVARIATE DATA=dset NOPRINT;
VAR var1 var2 var3 …varn;
BY byvar; (optional)
OUTPUT OUT=outname
N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;

PROC UNIVARIATE DATA=dset NOPRINT;
VAR var1 var2 var3 …varn;
BY byvar; (optional)
OUTPUT OUT=outname
N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std PPD
PPD
RUN;

- **Tables that need frequency counts:**

PROC FREQ DATA=dset NOPRINT;
BY byvar; (optional)
*TABLES var1*var2;*
OUTPUT OUT=outname;
RUN;

- **Tables that need exact or asymptotic 95% CIs between groups for proportions:**

PROC FREQ DATA=dset;
BY byvar; (optional)
*TABLES var1 * var2 / MEASURES RISKDIFF ALPHA=* CCI
EXACT MEASURES;
RUN;

Notes: 1 Estimates are computed for 2x2 tables only
2 This code also gives exact 95% CIs within group for binomial proportions

- **Tables that need 95% CIs within group for binomial proportions:**

PROC FREQ DATA=dset;
BY byvar; (optional)
TABLES var1;
EXACT BINOMIAL;
RUN;

- **Tables that need number of events/censored and probabilities of failure/survival at cut off times:**

```
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=LT INTERVALS=3,6,9,12,
18,24,;
    TIME duration*censor (0 or 1);
    ID subject;
    STRATA treatment;
RUN;
```

- **Tables that need life table with estimates of survival, with CIs and log rank test:**

```
PROC LIFETEST DATA=dset OUTSURV=LIFE METHOD=KM;
     TIME duration*censor (0 or 1);
    ID subject;
    STRATA treatment;
RUN;
```

- **The geometric mean is the antilog of the arithmetic mean of the logs:**

```
DATA dset;
    SET dset old;
    LOGx = LOG(x);
RUN;

PROC UNIVARIATE DATA=dset NOPRINT;
    VAR LOGx;
    OUTPUT OUT=outname
    MEAN=logmean;
RUN;

DATA outname;
    SET outname;
    geomean = EXP(logmean);
RUN;
```

5 Tables and Listings

5.1 Table Format

All output will be produced using SAS version 9.4 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e., draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the Sponsor name. The source listing number will appear in the bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7-* or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used to fit on both UK and US paper sizes.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean median and quartiles will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible, data will be decimally aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted as described in the programming notes in the shells. For data collected over several visits, SDTM. VISITNUM should be used to sort by visit. All listings should have the source dataset (ADaM or SDTM) referenced in a footnote. All tables, listings and figures will be collated into Microsoft Word documents (tables and listings as per ICH E3 Structure and content of clinical study reports sections, one for figures).

