NOVOTECH
The Asia Pacific CRO

STATISTICAL ANALYSIS PLAN

A PHASE 1B/2A DOSE-ESCALATION AND SAFETY /EFFICACY EVALUATION STUDY OF PEXA-VEC (THYMIDINE KINASE-DEACTIVATED VACCINIA VIRUS PLUS GM-CSF) IN COMBINATION WITH CEMIPLIMAB (REGN2810; ANTI-PD-1) IN PATIENTS WITH METASTATIC OR UNRESECTABLE RENAL CELL CARCINOMA (RCC)

Protocol No.: JX594-REN026, dated 24 November 2020 (Amendment 9 – US & Ex-US)

Investigational product: Pexastimogene Devacirepvec (Pexa-Vec)

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List of Abbreviations

Term	Abbreviation
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ADR	Adverse Drug Reaction
ADRG	Analysis Data Reviewer's Guide
AE(s)	Adverse Event(s)
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ATC	Anatomical Therapeutic Chemical
anti-PDL1	Anti-Programmed Death Cell Receptor Ligand
AST	Aspartate Transaminase
BOR	Best overall Response
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI(s)	Confident Interval(s)
CR	Complete Response
CRFs	Case Report Forms
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT(s)	Dose Limiting Toxicity(ies)
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOI	End of Infusion
EOT	End of Treatment

Term	Abbreviation
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
irAE	Immune-Related Adverse Event
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IT	Intratumoral
ITT	Intent-To-Treat
IV	Intravenous
KM	Kaplan-Meier
LD	Longest Diameter
LDH	Lactate Dehydrogenase
MDSC	Myeloid Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum Feasible Dose
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute (United States)
NCI-CTC	National Cancer Institute – Common Toxicity Criteria
NCS	Not Clinically Significant
NK	Natural Killer
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed-cell Death protein-1
Pexa-Vec	Pexastimogene Devacirepvec, JX-594
PFS	Progression Free Survival

Term	Abbreviation
pfu	Plaque Forming Units
PI 3-K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
PT	Preferred Term
PT/INR	Prothrombin Time/International Normalized Ratio
PTT	Partial Thromboplastin Time
RBC	Red blood Cell
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SD	Stable Disease/ Standard Deviation
SDRG	Study Data Reviewer's Guide
SDTMIG	Study Data Tabulation Model Implementation Guide
SLD	Sum of Longest Diameters
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TK	Thymidine Kinase
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell
WHO	World Health Organization
WNL	Within Normal Limits
XPT	SAS® Transport File

1.INTRODUCTION

This Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data collected for the SillaJen Inc. protocol JX594-REN026, titled: A Phase 1b /2a Dose-escalation and Safety/Efficacy Evaluation Study of Pexa-Vec (Thymidine Kinase-Deactivated Vaccinia Virus plus GM-CSF) in Combination with Cemiplimab (REGN2810 ; anti-PD-1) in Patients with Metastatic or Unresectable Renal Cell Carcinoma (RCC).

This version of the SAP was prepared following the latest version of the study protocol JX594-REN026 (Amendment 9 –US & Ex-US) dated 24 November 2020. Prior versions of the study protocol include:

- Amendment 1: 16 November 2017
- Amendment 2: 13 December 2017
- Amendment 3: 07 February 2018
- Amendment 4 – Ex-US: 08 May 2018
- Amendment 5 – Ex-US: 29 October 2018.
- Amendment 6 – Ex-US: 25 September 2019
- Amendment 7 – US & Ex-US: 08 January 2020
- Amendment 8 – US & Ex-US: 12 August 2020

Any deviations from the SAP, the reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be described the clinical study report (CSR).

This SAP supersedes the statistical considerations identified in the protocol.

2.PROJECT OVERVIEW

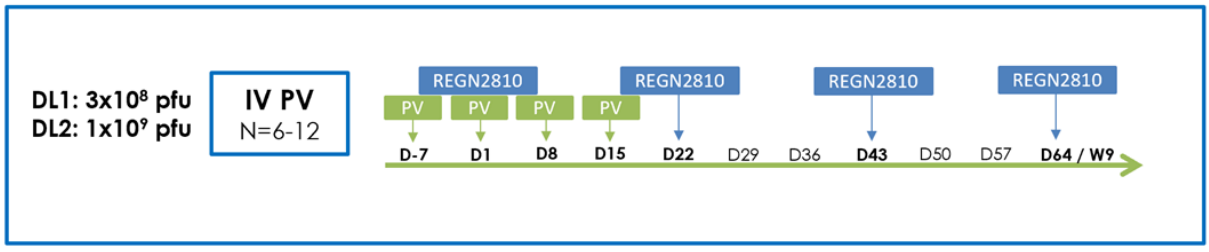
2.1.Description of the Study Design

This is a Phase 1b/2a, open-label, dose-escalation and safety/efficacy evaluation trial of Pexa-Vec administration plus Cemiplimab in patients with metastatic RCC. It is estimated that approximately 107 patients will be enrolled on the trial. Three to 12 patients may be enrolled in the Part 1 dose escalation and up to 101 patients will be enrolled in Part 2. Patients may be required to be replaced in the dose-escalation period due to insufficient exposure to the treatment regime. Up to a maximum of 3 patients will be replaced. The maximum number of patients to be enrolled in the study is 116.

2.1.1.Part 1 Enrollment

Patients will be treated with Pexa-Vec at one of 2 dose levels (Dose Level 1 at 3 × 10^8 plaque forming units [pfu] or Dose Level 2 at 1 × 10^9 pfu). Pexa-Vec will be administered via intravenous (IV) infusion weekly for 4 doses, beginning on Day –7.

Cemiplimab will be administered at a dose of 350 mg IV infusion every 3 weeks as previously established, beginning on Day 1. Three patients will be treated at Dose Level 1 unless a dose limiting toxicity (DLT), as defined within this protocol, is observed. Patients will be observed for a DLT during the IV treatment phase through Day 29, which includes all 4 Pexa-Vec IV infusions and 2 treatments of Cemiplimab. If a DLT does not occur in the first 3 patients, enrollment will proceed to Dose Level 2 where an additional 3 patients will be enrolled. However, if at any dose level one of the first 3 patients experiences a DLT, additional patients will be enrolled until a second patient experiences a DLT or until 6 total patients have been treated at that dose level, whichever comes first. If a second DLT is not experienced within the dose level, the next dose level or Part 2 may be initiated. If 2 patients in a dose level experience a DLT, enrollment will cease and the maximum tolerated dose (MTD) will be defined for Part 2. To ensure that no more than 2 patients experience a DLT within a dose level, enrollment will proceed with the first 2 patients, then once the first patient has completed the DLT period (e.g., Day 29), the third patient may be enrolled. Enrollment into Dose Level 2 or Part 2 cannot proceed until all 3, or 6 patients, in the previous dose level have completed the DLT period. If one of the first 3 patients experiences a DLT, additional patients will be enrolled one at a time with the next patient entered into the study only after the preceding patient has completed the DLT period.



2.1.2.Part 2 Enrolment

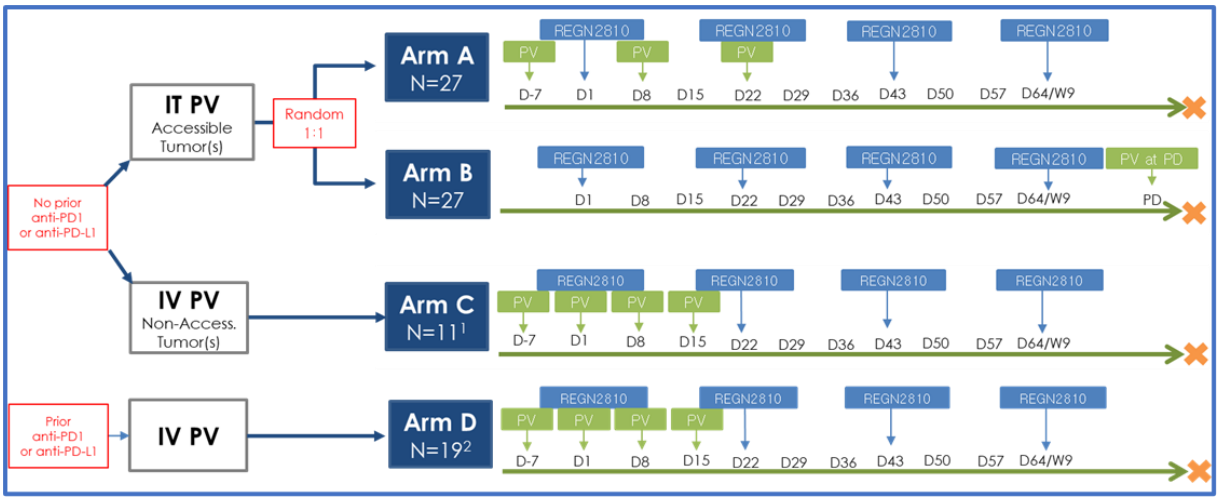
Up to an additional 101 patients will be enrolled in Part 2 of the study. There will be 4 treatment arms in Part 2: Arm A, Arm B, Arm C, and Arm D.

- Arm A/ Arm B: Patients naïve to anti-PD-1 or anti-PD-L1 with lesions accessible for biopsy and injection will be randomized into Arm A or Arm B and will receive intratumoral (IT) Pexa-Vec at the MTD/ maximum feasible dose (MFD) defined in Part 1.
- Arm C: Patients naïve to anti-PD-1 or anti-PD-L1 with no accessible lesions for IT injection will be placed into Arm C and will receive IV Pexa-Vec at the established MTD or MFD determined in the Part 1 portion of the study to assess the safety and tolerability of treatment with Pexa-Vec in combination with Cemiplimab.

- Arm D: Patients with prior treatment with anti-PD-1 or anti-PD-L1 will be placed on Arm D.

Biopsies may be collected in patients with lesions amenable to biopsy in Arm C and Arm D.

Patients will be assessed radiologically (CT), at Screening and every 9 weeks until documented progression or discontinuation beyond documented progression. After 1 year, patients will be assessed every 12 weeks from the end of the treatment (EOT) visit.



[1] N to be expanded to 20, pending clinical efficacy

[2] N to be expanded to 27, pending clinical efficacy

2.2.Objectives

2.2.1.Primary Objective

- Part 1: Determine the maximum tolerated dose (MTD) or maximum feasible dose (MFD) of Pexa-Vec administered by IV infusion in combination with IV-administered Cemiplimab
- Part 1 and 2: Determine the safety of Pexa-Vec administered by IV infusion or IT injection in combination with IV-administered Cemiplimab by assessing severity and frequency of adverse Events (AEs) and laboratory toxicity using Common Terminology Criteria for Adverse Events (CTCAE) v5
- Part 2: Evaluate anti-tumor activity and efficacy of IV or IT Pexa-Vec combined with IV Cemiplimab with respect to overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

2.2.2.Secondary Objective(s)

The secondary objectives of this study are:

- Determine progression free survival according to RECIST 1.1
- Determine the disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by RECIST 1.1
- Determine best radiographic response (based on RECIST 1.1)
- Evaluate anti-tumor activity and efficacy of IV or IT Pexa-Vec combined with IV Cemiplimab with respect to overall response rate (ORR) per immune-related RECIST (irRECIST)
- Determine the disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by irRECIST

- Best radiographic response (based on irRECIST)
- Estimate overall survival.

2.2.3.Exploratory Objective(s)

The exploratory objectives of this study are:

- To assess in the blood, the following immune parameters at Baseline, and on study Day 1 (excluding Arm B, Cemiplimab monotherapy), Day 22 (Day 43 in Arm D), End of Treatment, and Post Progression on anti-PD-1 monotherapy at Baseline, 2 weeks, and 4 weeks (Arm B only):
  - Tumor specific and Pexa-Vec specific cellular immune responses (including but not limited to assessment of B-cells, T-cells, activated T-cells, Natural Killer (NK) cells, regulatory T-cells, Myeloid Derived Suppressor Cells (MDSC))
  - Pexa-Vec and Cemiplimab specific humoral responses
  - Immune-related cytokines
- To assess in previously archived tumor biopsies (if available) and/or biopsied tumors at Baseline and on Study Day 8 (excluding Arm B, Cemiplimab monotherapy) and Day 57 (Arm B patients will undergo repeat biopsy at disease progression and 2 weeks after first Pexa-Vec):
  - Tumor microenvironment including T-cell, B-cells, NK cell, monocytes, macrophages, and other relevant immune cell subtypes of interest
  - Immune modulating proteins that may have predictive or prognostic value, including, but not limited to PD-L1, PD-1, and CTLA-4
  - Global changes in gene expression based on genome wide RNAseq analysis
  - Tumor mutational load based on whole exome sequencing of tumor and the matched germline blood DNA samples
  - Pexa-Vec infection and transgene expression
- Measure Cemiplimab and Pexa-Vec concentrations in serum and plasma, respectively.

2.3.Study Endpoints

Refer to Sections 8 and 9 for a detailed discussion of the study endpoints.

2.3.1.Primary Endpoints

- MTD or MFD of Pexa-Vec administered by IV infusions in combination with Cemiplimab
- Safety of Pexa-Vec administered by IV infusions or IT injections in combination with Cemiplimab as evaluated by incidence of all AEs, Grade 3 or greater AEs, serious adverse events (SAEs), AEs requiring discontinuation of study agent(s), and deaths according to National Cancer Institute – Common Toxicity Criteria (NCI-CTC) version 5
- ORR according to RECIST 1.1
  - This is the primary efficacy endpoint for Part 2 and the basis for the power calculations.

2.3.2.Secondary Endpoint(s)

- Progression free survival according to RECIST 1.1

- Disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by RECIST 1.1
- Best radiographic response (based on RECIST 1.1)
- ORR according to irRECIST
- Best radiographic response (based on irRECIST)
- Disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) by irRECIST
- Overall survival.

2.3.3.Exploratory Endpoint(s)

- To assess in the blood, the following immune parameters at Baseline and on Study Days 1 (excluding Arm B, Cemiplimab monotherapy), Day 22 (Day 43 in Arm D), End of Treatment, and Post Progression on anti-PD-1 monotherapy at Baseline, 2 weeks, and 4 weeks (Arm B only):
  - Tumor specific and Pexa-Vec specific cellular immune responses (including but not limited to assessment of B-cells, T-cells, activated T-cells, NK cells, regulatory T-cells, MDSC)
  - Pexa-Vec and Cemiplimab-specific humoral responses
  - Immune-related cytokines
- To assess in previously archived tumor biopsies (if available) and/or biopsied tumors at Baseline and on Study Day 8 (excluding Arm B, Cemiplimab monotherapy) and Day 57 (Arm B patients will undergo repeat biopsy at disease progression and 2 weeks after first Pexa-Vec):
  - Tumor microenvironment including T-cell, B-cell, NK cell, monocytes, macrophages, and other relevant immune cell subtypes of interest
  - Immune modulating proteins that may have predictive or prognostic value, including, but not limited to PD-L1, PD-1, CTLA-4
  - Global changes in gene expression based on genome-wide RNAseq analysis
  - Tumor mutational load based on whole exome sequencing of the tumor and the matched germline blood DNA samples
  - Pexa-Vec infection and transgene expression
- Concentration of Cemiplimab and Pexa-Vec in serum and plasma, respectively, after Pexa-Vec IV and IT (pre-dose, end-of-infusion/injection and Day 8) with Cemiplimab IV (pre-dose and end-of-Day 1 infusion, Day 8, as well as C_{trough}, and C_{eoi} throughout therapy).