5.3 Tables

Output Number	Output Title	U/R	Analysis	BICR data
Table 14.1.1.1	Subject Disposition (All Subjects)	U	FU1	
Table 14.1.1.2	Subject Disposition by Country (All Subjects)	U	FU1	
Table 14.1.1.3	Subject Disposition by Center (All Subjects)	R	FU1	
Table 14.1.1.4	Important Protocol Violations (All Subjects)	U	FU1	
Table 14.1.2.1.1	Demographics and Baseline Characteristics (Full Analysis Set)	U	FU1	
Table 14.1.2.1.2	Demographics and Baseline Characteristics by PD-L1 (Central results)– Part A Only	U	FU1	
Table 14.1.2.1.3	Demographics and Baseline Characteristics by PD-L1 (Central or Local results) – Part A Only (Full Analysis Set)	R	FU1	
Table 14.1.3.1	Past Medical History (Full Analysis Set)	U	FU1	
Table 14.1.3.2	Concomitant Diseases (Full Analysis Set)	U	FU1	
Table 14.1.4.1	Cancer History (Full Analysis Set)	U	FU1	
Table 14.1.4.2	History of HIV, HCV, HBV (Full Analysis Set)	U	FU1	
Table 14.1.4.3	Active Disease sites at Baseline (Full Analysis Set)	U	FU1	
Table 14.1.5.1	Previous Cancer Surgery, Radiotherapy and Systemic Anti-cancer Therapy (Full Analysis Set)	U	FU1	
Table 14.1.5.2	Previous systemic anti-cancer therapy (Full Analysis Set)	U	FU1	
Table 14.1.6.1	Prior Medications other than anti-cancer therapy (Full Analysis Set)	U	FU1	
Table 14.1.6.2	Medications used at study entry and Concomitant Medications (Full Analysis Set)	U	FU1	
Table 14.1.7	Concomitant Procedures (Full Analysis Set)	U	FU1	
Table 14.1.8.1	New Anti-cancer Therapy (Full Analysis Set)	U	FU1	
Table 14.1.8.2	Subsequent anti-cancer procedures (Full Analysis Set)	U	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Table 14.1.9.1	Efti Exposure and Compliance (Full Analysis Set)	U	FU1	
Table 14.1.9.2	Pembrolizumab Exposure and Compliance (Full Analysis Set)	U	FU1	
Table 14.1.9.3	Efti and Pembrolizumab Exposure and Compliance (Full Analysis Set)	R	FU1	
Table 14.1.10.1	Other Derived Variables (Full Analysis Set)	U	FU1	
Table 14.2.1.1.1	Overall Response Rate - iRECIST confirmed (Full Analysis Set)	U	FU1	Yes
Table 14.2.1.1.2	Overall Response Rate - iRECIST unconfirmed (Full Analysis Set)	R	FU1	Yes
Table 14.2.1.1.3	Overall Response Rate - RECIST 1.1 confirmed (Full Analysis Set)	R	FU1	Yes
Table 14.2.1.1.4	Overall Response Rate - RECIST 1.1 unconfirmed (Full Analysis Set)	R	FU1	Yes
Table 14.2.1.2.1	Overall Response Rate - iRECIST confirmed (Evaluable Analysis Set)	R	FU1	Yes
Table 14.2.1.2.2	Overall Response Rate - iRECIST unconfirmed (Evaluable Analysis Set)	R	FU1	Yes
Table 14.2.1.2.3	Overall Response Rate - RECIST 1.1 confirmed (Evaluable Analysis Set)	R	FU1	Yes
Table 14.2.1.2.4	Overall Response Rate - RECIST 1.1 unconfirmed (Evaluable Analysis Set)	R	FU1	Yes
Table 14.2.2.1.1	Duration of Response according to iRECIST (Full Analysis Set - - Responders Only)	U	FU1	Yes
Table 14.2.2.1.2	Duration of Response according to RECIST 1.1 (Full Analysis Set - Responders Only)	R	FU1	Yes
Table 14.2.3.1.1	Time to Response according to iRECIST (Full Analysis Set)	U	FU1	Yes
Table 14.2.3.1.2	Time to Response according to RECIST 1.1 (Full Analysis Set)	R	FU1	Yes
Table 14.2.4.1.1	Progression Free Survival according to iRECIST (Full Analysis Set)	U	FU1	Yes
Table 14.2.4.1.2	Progression Free Survival according to RECIST 1.1 (Full Analysis Set)	R	FU1	Yes
Table 14.2.4.2.1	Progression Free Survival according to iRECIST (Evaluable Analysis Set)	R	FU1	Yes
Table 14.2.4.2.2	Progression Free Survival according to RECIST 1.1 (Evaluable Analysis Set)	R	FU1	Yes
Table 14.2.5.1	Overall Survival (Full Analysis Set)	R	FU1	
Table 14.2.6.1	Autoantibodies and Anti-drug Antibodies against Efti (Full Analysis Set)	U	FU1	
Table 14.2.7.1.1	Circulating Biomarkers – Absolute values and change from Baseline (Full Analysis Set)	R	FU1	
Table 14.2.7.1.2	Circulating Biomarkers – Percentage change from Baseline (Full Analysis Set)	R	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Table 14.2.8.1.1.1.1	Overall Response Rate by PD-L1 – Central - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.1.1.2	Overall Response Rate by PD-L1 – Central - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.1.1.2.1	Overall Response Rate by PD-L1 - Central or Local - Part A: NSCLC 1st line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.1.2.2	Overall Response Rate by PD-L1- Central or Local- Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.2.1	Overall Response Rate by Sex - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.2.2	Overall Response Rate by Sex - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.2.3	Overall Response Rate by Sex - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.1.3.1	Overall Response Rate by Smoking Status - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.3.2	Overall Response Rate by Smoking Status - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.3.3	Overall Response Rate by Smoking Status - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.1.4.1	Overall Response Rate by Age - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.4.2	Overall Response Rate by Age - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.4.3	Overall Response Rate by Age - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.1.5.1	Overall Response Rate by ECOG Performance Status - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.5.2	Overall Response Rate by ECOG Performance Status - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.5.3	Overall Response Rate by ECOG Performance Status - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.1.6.1	Overall Response Rate by Overall ADA - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.6.2	Overall Response Rate by Overall ADA - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.6.3	Overall Response Rate by Overall ADA - Part C: HNSCC (Full Analysis Set)	R	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Table 14.2.8.1.7.1	Overall Response Rate by Region - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.7.2	Overall Response Rate by Region - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.7.3	Overall Response Rate by Region - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.1.8.1	Overall Response Rate by Tumor Type - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.9.1	Overall Response Rate by Resistance - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.10.1	Overall Response Rate by Prior cetuximab - Part C: HNSCC (Full Analysis Set)	U	FU1	
Table 14.2.8.1.11.1	Overall Response Rate by HPV status - Part C: HNSCC (Full Analysis Set)	U	FU1	