2.4.Sample Size, Assignment of Patients to Treatment Groups and Replacement Patients

2.4.1. Part 1, Dose Escalation Phase

Up to 12 DLT-evaluable patients are planned based on a 3+3 design. The actual sample size will depend on DLT occurrences. Dose Level 1 and 2, three patients will be treated at each dose level unless a DLT is observed. Patients will be observed for a DLT through Day 29. Enrollment will proceed to the next dose level if 0 of 3 patients experiences a DLT. If one of the first 3 patients experiences a DLT, additional patients will be enrolled until a second patient experiences a DLT (which defines the toxic dose; the dose level immediately preceding this toxic dose level will be determined as the MTD) or until 6 total patients have been treated,

whichever comes first. If a second DLT is not experienced within that cohort, dose-escalation may continue.

2.4.2. Part 2, Arm A vs Arm B

Efficacy will be evaluated comparing the objective response rate in the combination arm (Arm A) with the anti-PD-1 arm (Arm B). Patients with injectable lesions will be randomized to either Arm A or Arm B, stratified by number of prior therapies. The hypothesis test is powered based on a control rate of 21.5%, derived from nivolumab data, the anti-PD-1 agent approved for use in advanced RCC (Nivolumab package insert). A treatment effect corresponding to ORR of 43% (double the ORR of anti-PD-1 monotherapy) in Arm A (treatment difference of 21.5%) from a randomized comparison, would be encouraging for further study of the combination of Pexa-Vec and Cemiplimab in this patient population. The randomized design will provide support for the estimated effect size on ORR in spite of the unknown variability of the control estimate and effects of potential confounding factors. Notably, the ORR endpoint is selected in this randomized trial instead of progression free survival due to historical data with anti-PD-1 antibodies demonstrating that progression free survival may not be a reliable surrogate for anti-tumor activity or overall survival in RCC and other solid tumours (Motzer 2015, Borghaei 2015, Herbst 2016). To reject the null hypothesis that the combination (Arm A) will have no greater effect than the anti-PD1 alone (Arm B) with a power of 75% when the actual combination ORR in the population is 43% and a 1-sided alpha of 0.15, 27 patients will be enrolled into each Arm A and Arm B (n = 54).

2.4.3. Part 2, Arm C

For this dose-expansion cohort, the sample size is determined using a Simon 2-stage Minimax design with 1-sided alpha of 0.12 and power of 80%. Eleven patients will be enrolled in the first stage. If 3 or more patients experience a response, a further 9 patients will be enrolled and assessed for efficacy.

The null and alternative ORR rates (21.5% and 43%) are designed to test for a clinically meaningful treatment effect when compared to an estimated control arm response rate derived from a historical control, potentially worth pursuing further in clinical development.

2.4.4. Part 2, Arm D

For this dose-expansion cohort, the sample size is determined using a 2-stage design based on testing a null hypothesis ORR rate ≤5% versus alternative hypothesis ORR rate ≥20% with a probability of early termination of 75.5%, satisfying the 1-sided alpha of 5% and power of 80% constraints. Nineteen patients will be enrolled in the first stage. If 2 or more patients experience a response, a further 8 patients will be enrolled and assessed for efficacy.

The null and alternative ORR rates (5% and 20%) are designed to test for a clinically meaningful treatment effect of the 2nd line RCC treatment assuming an ineffective response rate of 5%. Because there is no response data of 2nd line check point blocker treatment available from RCC patient population refractory to 1st line check point blocker treatment, ORR of 20%, pooled from studies (Eichelberg 2008, Dudek 2009, Sablin 2009, Zama 2010, Porta 2011, Zimmerman 2009, Eichelberg 2015, Rini 2008) where standard of care (sunitinib) in the 2nd line setting was used.

3.STATISTICAL CONSIDERATIONS

3.1.Standard Operating Procedures and Software

The study data will be converted into Clinical Data Interchange Standards Consortium (CDISC)-compliant datasets based on the Study Data Tabulation Model Implementation Guide (SDTMIG) Version 3.3 and the Analysis Data Model Implementation Guide (ADaMIG) Version 1.1.

The SDTM data package will be based on raw data (clinical database and external data) and will include SAS® datasets and transport files (.XPT format) for each required SDTM domain, as well as the SDTM Case Report Tabulation Data Definition Specifications (CRT-DD) (define.xml Version 2.0) that describes the origin of the data and all of the derivations and imputations that were applied, and includes an SDTM-annotated CRF and the Study Data Reviewer's Guide (SDRG).

The ADaM datasets will be based on the SDTM datasets and will be used for the analysis. The ADaM data package will include SAS® datasets and transport files (.xpt format) for each analysis dataset, as well as the ADaM CRT-DD (define.xml Version 2.1) and the Analysis Data Reviewer's Guide (ADRG).

The SDTM and ADaM data packages will be validated using Pinnacle 21 Community (531 Plymouth Road, Suite 508, Plymouth Meeting, PA 19462) and the validation reports will be included with the respective data packages.

All data conversions and statistical analyses will be performed using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA) with program code prepared specifically for the study by qualified Novotech statisticians and SAS® programmers.

3.2.Data Review

Patient data will be reviewed to determine the eligibility of each patient for inclusion into each of the analysis populations defined in Section 4.

3.3.General Considerations

This Statistical Analysis Plan (SAP) will be finalized prior to locking of the study database for the analysis and will form the basis for the programming of the displays and analyses of the final study data. All statistical calculations will be performed using SAS® (Statistical Analysis Software Institute Inc., Cary, NC, USA) version 9.4 or later.

Unless otherwise stated, the following methods will be applied:

- Continuous variables: For continuous data, other than concentration-related PK data, descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean and median values will be displayed to one more decimal than the source data, and the SD values will be displayed to two more decimals than the source data for the specific variable.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the abovementioned rules.

- Categorical variables: Descriptive statistics will include n (the number of patients with no missing data), frequencies and percentages per category. Unless specifically stated otherwise, the number of participants in the group (for the specific analysis set) will be used as the denominator for all percentage calculations.

  Where required, two-sided 95% exact binomial confidence intervals (CI) (Clopper-Pearson) will be presented.

The number of decimal places for each analysed variable will be determined separately based on maximum number of decimal places in the source data. No rounding will be performed for the analysed variable values before descriptive statistics calculations.

The number of decimals for each descriptive statistical value will be determined by the following rules:

- Mean, median, 1-st and 3-rd quartiles: +1 decimal symbol compared to the analysed variable values
- Standard deviation: +2 decimal symbols compared to the analysed variable values
- Minimum and maximum values: the same as for the analysed variable values
- Percentages will be rounded to one decimal symbol
- CI will be presented with the number of decimal places equals to those for the point estimate.

The maximum number of decimal symbols in the statistical report is four. If some descriptive statistical value has more than four decimal symbols after above mentioned rules application, this value will be rounded to four decimal symbols.

- Kaplan-Meier (KM) method: Time-to-event endpoints will be analysed using the Kaplan-Meier method. Median and quartiles (25th and 75th percentiles) survival times and survival probability estimates at 6, 9 and 12 months will be presented together with the associated 95% CIs. In addition, the number of patients with an event and the number of censored patients will also be reported. Censoring as applicable to specific endpoints are defined under section 3.4. The corresponding Kaplan-Meier survival plot will also be presented. Censored patients will be marked on the Kaplan Meier survival plot, the number of patients at risk, and the associated KM estimates by interval unit will be displayed under the x-axis.
- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings in chronological order.
- Assessment windows: All assessments will be included in the data listings and the protocol specified visit windows will be applied to include assessments that were not performed on the protocol specified visit days.
- Result display convention: Results will be centre-aligned in all summary tables and listings. Patient numbers, visit, and parameter labels and comments may be left-aligned if required.
- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:
    - Date only: YYYY-MM-DD
    - Date and time: YYYY-MM-DD/HH:MM

If only partial information is available, unknown components of the date or time will be presented as ‘UK’ (Unknown), i.e., ‘2016-UK-UK’.

3.4.Key Definitions

The following definitions will be used:

- Date of the first administration of the IP: The date of the first study treatment administration is defined as the earliest date on which a study treatment [Pexa-Vec IV /IT infusion or Cemiplimab IV infusion] was administered as reported on the appropriate eCRF pages.
- Date of the Last Study Treatment Administration: The date of the last study treatment administration is defined as the latest known date on which a study treatment was administered.
- Baseline: The Baseline value is defined as the last available valid, non-missing observation for each patient prior to first study treatment administration on Cycle 1 Day "- 7" (for study Part 1 / Part 2 - Arm C and Arm D and study Part 2 – Arm A) and on Cycle 1 Day 1 (for study Part 2 – Arm B). Repeat and unscheduled assessments will be included in the derivation of the Baseline values.
- Nadir Value: The nadir value at a specific visit is defined as the smallest value observed at any visit from the date signed informed consent, prior to the current visit. The Baseline value will be used as the nadir value if no post-baseline assessment is available.
- Absolute Change from Baseline: The absolute change from Baseline value is defined as the difference between the result collected/derived at a post-baseline visit and the Baseline value.

  The change from Baseline value at each post-baseline visit will be calculated for all continuous parameters using the following formula:

  Absolute Change from Baseline Value = Result at post-baseline visit – Baseline Value

  The change from Baseline value will only be calculated if the specific post-baseline visit result and the Baseline value for the parameter are both available and will be treated as missing otherwise. In the data listings, the change values will be set to 'blank i.e. "-" for pre-baseline assessments.

  The same rules will be followed to calculate the change from nadir values.
- Percentage Change from Baseline: The percentage change from Baseline value is defined as the ratio of change from Baseline and the Baseline value, expressed as a percentage.

  The percentage change from Baseline value at each post-Baseline visit will be calculated for all continuous parameters using the following formula:

  Percentage Change from Baseline Value (%) = (Change from Baseline / Baseline Value) * 100

  The percentage change from Baseline value will only be calculated if the specific post-Baseline visit change from Baseline value is available and will be treated as missing otherwise. In the data listings, the percentage change values will be set to blank i.e. "-" for pre-baseline assessments.

  The same rules will be followed to calculate the percentage change from nadir values.

- Age: Completed years, at screening will be defined as:
  Age (years) = integer value ((Date Signed Informed Consent – Month &Year of Birth + 1) / 365.25)
  In case of missing day, day only:
  Age [years]: (year/month of given informed consent – year/month of birth)

In case only year of birth is given:

Age [years]: (year of given informed consent - year of birth)

The integer part of the calculated age will be used for reporting purposes.

- Study Day: The study day of an event is defined as the relative day of the event starting with the date of the first study treatment administration (reference date) as Day -7 (for study Part 1 / Part 2 - Arm C and Arm D and study Part 2 – Arm A) and as Day 1 (for study Part 2 – Arm B).

  The study day of events occurring before the first study treatment administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Treatment Administration)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Treatment Administration) + 1

  Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

- Dose Limiting Toxicity (DLT): A DLT is defined as any of the following treatment-related AEs that are evaluated and reported through Day 29 of the dose-escalation (Part 1) phase of the study:
  - Grade 4 hematologic toxicity lasting ≥7 days except:
    - Grade 4 lymphopenia without clinically relevant sequelae
    - Grade 4 thrombocytopenia not associated with a clinically significant bleeding event
  - All Grade 3 and Grade 4 non-hematologic toxicity that represent a 2-grade increase over baseline except:
    - Grade 3 flu-like symptoms (specifically fatigue, malaise, headache, and myalgia) lasting <14 days
    - Grade 3–4 fever lasting <3 days
    - Grade 3 hypotension lasting <24 hours
    - Grade 3–4 alopecia, hair or skin discoloration
    - Grade 3–4 nausea, vomiting and diarrhea lasting <7days
    - Grade 3–4 hypothyroidism responsive to hormone therapy
    - Grade 3 hyponatremia without clinical significance
    - Grade 3–4 non-hematologic toxicity without clinical significance (e.g., transient, asymptomatic elevation of amylase or lipase)
  - Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - The abnormality leads to hospitalization
  - Grade 3 or greater cardiac toxicity that does not decrease to a Grade 1 event 72 hours after initiation of maximal supportive care

  - Grade 3 and Grade 4 thrombocytopenia with clinically significant bleeding associated with Pexa-Vec
  - Grade ≥3 febrile neutropenia
    - If Grade 3, the event must (in the judgement of both the Investigator and Sponsor) A) be clinically significant and B) require intervention (e.g. G-CSF, antibiotic therapy) for resolution of the event
  - Grade 5 toxicity.

- Adverse Event of Special Interest (AESI) for this study include the following:
  - Any AE that meets DLT criteria
  - Grade 2 or greater infusion-related reactions
  - Grade 2 or greater allergic/hypersensitivity reactions
  - Myocarditis of any grade.
  - • Grade 3 or greater Immune-Related (irAE) (refer to Section 7.A.3.b of the Protocol), or Grade 2 or greater Uveitis (refer to Section 7.A.3.a of the Protocol)
  - • An irAE of any grade in a patient previously treated with a Phosphatidylinositol 3-kinase (PI 3-K) inhibitor
- Adverse Drug Reaction (ADR): All noxious and unintended responses to the IP related to any dose or to a study specific procedure as determined by the Investigator or the Sponsor.
- Laboratory Abnormality: A laboratory abnormality is reported as an AE if it is out of range and considered by the Investigator as clinically significant (i.e., with clinical manifestations or requiring treatment or clinical management).
- Suspected Unexpected Serious Adverse Drug Reaction (SUSAR): Any unexpected SAE considered as related to the IP or to a study specific procedure.
- Overdose: An overdose is an administration of the IP at a higher dose than the highest dose already tested in clinical studies or higher than known therapeutic doses or higher than the dose planned according to the schedule of administration.

  Overdose is not be considered an AE. However, if the patient experiences an AE/SAE related to this overdose, it should be reported as such.
- Overall response rate (ORR): The ORR is defined as the proportion of patients whose best overall response is either complete response (CR) or partial response (PR).
- Best overall Response (BOR): The BOR is the best response recorded from the randomization until disease progression. The best overall response will be derived based on the reported Investigator overall response assessments, as well as based on the derived overall response assessments

Table 1: RECIST v1.1 Best Overall Response Criteria (Confirmation of CR and PR)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
	PR	SD, PD or PR [a]

	SD	SD provided minimum criteria for SD duration met, otherwise, PD
	PD	SD provided minimum criteria for SD duration met, otherwise, PD
	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
	PR	PR
	SD	SD
	PD	SD provided minimum criteria for SD duration met, otherwise, PD
	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Progressive Disease.
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, original CR should be changed to PR and the best response is PR.

- Duration of Response (DOR): For patients with ORR, the DOR will be defined as the duration from the first response of CR or PR until the first date of either confirmed disease progression or death.
- Disease control rate (DCR): The DCR is defined as the proportion of patients whose best overall response is either CR, PR, or Stable Disease (SD).
- Responders: Responders are defined as patients with a best overall response of CR or PR.
- Non-responders: Non-responders are defined as patients with a best overall response of SD or PD or missing.
- Progression free survival (PFS): The PFS is defined as the duration (weeks) between the date of first study treatment to the date of first documented radiographic tumor or death due to any cause, whichever comes first. Patients will be censored under the following:
    a. If a patient has not had a progression free survival event at the cut-off date for analysis, progression free survival will be censored at the date of last evaluable tumor assessment before the cut-off.
    b. If a progression is observed after 2 or more missing or non-evaluable tumor assessments, then the date of progression will be censored at the latest occurring evaluable tumor assessment before missing; for a progression observed after a single missing or non-evaluable tumor assessment, the actual date of disease progression will be used.