Table 14.2.8.1.12.1	Overall Response Rate by Prior Therapy - Part B: NSCLC 2nd line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.13.1	Overall Response Rate by Maximum Absolute Lymphocyte count (ALC) change - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.1.13.2	Overall Response Rate by Maximum Absolute Lymphocyte count (ALC) change - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.1.13.3	Overall Response Rate by Maximum Absolute Lymphocyte count (ALC) change - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.2.1.1.1	Survival Analysis Endpoints by PD-L1 - Central - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.1.1.2	Survival Analysis Endpoints by PD-L1 – Central - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.2.1.2.1	Survival Analysis Endpoints by PD-L1 – Central or Local - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.1.2.2	Survival Analysis Endpoints by PD-L1- Central or Local- Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.2.2.1	Survival Analysis Endpoints by Sex - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.2.2	Survival Analysis Endpoints by Sex - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.2.2.3	Survival Analysis Endpoints by Sex - Part C: HNSCC (Full Analysis Set)	R	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Table 14.2.8.2.3.1	Survival Analysis Endpoints by Smoking Status - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.3.2	Survival Analysis Endpoints by Smoking Status - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.2.3.3	Survival Analysis Endpoints by Smoking Status - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.2.4.1	Survival Analysis Endpoints by Age - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.4.2	Survival Analysis Endpoints by Age - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.2.4.3	Survival Analysis Endpoints by Age - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.2.5.1	Survival Analysis Endpoints by ECOG Performance Status - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.5.2	Survival Analysis Endpoints by ECOG Performance Status - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.2.5.3	Survival Analysis Endpoints by ECOG Performance Status - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.2.6.1	Survival Analysis Endpoints by Overall ADA - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.6.2	Survival Analysis Endpoints by Overall ADA - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.2.6.3	Survival Analysis Endpoints by Overall ADA - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.2.7.1	Survival Analysis Endpoints by Region - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.7.2	Survival Analysis Endpoints by Region - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.2.7.3	Survival Analysis Endpoints by Region - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.2.8.1	Survival Analysis Endpoints by Tumor Type - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.9.1	Survival Analysis Endpoints by Resistance - Part B: NSCLC 2nd line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.10.1	Survival Analysis Endpoints by Prior cetuximab - Part C: HNSCC (Full Analysis Set)	U	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Table 14.2.8.2.11.1	Survival Analysis Endpoints by HPV status - Part C: HNSCC (Full Analysis Set)	U	FU1	
Table 14.2.8.2.12.1	Survival Analysis Endpoints by Prior Therapy - Part B: NSCLC 2nd line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.13.1	Survival Analysis Endpoints by Maximum Absolute Lymphocyte count (ALC) change - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.2.13.2	Survival Analysis Endpoints by Maximum Absolute Lymphocyte count (ALC) change - Part B: NSCLC 2nd line (Full Analysis Set)	R	FU1	
Table 14.2.8.2.13.3	Survival Analysis Endpoints by Maximum Absolute Lymphocyte count (ALC) change - Part C: HNSCC (Full Analysis Set)	R	FU1	
Table 14.2.8.3.1	Overall Survival (OS) by Response - Part A: NSCLC 1st line (Full Analysis Set)	U	FU1	
Table 14.2.8.3.2	Overall Survival (OS) by Response - Part B: NSCLC 2nd line (Full Analysis Set)	U	FU1	
Table 14.2.8.3.3	Overall Survival (OS) by Response - Part C: HNSCC (Full Analysis Set)	U	FU1	
Table 14.2.9.1.1	[redacted]	R	FU1	
Table 14.3.1.1	Summary of Treatment-emergent Adverse Events (Safety Population)	U	FU1	
Table 14.3.1.2	Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)	U	FU1	
Table 14.3.1.3	Tabulation of all treatment-related Treatment-emergent adverse events (Safety Population)	U	FU1	
Table 14.3.1.4	Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.1.5	Fatal Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.1.6	Treatment-emergent Adverse Events Leading to Permanent Discontinuation of Efti by System Organ Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.1.7	Treatment-emergent Adverse Events Leading to Permanent Discontinuation of Pembrolizumab by System Organ Class and Preferred (Safety Population)	R	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Table 14.3.1.8	Treatment-emergent Adverse Events Leading to Discontinuation from Study by System Organ Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.1.9	Treatment-emergent Events of Clinical Interest by System Organ Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.1.10	Treatment-emergent Adverse Events by Severity, System Organ Class and Preferred Term (Safety Population)	U	FU1	
Table 14.3.1.11	Local injection site reactions Treatment-emergent Adverse Events by Severity, System Organ Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.1.12	Treatment-emergent Adverse Events irrespective of relatedness to study drug by Severity, System Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.1.13	Treatment-emergent Adverse Events related to Eftilagimod and/or Pembrolizumab by Severity, System Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.1.14	Treatment-emergent systemic inflammatory response events with in 24 hrs from efti administration (Safety Population)	R	FU1	
Table 14.3.1.15	Treatment-emergent irAEs (Adverse reactions – Related to either pembro and/or efti) (Safety Population)	R	FU1	
Table 14.3.1.16	Treatment Emergent Adverse events with CTCAE Grade ≥ 3 by system organ class and preferred term (Safety Population)	R	FU1	
Table 14.3.1.17	Treatment Emergent Adverse events with CTCAE Grade ≥ 3 by Relationship to Efti, to pembro, to efti and/or pembro by System Organ Class and Preferred Term (Safety Population)	R	FU1	
Table 14.3.5.1.1	Hematology Results and Changes from Baseline (Safety Population)	U	FU1	
Table 14.3.5.1.2	Biochemistry Results and Changes from Baseline (Safety Population)	R	FU1	
Table 14.3.5.1.3	Coagulation Results and Changes from Baseline (Safety Population)	R	FU1	
Table 14.3.5.1.4	Thyroid Function Results and Changes from Baseline (Safety Population)	R	FU1	
Table 14.3.5.1.5	Microscopic Urinalysis Results and Changes from Baseline (Safety Population)	R	FU1	
Table 14.3.5.2	Liver Function Test Elevations (Safety Population)	U	FU1	

Sponsor:	Immutep S.A.S.	Protocol Number:	TACTI-002 (IMP321-P015); Keynote-PN798

Output Number	Output Title	U/R	Analysis	BICR data
Table 14.3.5.3.1	Shift Table of Laboratory Test Results between Baseline and worst NCI-CTCAE grading – Hematology (Safety Population)	U	FU1	
Table 14.3.5.3.2.1	Shift Table of Laboratory Test Results between Baseline and worst NCI-CTCAE grading – Biochemistry I (Safety Population)	R	FU1	
Table 14.3.5.3.2.2	Shift Table of Laboratory Test Results between Baseline and worst NCI-CTCAE grading – Biochemistry II (Safety Population)	U	FU1	
Table 14.3.5.3.2.3	Shift Table of Laboratory Test Results between Baseline and worst NCI-CTCAE grading – Thyroid Function (Safety Population)	R	FU1	
Table 14.3.5.3.3	Laboratory Results – Hematology – Shift Table (Safety Population)	U	FU1	
Table 14.3.5.3.4	Laboratory Results – Biochemistry – Shift Table (Safety Population)	R	FU1	
Table 14.3.5.3.5	Laboratory Results – Coagulation – Shift Table (Safety Population)	R	FU1	
Table 14.3.5.3.6	Laboratory Results – Thyroid Function – Shift Table (Safety Population)	R	FU1	
Table 14.3.5.3.7	Laboratory Results – Urinalysis – Shift Table (Safety Population)	R	FU1	
Table 14.3.6	Vital Signs Results and Changes from Baseline (Safety Population) e	U	FU1	
Table 14.3.7	12-lead ECG Results and Changes from Baseline (Safety Population)	U	FU1	
Table 14.3.8.1	ECOG Performance Status (Safety Population)	U	FU1	

FU1 = Follow up analysis 1

5.4 Listings

Output Number	Output Title	U/R	Analysis	BICR data
Listing 14.3.2.1	Listing of Deaths	U	FU1	
Listing 14.3.2.2	Listing of Fatal Treatment-emergent Adverse Events	U	FU1	
Listing 14.3.2.3	Listing of Serious Treatment-emergent Adverse Events	R	FU1	
Listing 14.3.2.4.1	Listing of Treatment-emergent Adverse Events Leading to Discontinuation from treatment (efti or Pembro)	R	FU1	
Listing 14.3.2.4.2	Listing of Treatment-emergent Adverse Events Leading to Discontinuation from Study	U	FU1	
Listing 14.3.2.5	Listing of Treatment-emergent Events of Clinical Interest	R	FU1	
Listing 14.3.4	Listing of Abnormal Laboratory Results	U	FU1	
Listing 16.2.1.1	Subject Disposition	U	FU1	
Listing 16.2.1.2	Listing of subjects who permanently discontinued treatment Efti and Pembro (Safety Population)	R	FU1	
Listing 16.2.2	Important Protocol Deviations	U	FU1	
Listing 16.2.3	Exclusions from Analysis Populations	U	FU1	
Listing 16.2.4.1	Demographics/Baseline Characteristics	U	FU1	
Listing 16.2.4.2	Smoking History	U	FU1	
Listing 16.2.4.3	Medical/Surgical History	U	FU1	
Listing 16.2.4.4.1	Cancer History – Part I	U	FU1	
Listing 16.2.4.4.2	Cancer History – Part II	U	FU1	
Listing 16.2.4.5	History of HIV, HCV, HBV, HPV and PD-L1	U	FU1	
Listing 16.2.4.6	Prior and Subsequent Cancer Surgery	U	FU1	
Listing 16.2.4.7	Prior Radiotherapy	U	FU1	
Listing 16.2.4.8	Prior Systemic Anti-cancer Therapy	U	FU1	
Listing 16.2.4.9	Medications	U	FU1	
Listing 16.2.4.10	Concomitant Surgical/Medical Procedures	U	FU1	
Listing 16.2.4.11	Other Derived Variables – Subgroup Variable	U	FU1	
Listing 16.2.4.12	Other Derived Variables – Subgroup Lab parameters	U	FU1	
Listing 16.2.5.1	Efti Administration, Exposure and Compliance	U	FU1	
Listing 16.2.5.2	Pembrolizumab Administration, Exposure and Compliance	U	FU1	
Listing 16.2.5.3	Visit Dates	U	FU1	
Listing 16.2.5.4	Comments	U	FU1	
Listing 16.2.6.1	Target Lesions	U	FU1	Yes
Listing 16.2.6.2	Non-target Lesions	U	FU1	Yes
Listing 16.2.6.3	New Lesions	U	FU1	Yes

Output Number	Output Title	U/R	Analysis	BICR data
Listing 16.2.6.4	Assessment of Anti-Tumor Activity	U	FU1	Yes
Listing 16.2.6.5	Derived Efficacy Results	U	FU1	Yes
Listing 16.2.6.6	New Systemic Anti-cancer Therapy	U	FU1	
Listing 16.2.6.7	Immunogenicity Results (Autoantibodies and Anti-drug Antibodies against Efti)	U	FU1	
Listing 16.2.6.8	Circulating Biomarker Results	U	FU1	
Listing 16.2.6.9	Tumor Growth Kinetics	U	FU1	Yes
Listing 16.2.6.10	Subsequent anti-cancer procedures	U		
Listing 16.2.7.1	Adverse Events	R	FU1	
Listing 16.2.7.2	Listing of local injection site reactions	R	FU1	
Listing 16.2.7.3	Adverse events meeting the SMQ "Hypersensitivity"	R	FU1	
Listing 16.2.7.4	Systemic inflammatory response event with in 24 hrs from efti intake	U	FU1	
Listing 16.2.7.5	Treatment-emergent irAEs (Adverse reactions – Related to either pembro and/or efti)	R	FU1	
Listing 16.2.8.1	Laboratory Results - Hematology	U	FU1	
Listing 16.2.8.2	Laboratory Results – Biochemistry	R	FU1	
Listing 16.2.8.3	Laboratory Results – Thyroid Function	R	FU1	
Listing 16.2.8.4	Laboratory Results – Coagulation	R	FU1	
Listing 16.2.8.5	Laboratory Results - Urinalysis	U	FU1	
Listing 16.2.8.6	Pregnancy Test	U	FU1	
Listing 16.2.8.7	Vital Signs	U	FU1	
Listing 16.2.8.8	12-lead ECG	U	FU1	
Listing 16.2.8.9	ECOG Performance Status	U	FU1	
Listing 16.2.8.10	Physical Examination	U	FU1	