Table 2: Outcome and Events Dates for PFS Analyses

Scenario	Date of Event/ Censoring	Outcome
PD or Death	Date of progression or death	Event
No PD and No Death	Date of last evaluable tumor assessment before the cut-off	Censored
PD after 2 or more missing or non-evaluable tumor assessments,	Date of the latest occurring evaluable tumor assessment before missing;	Censored
Withdrawal of consent	last contact date/ last assessment visit	Censored
Lost to follow-up	last contact date	Censored

The PFS time will be calculated as follows:

PFS time (weeks) = ((Date of Progression/Death/Censoring - Date of First Study Treatment Administration) + 1) / 7

- Overall Survival (OS) Time: The OS time is defined as the duration (weeks) between the time from first study treatment until death from any cause. Patients will be censored at the last contact date confirmed patient is alive. If the last contact date is not available, the latest date of all of assessment dates including dates on log data form should be used for censoring.

  OS time (weeks) = ((Date of Death/Censoring - Date of First Study Treatment Administration) + 1) / 7
- Sum of longest diameters (SLD) (cm): The SLD of the target lesions is derived as the sum of the individual longest diameter values reported for each target lesions at a specific visit.
- SLD nadir value: The SLD nadir at a specific visit is defined as the smallest SLD at any visit after the start of treatment, prior to the current visit. The Baseline SLD will be used as the nadir value if no post-baseline assessment is available.
- Cumulative dose: sum of doses received during each treatment.
- Cumulative Injection volume: This will be derived as the sum of all the injection volumes administered during a specific visit, cycle and during the overall study.
- Total duration of study treatment: This will incorporate the dosing regimen of Pexa-Vec (bi-weekly dosing) and Cemiplimab (3-weekly dosing) as follows.
  - Pexa-Vec IV Infusion duration: (date of the last dose – date of first dose) +14.
  - Cemiplimab duration: (date of the last dose – date of first dose) +21.
- Prior medications: Prior medications are defined as any medication where the use was stopped prior to the first administration of study drug.
- Concomitant medications: Concomitant medications are defined as any medication (other than the study drug) that was used at least once after the first administration of study drug. Medications that were stopped on the same date as the first study drug administration will be analysed as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant.

3.5.Hypothesis Testing

No formal hypothesis testing will be performed for the study part 1, **Dose Escalation Phase**.

- **ORR according to RECIST 1.1 (Primary Endpoint 3-primary efficacy endpoint for Part 2)**

  For the hypothesis test below performed on the primary efficacy endpoint, one-sided CIs will be presented.

  - **Arm A vs Arm B**
    - The null hypothesis that the combination (Arm A) will have no greater effect on ORR than the anti-PD1 alone (Arm B) will be tested using two sample, 1-sided test of difference of proportions. The one-sided 85% CI and the p-values will be calculated using the Cochran-Mantel-Haenszel test with the stratification factor for number of prior therapies at alpha level of 0.15. In case the assumptions of the Cochran-Mantel-Haenszel test are violated due to a small number of subjects in some strata (i.e., number of subjects ≤ 10 in at least one of the stratum), the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option) will be used.
  - **Arm C Expansion**
    - For this dose-expansion cohort a Simon two-stage design Minimax design (Simon, 1989) was used. The null hypothesis that the true response rate is 21.5% will be tested against a one-sided alternative. This design yields a one-sided alpha of 0.12 and power of 80% when the true response rate is 43%. If participation in Arm C does not stop in the first stage (i.e. the attained sample size is the same as the planned sample size at the stopping stage), the one-sided 88% CIs will be obtained using Koyama and Chen (2008) corrected p-value method. If the participation in Arm C stops in the first stage, then the one-sided CIs will be calculated using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).
  - **Arm D Expansion**
    - For this dose-expansion cohort testing a null hypothesis ORR rate ≤5% versus alternative hypothesis ORR rate ≥20% with a probability of early termination of 75.5%, (1-sided alpha of 5% and power of 80% constraints) is planned. The null and alternative ORR rates (5% and 20%) are designed to test for a clinically meaningful treatment effect of the 2nd line RCC treatment assuming an ineffective response rate of 5%. If participation in Arm D does not stop in the first stage (i.e. the attained sample size is the same as the planned sample size at the stopping stage), the one-sided 95% CIs will be obtained using Koyama and Chen (2008) corrected p-value method. If the participation in Arm D stops in the first stage, then the one-sided CIs will be calculated using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).

For each of comparison with other groups, the above tests will also be performed at alpha level of 0.05 and the 95%CIs and associated p-values reported.

3.6.Multiple Comparisons and Multiplicity

Not applicable for this study.

3.7.Handling of Missing Data

All data will be analysed as collected and missing values will not be imputed or replaced.

3.8.Coding of Events and Medications

Medical history conditions and surgical procedures and AE verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DDE March 2018 LT) or the latest version in use. Medications will be mapped to the full WHO-DD Anatomical Therapeutic Chemical (ATC) class hierarchy, but the ATC Level 4, and preferred terms will be of primary interest for the analysis.

3.9.Treatment Group and Visit Display Conventions

The following treatment label will be used in all outputs:

Part 1:

- Cohort 1 (3*10^8 pfu)
- Cohort 2 (1*10^9 pfu)

Part 2:

- Arm A
- Arm B
- Arm C
- Arm D

The following visit labels will be used in all outputs. All visits will be displayed in chronological order:

- Screening
- Baseline
- Cycle 1
    - Day -7
    - Day 1
    - Day 8
    - Day 15
    - Day 22
    - Day 43
    - Day 57
    - Day 64
- Anti-PD1 Maintenance
    - Q3 Week
    - Q9 Weeks
- Confirmed Progressive Disease (PD)
    - Post PD
    - Post PD Week 2
    - Post PD Week 4
- Pexa-Vec Booster Visit (x=an incremental number)
    - Pexa-Vec IT Booster Visit x
    - Pexa-Vec IV Booster Visit x
- Radiographic Follow-Up Visit x (x=an incremental number)
- End of Treatment
- Survival Follow-Up Visit x (x=an incremental number)
- Safety Follow-up
- Unscheduled.

4.ANALYSIS POPULATIONS

4.1.Population Descriptions

Three analysis sets are defined for this study: Intent-to-Treat (ITT) population, Safety (SAF) population and per protocol population (PP). Data for screen failures will not be included in any summary tables, figures, or data listings (except Eligibility Criteria, Screen Failure listings and disposition information).

Furthermore, any additional exploratory analysis not identified in the SAP will be identified in the final CSR as exploratory post hoc analyses, including analyses for additional study populations or subgroups of interest. PK analysis results for Pexa-Vec will be included in the body of CSR, whereas PK analysis for Cemiplimab and other exploratory sample analyses will be conducted by sponsor's partner company and their reports will be appended to the CSR.

4.1.1. Intent-to-Treat (ITT) population

The ITT population will comprise all enrolled patients. The ITT set will be used for Baseline and demographic summaries, as well as the efficacy analyses.

4.1.2.Safety (SAF) population

The safety population will comprise all patients who receive at least one dose of any one component of the study treatment (Pexa-Vec or Cemiplimab). The occurrence of death also constituted a valid safety assessment. Patients will be analysed according to the treatment they actually received. The safety population will be the population for safety and drug exposure analyses.

4.1.3. The Per Protocol (PP) population

The per protocol population will comprise all patients from the ITT population without any protocol deviations thought to affect the efficacy, who have completed a minimum exposure requirement. The minimum exposure requirement is dependent on Arm enrolled. From Arm A, the minimum exposure is at least one Pexa-Vec injection and at least one Cemiplimab infusion. For Arm B, the minimum exposure is at least one Cemiplimab infusion. For Arm C and Arm D, the minimum exposure is at least one Pexa-Vec infusion and at least one Cemiplimab infusion. However, if a patient was discontinued for AE, or died before the required exposure could be met, that patient will still be included in per protocol population.

4.1.4.Pharmacokinetic (PK) Population

All patients who received at least one dose of study drug (Pexa-vec IV/IT) drug and have any measurable plasma concentration of Pexa-Vec at any time point and have a sufficient PK profile that allows the calculation of at least one PK parameter will be included in the PK population. An evaluable concentration-time profile will be determined at the discretion of the pharmacokineticist following examination of patients with dosing, PK sampling or protocol deviations that could potentially affect the PK profile. The PK population will be used for the PK analyses.

The PK population will be used for the summaries of all PK parameters. Rejected data will be listed together with the rationale.

4.1.5.Subgroups

Subgroup analyses for ORR based on RECIST v1.1, progression free survival (PFS) time based on RECIST v1.1, and overall survival (OS) time will be performed for the following subgroup of defined below.

· Subgroup 1: Participants enrolled into Part 2 who were without previous systematic treatment (Except Arm D)

· Subgroup 2: Participants enrolled into Part 2 who had previous systematic treatment (Except Arm D)
· Subgroup 3: Participants enrolled into Arm D who had only 1st line of therapy
· Subgroup 4: Participants enrolled into Arm D who had more than or equal to 2nd line of therapy

5.SUBJECT DISPOSITION AND ANALYSIS POPULATIONS

Categorical variables will be summarized using frequencies and percentages. The summary table and listings will be based on the ITT population.

5.1.Analysis Populations

The number of patients included in of each of the defined analysis populations will be summarized using frequencies and percentages.

In addition, the inclusion/exclusion of each patient into/from each of the defined analysis populations, as well as the reasons for the exclusion (where applicable) will be listed.

5.2.Patient Disposition

The number and percentage of patients completing or discontinuing from the study as well as the primary reason for discontinuation will be presented in the subject disposition table. The denominator for the reason for discontinuation percentage calculations will be the number of patients that enrolled in the study. The following will be summarised for all parts:

- Number of patients who completed End of Treatment (EOT) visit
- Number of patients who completed safety follow-up visit
- Number of patients who completed the active study participation
- Number of patients who were followed-up for overall survival after safety follow up visit

For Arm B, the following additional summaries will be provided:

- The number of patients whose progressive disease were confirmed
- The number of patients who completed at least post PD visit (denominator is the number of patients with confirmed PD).

The number of patients who completed all of 3 post PD visits (denominator is the number of patients with confirmed PD).

All patient disposition information collected at the Completion or Discontinuation eCRF page will be listed together with the date that the patient signed informed consent, the protocol version date that the patient consented to, the analysis populations into which the patient are include and the dates of the first and last Pexa-Vec and Cemiplimab administrations.

6.PROTOCOL DEVIATIONS

A protocol deviation is any non-compliance with the clinical trial protocol, GCP, or other study requirements (e.g., SOPs, study specific instructions, etc.). The non-compliance may be either on the part of the patient, the investigator, or the study site staff.

Protocol deviations may include, but are not limited to the following:

- Violation of inclusion/exclusion criteria
- Missed or out of window assessments
- Non-compliance to study medication use (i.e., study drug was not applied per the protocol guidelines)
- Use of prohibited concomitant medications, treatments or procedures
- Deviation from study specific instructions.

All reported protocol deviations will be listed.

7.DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and other Baseline information collected during the screening period will be presented based on ITT population. Results will be presented for Part 1 and Part 2 in the summary tables.

Continuous variables will be summarized as described in Section 3.3 and categorical variables will be summarized using frequencies and percentages.

7.1.Demography and Baseline Characteristics

Demographic and Baseline characteristics data will be summarized and listed. Supporting information, as well as information reported as free text will be included in the data listing. Demographic and Baseline characteristics data include:

- Age (years)
- Gender ('Male', 'Female')
- Female of Childbearing Potential ('Yes', 'No')
- Race n (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Vaccination for smallpox received n (Yes, No, Unknown)
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline BMI
- Baseline tumor size of target lesions (collected at screening visit), based on the central and local assessment respectively
- Cardiac consultation
- Cardiac clearance

All information collected on the Demographics eCRF page will be included in the listing.

7.2.Disease Status, Prior RCC Therapies/Interventions and Medical History

The duration from the RCC Diagnosis to enrolment (months) will be calculated as (Date of informed consent - Date of initial diagnosis) / 30.4375.

Baseline disease status, including the method of diagnosis, tumor differentiation, RCC subtype, Karnofsky Performance status will be summarized and listed. The number of patients with and without ('Yes', 'No') prior systemic therapies with response will be included in Prior RCC therapy summary table.

The history of prior systemic therapies summary table will present frequencies and percentages for the number of patients that have received each type of therapy (based on the Medical Monitor's classification), as well as frequencies and percentages for the number of different types of therapies that each patient received.

Prior RCC mediations will be summarized by the assigned ATC Level 1 & 2 and by preferred terms within the ATC term hierarchy. Within each category, the number of patients who used the medication (frequency and percentage) will be presented. Patients who used the same medication on multiple occasions will only be counted once in the specific category (ATC or PT). ATC terms will be sorted alphabetically, and PTs will be sorted alphabetically within ATC terms. In addition to the summaries by the coded terms, the number of patients who used at least one Prior RCC medication during the study will be presented.

Disease Status, Prior RCC Therapies/Interventions and Medical History will be included in the listings.

7.3.Medical History

Medical history conditions and surgical procedures will be summarized by SOC and by PT within SOC. Within each category, the number of patients who experienced a condition/procedure (frequency and percentage) and the actual number of events (frequency only) will be presented. Patients who experienced the same condition/procedure on more than one occasion (based on the specific category) will only be counted once in each relevant category (SOC and PT), but all conditions/procedures will be included in the event frequencies.

In addition to the coded terms, the number of patients with at least one medical history condition or historical surgical procedure and the total number of events will be presented.

All information that was collected on the Medical History eCRF page as well as the coded MedDRA terms will be included in the listings.

7.4.Inclusion/Exclusion Criteria Exceptions and Eligibility Criteria

The overall subject eligibility responses, as well as the violation of specific inclusion/exclusion criteria collected on the Eligibility Criteria eCRF pages, as well as Re-treatment Eligibility Criteria collected on the “Cemiplimab Re-treatment Eligibility” and “Pexa-Vec Re-treatment Eligibility” eCRF pages will be listed.

8.TREATMENTS

8.1.Study Drug Exposure

Study treatment comprises of an IV infusion or IT injection of Pexa Vec in combination with IV infusion of Cemiplimab. Study drug administration and treatment exposure results will be presented using the Safety Population. The derived and collected exposure parameters will be summarized and listed using descriptive statistics.
Exposure to Pexa-Vec and Cemiplimab will be provided by summarizing the cumulative dose in each treatment session (in pfu, corrected if not complete) and for the following:

- Cycle 1
- Anti-PD1 Maintenance,
- Confirmed PD Visits
- Booster Visits.

The duration of study treatment will be summarized for of Pexa-Vec and Cemiplimab respectively, and in total. For Arm A – Pexa-Vec injection, the cumulative injection volume for all the injections, and average injection volume received for each treatment session will be summarized.

All information from “Pexa-Vec Dosing” and “Cemiplimab Dosing” eCRF pages will be listed.

8.2.Concomitant Medications

Medication use will be reviewed during the study and medication use will be documented on the Concomitant Medication eCRF page. In addition, subsequent anti-cancer therapies collected via survival follow-up visits will be listed and summarized.