FU1 = Follow up analysis 1

5.5 Figures

Output Number	Output Title	U/R	Analysis	BICR data
Figure 14.2.1.1.1	Duration of Response according to iRECIST - Investigator (Part A - Full Analysis Set - Responders Only)	U	FU1	
Figure 14.2.1.1.2	Duration of Response according to iRECIST - Investigator (Part C - Full Analysis Set - Responders Only)	R	FU1	
Figure 14.2.1.1.3	Duration of Response according to RECIST 1.1 - Investigator (Part A - Full Analysis Set - Responders Only)	R	FU1	
Figure 14.2.1.1.4	Duration of Response according to RECIST 1.1 - Investigator (Part C - Full Analysis Set - Responders Only)	R	FU1	
Figure 14.2.1.2.1	Duration of Response according to iRECIST (Investigator) by PD-L1 central (Part A) (Full Analysis Set - Responders Only)	U	FU1	
Figure 14.2.1.2.2	Duration of Response according to RECIST 1.1 (Investigator) by PD-L1 central (Part A) (Full Analysis Set - Responders Only)	R	FU1	
Figure 14.2.1.2.3	Duration of Response according to iRECIST (Investigator) by PD-L1 central or local (Part A) (Full Analysis Set - Responders Only)	R	FU1	
Figure 14.2.1.2.4	Duration of Response according to RECIST 1.1 (Investigator) by PD-L1 central or local (Part A) (Full Analysis Set - Responders Only)	R	FU1	
Figure 14.2.1.2.5	Duration of Response according to iRECIST (Investigator) by PD-L1 central (Part C) (Full Analysis Set - Responders Only)	R	FU1	
Figure 14.2.1.2.6	Duration of Response according to RECIST 1.1 (Investigator) by PD-L1 central (Part C) (Full Analysis Set - Responders Only)	R	FU1	
Figure 14.2.2.1.1	Progression Free Survival according to iRECIST - Investigator (Part A - Full Analysis Set)	U	FU1	
Figure 14.2.2.1.2	Progression Free Survival according to iRECIST - Investigator (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.1.3	Progression Free Survival according to iRECIST - Investigator (Part C - Full Analysis Set)	R	FU1	
Figure 14.2.2.1.4	Progression Free Survival according to RECIST 1.1 - Investigator (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.2.1.5	Progression Free Survival according to RECIST 1.1 - Investigator (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.1.6	Progression Free Survival according to RECIST 1.1 - Investigator (Part C - Full Analysis Set)	R	FU1	
Figure 14.2.2.2.1	Progression Free Survival according to iRECIST - Investigator (Part A – Evaluable Analysis Set)	R	FU1	
Figure 14.2.2.2.2	Progression Free Survival according to iRECIST - Investigator (Part B - Evaluable Analysis Set)	R	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Figure 14.2.2.2.3	Progression Free Survival according to iRECIST - Investigator (Part C - Evaluable Analysis Set)	R	FU1	
Figure 14.2.2.2.4	Progression Free Survival according to RECIST 1.1 - Investigator (Part A - Evaluable Analysis Set)	R	FU1	
Figure 14.2.2.2.5	Progression Free Survival according to RECIST 1.1 - Investigator (Part B - Evaluable Analysis Set)	R	FU1	
Figure 14.2.2.2.6	Progression Free Survival according to RECIST 1.1 - Investigator (Part C - Evaluable Analysis Set)	R	FU1	
Figure 14.2.2.3.1.1	Progression Free Survival according to iRECIST (Investigator) by PD-L1 central (Part A - Full Analysis Set)	U	FU1	
Figure 14.2.2.3.1.2	Progression Free Survival according to RECIST 1.1 (Investigator) by PD-L1 central (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.1.3	Progression Free Survival according to iRECIST (Investigator) by PD-L1 central or local (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.1.4	Progression Free Survival according to RECIST 1.1 (Investigator) by PD-L1 central or local (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.1.5	Progression Free Survival according to iRECIST (Investigator) by Tumor type (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.1.6	Progression Free Survival according to RECIST 1.1 (Investigator) by Tumor type (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.1.7	Progression Free Survival according to iRECIST (Investigator) by ALC Change (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.1.8	Progression Free Survival according to RECIST 1.1 (Investigator) by ALC Change (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.2.1	Progression Free Survival according to iRECIST (Investigator) by PD-L1 central or local (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.2.2	Progression Free Survival according to RECIST 1.1 (Investigator) by PD-L1 central or local (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.2.3	Progression Free Survival according to iRECIST (Investigator) by tumor resistance (primary vs secondary) (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.2.4	Progression Free Survival according to RECIST 1.1 (Investigator) by tumor resistance (primary vs secondary) (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.2.5	Progression Free Survival according to iRECIST (Investigator) by Prior Therapy (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.2.6	Progression Free Survival according to RECIST 1.1 (Investigator) by Prior Therapy (Part B - Full Analysis Set)	R	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Figure 14.2.2.3.2.7	Progression Free Survival according to iRECIST (Investigator) by ALC Change (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.2.8	Progression Free Survival according to RECIST 1.1 (Investigator) by ALC Change (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.3.1	Progression Free Survival according to iRECIST (Investigator) by PD-L1 central (Part C - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.3.2	Progression Free Survival according to RECIST 1.1 (Investigator) by PD-L1 central (Part C - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.3.3	Progression Free Survival according to iRECIST (Investigator) by Maximum ALC Change (Part C - Full Analysis Set)	R	FU1	
Figure 14.2.2.3.3.4	Progression Free Survival according to RECIST 1.1 (Investigator) by Maximum ALC Change (Part C - Full Analysis Set)	R	FU1	
Figure 14.2.3.1.1	Overall Survival Part A (Full Analysis Set)	U	FU1	
Figure 14.2.3.1.2	Overall Survival Part B (Full Analysis Set)	R	FU1	
Figure 14.2.3.1.3	Overall Survival Part C (Full Analysis Set)	R	FU1	
Figure 14.2.3.2.1.1	Overall Survival by PD-L1 central (Part A - Full Analysis Set)	U	FU1	
Figure 14.2.3.2.1.2	Overall Survival by PD-L1 central or local (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.3.2.1.3	Overall Survival by Tumor type (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.3.2.1.4	Overall Survival by ALC Change (Part A - Full Analysis Set)	R	FU1	
Figure 14.2.3.2.2.1	Overall Survival by PD-L1 central or local (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.3.2.2.2	Overall Survival by tumor resistance (primary vs secondary) (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.3.2.2.3	Overall survival by prior therapy (Part B – Full Analysis Set)	R	FU1	
Figure 14.2.3.2.2.4	Overall Survival by ALC Change (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.3.2.3.1	Overall Survival by PD-L1 central only (Part C - Full Analysis Set)	R	FU1	
Figure 14.2.3.2.3.2	Overall Survival by ALC Change (Part C - Full Analysis Set)	R	FU1	
Figure 14.2.4.1	[redacted] according to RECIST 1.1 (Investigator) (Part A - Full Analysis Set)	U	FU1	
Figure 14.2.4.2	[redacted] according to RECIST 1.1 (Investigator) (Part B - Full Analysis Set)	R	FU1	
Figure 14.2.4.3	[redacted] according to RECIST 1.1 (Investigator) (Part C - Full Analysis Set)	R	FU1	