Concomitant mediations will be summarized by the assigned ATC Level 4 and by preferred terms within the ATC term hierarchy. Within each category, the number of patients who used the medication (frequency and percentage) will be presented. Patients who used the same medication on multiple occasions will only be counted once in the specific category (ATC or PT). ATC terms will be sorted alphabetically, and PTs will be sorted alphabetically within ATC terms. In addition to the summaries by the coded terms, the number of patients who used at least one concomitant medication during the study will be presented.

All information that was collected on the Concomitant Medications eCRF as well as the coded WHO-DD terms will be included in the listings. Furthermore, the relative medication start and stop days (refer to Section 3.4) will be present where complete medication start and stop dates are available. Listings will be sorted by patient and by medication start and stop dates within patient.

Prior medication use (history of medication use) will be listed as part of the patient baseline characteristics outputs. Concomitant medications will be listed separately.

The number of patients on subsequent anti-cancer therapies and response to these therapies will be included in subsequent anti-cancer therapy summary table. The summary table will present frequencies and percentages for the number of patients that have received each type of therapy as well as frequencies and percentages for the number of different types of therapies that each patient received.

9.PHARMACOKINETIC ANALYSIS OF PEXA-VEC

Analyses of PK data from this trial will be limited to concentration time profiles of Pexa-Vec only. No PK parameters will be calculated. The summary of PK concentration-time data will be based on the PK Population.

Plasma Pexa-Vec PK samples respectively will be collected after Pexa-Vec IV / IT at the timepoints specified in the study protocols schedule of events (refer to page 82-91, and section 6.F.10):

- Pre-dose,
- End-of-infusion/injection

Plasma Pexa-Vec concentrations will be listed by subject, dose level, and nominal (scheduled) sampling time. Pexa-Vec concentrations will be summarized by dose level and nominal sampling time. Plasma concentrations that are below the limit of quantitation (BLQ) will be set to 0 for calculation of summary statistics for concentration data at each time point, except geometric statistics (geometric mean and geometric CV%). For the calculation of the geometric statistics they will be treated as equal to the Lower Limit of Quantification (LLQ). Missing values will be omitted from the calculation of descriptive statistics.

The actual blood sampling dates and times relative to dosing time will be listed by study group (dose level), subject and nominal sampling time, with time deviation calculated, for all subjects with available plasma or serum concentration data, including subjects excluded from the PK Analysis Population if any.

Figures of individual plasma concentration vs. actual time profiles for Pexa-Vec, will be produced on linear and semi-log scales. Mean and median plasma Pexa-Vec concentration vs. nominal time curves for all dose levels/treatments in will be plotted on linear and semi-log scale.

10.EFFICACY ANALYSES

The efficacy endpoints will be analysed based on the methods described in Section 3.3 and 3.5. Efficacy analyses will be performed for Part 2 only.

All efficacy endpoints will be summarized based on ITT and PP populations and listed based on the ITT population, unless specifically stated otherwise. Percentages will be based on the number of patients in the appropriate analysis population, unless specifically stated otherwise. In the case that the subjects in ITT population are the same as subjects in PP population, only the results based on ITT population will be presented. The primary endpoint for the Part 2 of the study (ORR) will be based on central assessment using RECIST V1.1.

10.1. Overall Response Rate based on RECIST v1.1 and irRECIST

Analyses of ORR will be performed based on central assessments using RECIST 1.1, central and local assessments using irRECIST.

ORR, as per central RECIST V1.1 for Part 2 will be summarised at each protocol scheduled time point, using frequency tabulations. 85%CI, 88%CI and 95%CI will be reported for Arms A and B, Arms C, and Arms D, respectively. Analysis will be repeated for the assessments using central and local irRECIST

The CIs and p-value for Arm A vs Arm B comparison of difference in ORR, and CIs for ORR in Arm C and D will be obtained as described in Section 3.5.

The number and percentage of subjects in each ORR category (CR, PR, SD, PD or Not Evaluable) will also be presented.

10.2. Disease Control Rate (DCR)

DCR will also be summarised at each protocol scheduled time point, using frequency tabulations. Exact 95% CI for the DCR will also be presented.
Subjects with “Not Evaluable” response will be included in the denominator when calculating the percentage).

10.3. Progression Free Survival (PFS) Time Analysis

PFS time will be summarized using the KM method described in Section 3.3. Results will be presented for responders, non-responders and all patients overall in the summary tables and figures (as appropriate). For summary tables, hazard ratio comparing the risk in arm A to arm B and the associated 95% CI will be presented. The hazard ratio will be estimated using a Cox’s Proportional Hazard model stratified by the randomization strata (i.e. number of prior therapies). Each stratum will define a separate baseline hazard function (using the 'STRATA' statement in SAS PROC PHREG). Ties will be handled by replacing the proportional hazards model by the discrete logistic model (i.e., ties=discrete option in SAS PHREG procedure).

Frequency (number and percentage) of subjects with each event type (PD or death) and censoring reasons will be presented by treatment arm. Censoring reasons are as follows:

- No Death and No PD (Ongoing in the study without an event)
- No adequate post-baseline assessment
- Event after 2 or more missing or inadequate post-baseline assessments
- Withdrawal of consent
- Lost to follow-up (this includes lost to follow-up status collected on the eCRF page prior to the analysis cut-off)

The PFS time or censoring time and the reasons for censoring will also be presented in a subject listing.

10.4.Overall Survival (OS) Time

OS time will be summarized using the KM method described in Section 3.3. Results will be presented for responders, non-responders and all patients overall in the summary tables and figures (as appropriate). For summary tables, hazard ratio comparing the risk in arm A to arm B and the associated 95% CI will be presented. The hazard ratio will be estimated using a Cox's Proportional Hazard model stratified by the randomization strata (i.e. number of prior therapies). Each stratum will define a separate baseline hazard function (using the 'STRATA' statement in SAS PROC PHREG). Ties will be handled by replacing the proportional hazards model by the discrete logistic model (i.e., ties=discrete option in SAS PHREG procedure).

Frequency (number and percentage) of subjects who died and censoring reasons will be presented by treatment arm. Censoring reasons are as follows:

- Ongoing in the study without an event
- Withdrawal of Consent
- Lost to follow-up (this includes lost to follow-up status collected on the eCRF page prior to the analysis cut-off)

The OS time or censoring time and the reasons for censoring will also be presented in a subject listing

10.5.Tumor Measurements based on RECIST v1.1 and irRECIST (central, local)

Lesions will be classified as target lesions and non-target tumors based on the information reported on the eCRF page in case of local assessment based on irRECIST. New tumors are defined as any lesion that was not present at Screening and that was first observed after the initiation of treatment. Analyses will be performed based on central assessments using RECIST 1.1 and irRECIST. irRECIST will also be performed by a local reader.

The SLD at each visit will be derived for each of the following groups of tumors:

- irRECIST
  - Target tumors
  - New tumors
  - Tumor Burden (sum of target and new tumors).
- RECIST
  - Tumor Burden (sum of target tumors)

The individual tumor measurement data and the derived SLD results will only be listed. The derived SLD data will be summarized and listed. All data collected at scheduled and unscheduled visits will be included in the listings.

The change from Baseline and percentage change from Baseline to each post-baseline visit values will be calculated for the SLD values for each of the defined tumor groups. The change from nadir and percentage change from nadir values will also be calculated.

Spider plot will be used to present percentage change in tumor size from baseline over time for each subject. This plot will be classified by response (CR/PR/SD/PD) and different colors will be used for patients. This will be repeated for each cohort.

In addition, waterfall plot will be used to present best percentage change in tumor size from baseline. This plot will display the reduction in tumor size in ascending order with the subjects with the most reduction on the right. Each subject is represented by a bar classified by the treatment. The type of response will be shown at the end of the bar (e.g. CR, PD etc)

The summary of SLD table will present summary statistics (refer to Section 3.3) for the derived values, the change from Baseline values and the percentage change from Baseline values at each scheduled post-baseline visit for each of the defined tumor groups.