Output Number	Output Title	U/R	Analysis	BICR data
Figure 14.2.5.1	Waterfall Plot of Best Percent Change from Baseline of Sum of Target Lesion Diameters (Investigator) by PD-L1 central or local - Part A (Full Analysis Set)	U	FU1	
Figure 14.2.5.2	Waterfall Plot of Best Percent Change from Baseline of Sum of Target Lesion Diameters (Investigator) by PD-L1 central or local - Part B (Full Analysis Set)	R	FU1	
Figure 14.2.5.3	Waterfall Plot of Best Percent Change from Baseline of Sum of Target Lesion Diameters (Investigator) by PD-L1 central or local - Part C (Full Analysis Set)	R	FU1	
Figure 14.2.6.1	Variation of sum of best target lesions (iRECIST) (Investigator) Part B (Full Analysis Set)	U	FU1	
Figure 14.2.6.2	Variation of sum of best target lesions (iRECIST) (BICR) Part B (Full Analysis Set)	R	FU1	Yes
Figure 14.2.7.1.1	Box Plot of ALC Change by confirmed iBOR (iCR+iPR vs Others) - iRECIST - Part A (Full Analysis Set)	U	FU1	Yes
Figure 14.2.7.1.2	Box Plot of ALC Change by confirmed Best Disease Control (iCR+iPR+iSD vs Others) - iRECIST - Part A	U	FU1	Yes
Figure 14.2.7.2.1	Box Plot of ALC Change by confirmed iBOR (iCR+iPR vs Others) - iRECIST - Part B (Full Analysis Set)	R	FU1	Yes
Figure 14.2.7.2.2	Box Plot of ALC Change by confirmed Best Disease Control (iCR+iPR+iSD vs Others) - iRECIST - Part B	R	FU1	Yes
Figure 14.2.7.3.1	Box Plot of ALC Change by confirmed iBOR (iCR+iPR vs Others) - iRECIST - Part C (Full Analysis Set)	R	FU1	Yes
Figure 14.2.7.3.2	Box Plot of ALC Change by confirmed Best Disease Control (iCR+iPR+iSD vs Others) - iRECIST - Part C (Full Analysis Set)	R	FU1	Yes
Figure 14.2.8.1.1	Overall Survival Kaplan-Meier plot by iBOR (confirmed iCR+iPR vs Unconfirmed iPR+iSD vs iPD+iNA/NE) – Investigator – iRECIST - Part A (Full Analysis Set)	U	FU1	
Figure 14.2.8.1.2	Overall Survival Kaplan-Meier plot by iBOR (confirmed iPR+iSD vs iPD+iNA/NE) – Investigator – iRECIST - Part B (Full Analysis Set)	U	FU1	
Figure 14.2.8.1.3	Overall Survival Kaplan-Meier plot by iBOR (confirmed iCR+iPR vs Unconfirmed iPR+iSD+PD+NA/NE) – Investigator - iRECIST - Part C (Full Analysis Set)	U	FU1	

FU1 = Follow up analysis 1

Tables, Listings, and Figures will follow the format of:

- TACTI002_(P015)_Version_3 _Shells_31Jan2024;

5.6 Appendices

5.6.1 Tumor growth kinetics analysis in Part B - List of patients and their lesions

List of patients and their lesions which should be part of Tumor growth kinetics analysis in Part B are indicated in bold font.

Pt ID	Confirmatory Pre-baseline target lesions (reference scan)	Baseline target lesions	Comments
AU0111	**LIVER 4A**	**LIVER Seg 4A/VIII**	LIVER 4A only
	LIVER Seg VII/VIII	LIVER Seg V	
	OTHER Kidney RIGHT	LYMPH NODE Para-aortic	
AU0204	**LUNG Left lower lobe lung nodule LEFT**	LUNG Subpleural nodule right lower lung lobe RIGHT	Yes but only these two:
	LYMPH NODE Anterior mediastinal lymph node	**LUNG Left Lower lobe nodule LEFT**	LUNG Left lower lobe lung nodule LEFT LYMPH NODE Anterior mediastinal lymph node
		LYMPH NODE Anterior mediastinal lymph node	
		LYMPH NODE Retrocrural Lymph Node	
AU0208	**LUNG Right Lung Lower Lobe RIGHT**	**LUNG Right lower lobe RIGHT**	Yes, both lesions
	LUNG Left Lung Lower Lobe LEFT	**LUNG Left lower lobe LEFT**	
ES1104	N/A	LUNG left hilar lung LEFT	No
		LYMPH NODE left supraclavicular lymph node LEFT	
ES1117	**LUNG lower right lobe RIGHT**	LYMPH NODE under the chin	Yes but only LUNG lower right lobe RIGHT
	LYMPH NODE right hilar RIGHT	**LUNG lower right lobe RIGHT**	
	OTHER pleura RIGHT	LUNG post-costophrenic in lower right lobe RIGHT	
	SUPRARENAL GLAND right adrenal RIGHT		
	SUPRARENAL GLAND left adrenal LEFT		
ES1151	**LUNG upper right lobe RIGHT**	LYMPH NODE left subcarinal LEFT	

Pt ID	Confirmatory Pre-baseline target lesions (reference scan)	Baseline target lesions	Comments
		LUNG upper right lobe RIGHT	Yes but only LUNG upper right lobe RIGHT
ES1319	N/A	LYMPH NODE Hilium RIGHT	No
ES1406	LUNG left upper lobe mass LEFT	OTHER right laterocervical mass RIGHT	No
		LUNG left lower lobe mass LEFT	
		CHEST WALL lower periesophagic mass	
ES1423	CHEST WALL left hiliar mass LEFT	CHEST WALL superior pleuropulmonar mass LEFT	No
		CHEST WALL pleuropulmonar caudal metastasis LEFT	
		LIVER liver metastasis next to sickle ligament RIGHT	
		OTHER kidney metastasis LEFT	
ES1424	**LUNG left parahiliar lung mass LEFT**	**LUNG left parahiliar lung mass LEFT**	Yes but only LUNG left parahiliar lung mass LEFT
	LUNG right upper lobe mass RIGHT	LUNG right lower lobe lung mass RIGHT	
		LIVER liver metastasis on S.VIII RIGHT	
		LIVER liver metastasis on S.IV RIGHT	
		OTHER umbilical implant NOT APPLICABLE	
ES1429	N/A	LYMPH NODE left hiliar lymph node LEFT	No
		LYMPH NODE subcarinal lymph node	
		LUNG right hiliar lung mass RIGHT	
ES1430	**LUNG right lower lobe lung mass RIGHT**	**LUNG right lower lobe lung mass RIGHT**	Yes
	LYMPH NODE right hiliar lymph node RIGHT	**LYMPH NODE right hiliar lymph node RIGHT**	
ES1434	**LUNG lung mass RIGHT**	**LUNG lung mass RIGHT**	Yes but only LUNG lung mass RIGHT
		OTHER pancreatic area	
		BONE right iliac mass with soft tissue RIGHT	
UK2106	LYMPH NODE Precarinal lymph node	**LUNG Left upper lobe lung nodule LEFT**	

Pt ID	Confirmatory Pre-baseline target lesions (reference scan)	Baseline target lesions	Comments
	LYMPH NODE Aortopulmonary lymph node	LYMPH NODE Anterior mediastinal, retrosternal, node	Yes, but only left upper lobe lung lesion
	LUNG Left upper lobe spiculated lung mass LEFT	LYMPH NODE Peripancreatic node	
		OTHER Peritoneal nodule right flank RIGHT	
UK2107	**SUPRARENAL GLAND Right adrenal mass RIGHT**	**SUPRARENAL GLAND Right adrenal mass RIGHT**	Yes
	SUPRARENAL GLAND Left adrenal mass LEFT	**SUPRARENAL GLAND Left adrenal mass LEFT**	
UK2108	N/A	LYMPH NODE Supraclavicular fossa lymph node LEFT	No
UK2109	LYMPH NODE Right lower paratracheal node RIGHT	LYMPH NODE Subcarinal node	No
	LYMPH NODE Right upper paratracheal node RIGHT	LYMPH NODE Right paratracheal node RIGHT	
		LUNG Left lower lobe lung metastasis LEFT	
UK2110	**LUNG Right upper lobe lung mass RIGHT**	**LUNG Upper Lobe RIGHT**	Yes
UK2116	N/A	LUNG Right lower lobe mass RIGHT	No
		LUNG Left lower lobe nodule LEFT	
		SUPRARENAL GLAND Right adrenal nodule RIGHT	
UK2118	**LUNG Right upper lobe RIGHT**	**LUNG T1 Right upper lobe RIGHT**	Yes
	LUNG Right upper lobe RIGHT	**LUNG T2 Right upper lobe RIGHT**	
UK2202	**LUNG Right upper lobe nodule RIGHT**	**LUNG Right upper lobe nodule RIGHT**	Yes
UK2206	**LUNG Left lingular metastasis LEFT**	**LUNG Left lingular metastasis LEFT**	Yes
	LUNG Lower lobe metastasis LEFT	**LUNG lower lobe metastasis LEFT**	
UK2207	**LUNG Right upper lobe pulmonary mass RIGHT**	**LUNG Upper lobe pulmonary mass RIGHT**	Yes
UK2209	**LUNG Right upper lobe lesion RIGHT**	**LUNG Right upper lobe lesion RIGHT**	Yes
UK2210	**LYMPH NODE Station 2R right paratracheal node RIGHT**	**LYMPH NODE Station 2R right paratracheal node RIGHT**	Yes
	LYMPH NODE Right hilar nodal mass RIGHT	**LYMPH NODE Right hilar nodal mass RIGHT**	
UK2211	**LUNG Right upper lobe nodule RIGHT**	**LUNG Right upper lobe nodule RIGHT**	Yes

Pt ID	Confirmatory Pre-baseline target lesions (reference scan)	Baseline target lesions	Comments
UK2212	**LYMPH NODE Right Paratracheal Lymph Node RIGHT**	**LYMPH NODE Right Paratracheal Lymph Node RIGHT**	Yes
	LYMPH NODE Left Para-aortic Lymph Node LEFT	**LYMPH NODE Left Para-aortic Lymph Node LEFT**	
UK2301	**LUNG Lower lobe LEFT**	**LUNG Lower lobe LEFT**	Yes
US3105	LUNG Left infrahiliar nodule LEFT	LYMPH NODE pre carinal lymph node	No
US3108	**BONE Sacrum LEFT**	**BONE Sacrum LEFT**	Yes
	LUNG Right posterior apical lesion RIGHT	**LUNG Right posterior apical lesion RIGHT**	
	LUNG Left posterior apical lesion LEFT	**LUNG Left posterior apical lesion LEFT**	
		BONE Right iliac mass RIGHT	
US3109	**LUNG Posterior right upper lobe lesion RIGHT**	**LUNG Posterior right upper lobe lesion RIGHT**	Yes
	LUNG Superior segment right lower lobe RIGHT	**LUNG Superior segment right lower lobe RIGHT**	
US3114	LUNG Left Upper lobe spiculated mass LEFT	**LUNG Anterior segment of the right upper lobe RIGHT**	Yes, but only the three lesions in bold
	LUNG Anterior segment of the right upper lobe RIGHT	**OTHER Pleural based mass posterior midlung RIGHT**	
	OTHER Right Pleura, posterior midlung RIGHT	**OTHER Right lateral pleural mass RIGHT**	
	OTHER Right lateral pleural mass RIGHT	LUNG Right posterior costophrenic angle RIGHT	
		BONE L1 right vertebral body RIGHT	
US3120	LUNG Right Upper lobe mass RIGHT	LUNG Right Middle Lobe mass RIGHT	No
		LUNG Right lower lobe mass RIGHT	
US3123	LUNG left upper lobe nodule LEFT	LUNG left anterior apex spiculated nodule LEFT	No
		LUNG left lower lobe nodular opacity LEFT	
		LYMPH NODE mediastinal lymph node	
		LIVER right lobe liver RIGHT	
		LIVER second right lobe liver nodule RIGHT	
US3401	**LYMPH NODE anterior mediastinal RIGHT**	LYMPH NODE base of neck RIGHT	Yes but only LYMPH NODE

Pt ID	Confirmatory Pre-baseline target lesions (reference scan)	Baseline target lesions	Comments
		LYMPH NODE anterior mediastinal RIGHT	anterior mediastinal RIGHT
		SUPRARENAL GLAND RIGHT ADRENAL RIGHT	
US3402	**LUNG Left Mass LEFT**	**LUNG Left Mass LEFT**	Yes
	LUNG Right Mass RIGHT	**LUNG Right Mass RIGHT**	

5.6.2 Subgroup for Part B (Prior Therapy anti-PD-(L)1-based – cat)

Derivation of previous therapy is provided by Immutep medical team to be integrated in the program based in below categorization.

Previous Therapy = Anti-PD-X + chemo vs Anti-PD-X alone or Anti-PD-X alone + ICI

Anti-PD-(L)1	**ICI (Immune Checkpoint Inhibitors)**	**Chemotherapy**
Pembrolizumab	Ipilimumab	Carboplatin
Durvalumab		Cisplatin
Nivolumab		Pemetrexed / Pemetrexed Disodium
Atezolizumab		Gemcitabine
Avelumab		Paclitaxel

5.7 References

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