10.6.Exploratory Endpoints - Tumor Biopsies

Tumor biopsies (biomarker analysis) were performed at the visits specified the Time and Events Schedule (see Section 6.D of Protocol) and the relevant information was reported on the Tumor Biopsy eCRF page.

The results of the biomarker analysis do not form part of this analysis plan and will be reported separately.

10.7.Radiographic Imaging

Radiographic imaging of tumours (MRI/CT/ Nuclear Bone Scan/Ultrasound) will be performed at the visits specified in the Time and Events Schedule (see Section 6.D of Protocol).

All findings will be reported on the Medical Imaging eCRF pages:

Radiographic imaging findings will only be listed. All data collected at scheduled and unscheduled visits will be included in the listings.

The listing of radiographic imaging findings will include all the information (fields) that was collected on the Radiographic imaging eCRF pages as well as the relative study day of the examination (refer to Section 3.4).

11.SAFETY ANALYSES

Statistical methods for the safety analyses will be descriptive in nature and no inferential analyses will be performed. Endpoints will be summarized by treatment group based on the methods described in Section 3.3.

Safety endpoints include AEs, safety laboratory assessments, vital signs and physical examination assessments, laboratory assessments, the use of concomitant medications and study drug exposure.

Safety endpoints will be analysed based on the SAF population.

11.1.Adverse Events

11.1.1.Part 1, Dose Escalation Phase

Up to 12 DLT-evaluable patients are planned based on a 3+3 design. The actual sample size will depend on DLT occurrences. Dose Level 1 and 2, three patients will be treated at each dose level unless a DLT is observed. Patients will be observed for a DLT through Day 29. Enrollment will proceed to the next dose level if 0 of 3 patients experiences a DLT. If one of the first 3 patients experiences a DLT, additional patients will be enrolled until a second patient experiences a DLT (which defines the toxic dose; the dose level immediately preceding this toxic dose level will be determined as the MTD) or until 6 total patients have been treated, whichever comes first. If a second DLT is not experienced within that cohort, dose-escalation may continue

11.1.2.Part 1 and Part 2.

All AEs will be coded using the MedDRA (version 20.1 or later) with System Organ Class (SOC) and Preferred Term (PT) names.

Only treatment-emergent AEs will be analyzed. Treatment-emergent adverse events (TEAEs) are defined as AEs that started on or after the first study drug administration.

Serious AEs (SAEs) are defined as AEs where the events are reported as ‘Serious’.

Severe AEs are defined as AEs where the Common Terminology Criteria for Adverse Events (CTCAE) severity grading is reported as ‘Grade 3’ (Severe), ‘Grade 4’ (Life-Threatening) or ‘Grade 5’ (Fatal). Missing severity gradings will be analysed as ‘Severe’.

Adverse events of special interest are defined as events that were reported to be of interest on the Adverse Events eCRF page.

Adverse events will be reviewed during the study and all events will be reported on the Adverse Events eCRF page.

All tables will present the number of patients who experienced an AE (frequency and percentage) and the actual number of AEs (frequency only), within each specific category. Patients who experienced multiple AEs will only be counted once in each relevant category (SOC and PT), but all events will be included in the event frequencies. System organ class terms will be sorted in decreasing order of frequency, and PTs will be sorted by decreasing order of frequency within SOCs based on the overall number of patients. In addition to the summaries by the coded terms, the number of patients who experienced at least one TEAE will be presented. Where appropriate, the results for severe TEAEs, as well as treatment-related TEAEs will also be presented in the same table.

Tables will only include TEAEs.

The number and percentage of patients reporting adverse events and number of adverse events will be summarized for following table categories:

- All TEAE

- TEAEs considered as Dose-Limiting Toxicity (DLT)[1]
- Serious TEAEs
- Grade 3 or 4 TEAEs
- TEAEs by severity grade (according to CTCAE v.5.0)
- TEAEs by relationship to study drug (Pexa-Vec IV infusion/Pexa-Vec IT jnjection /Cemiplimab IV infusion)
- Grade 3 or 4 adverse events considered as related to the study drug (Pexa-Vec IV infusion / Pexa-Vec IT Injection/ Cemiplimab IV infusion)
- TEAEs leading to discontinuation from study
- TEAEs resulting in interruption of drug (Pexa-Vec IV infusion /Pexa-Vec IT injection/ Cemiplimab IV infusion) administration
- TEAEs resulting in withdrawal of treatment with the drug (Pexa-Vec IV infusion/ Pexa-Vec IT injection / Cemiplimab IV infusion)
- TEAEs of Special Interest
- TEAEs leading to death

In the tables for AEs by relation to study drugs and by severity grade patients with AEs will be counted only once with highest relation/severity. All AEs will be counted according to their relation/severity.

The summary of TEAEs by severity grading table will include the number of patients who experienced at least one TEAE, the number of patients who experienced at least one TEAE within each severity grading (Grade 1 - Grade 5) and the corresponding number of events within each grading. In addition, the TEAE data will be summarized by SOC, preferred term within SOC for each of severity gradings. Patients who experienced multiple TEAEs under a specific PT will only be counted once under the reported severity grading, but all events under the grading will be included in the event counts.

The summary of TEAEs by drug relationship tables will include the number of patients who experienced at least one TEAE, the number of patients who experienced at least one TEAE within each relationship category (‘Related’, ‘Not Related’ or ‘N/A) and the corresponding number of events within each category. In addition, the TEAE data will be summarized by SOC, preferred term within SOC for each of relationship category. Patients who experienced multiple TEAEs under a specific PT will only be counted once under the reported category, but all events under the category will be included in the event counts.

All information that was collected on the Adverse Events eCRF as well as the coded MedDRA terms and the relative study start and end days will be included in the listings. Listings will be sorted by patient and by event start and end dates within patient. Separate listings will be created for all AEs overall, SAEs, AEs related to study drugs, AEs of special interest and AEs that lead to study drug withdrawals.

11.2.Safety Laboratory Assessments

Blood and urine samples will be collected at the visits specified the Time and Events Schedule (see Section 6.D of Protocol) to conduct hematology, chemistry, coagulation, thyroid function, serology and urinalysis analyses.

The following tests will be performed within each of the specified test panels, and the results and unit measures (as appropriate) will be reported on the corresponding eCRF pages:

The following laboratory tests will be taken at various time points through the study:

- Hematology:

[1] Adverse events considered as Dose-Limiting Toxicity (DLT) will be summarized by system organ class (SOC) and preferred term (PT) for each dose cohort and overall for Safety population.

  - WBC count with differentials (absolute only). In case only % are captured, calculate the absolute value as WBC count * % differential
    - absolute Neutrophils
    - absolute Lymphocytes
    - absolute Monocytes
    - absolute Eosinophils
    - absolute Basophils
  - hemoglobin
  - hematocrit,
  - RBC,
  - MCH
  - MCHC
  - MCV
  - MPV
  - platelet count

- Chemistry Panel:
  - Alanine Aminotransferase (ALT)
  - Albumin
  - Alkaline phosphatase (ALP)
  - Amylase
  - Aspartate Transaminase (AST)
  - Bicarbonate (CO_2)
  - Blood urea nitrogen (BUN)
  - Calcium
  - Chloride
  - Creatinine
  - Glucose
  - Lactate dehydrogenase (LDH)
  - Lipase
  - Magnesium
  - Potassium
  - Sodium
  - Total protein
  - Total bilirubin.

- Coagulation:
  - Activated partial thromboplastin time (APTT)
  - INR
  - prothrombin time (PT)

- Thyroid function testing:
  - TSH
  - Free T3
  - Free T4
- Troponin (“I” or “T”)
- Hepatitis B and C panels:
  - HBV surface antibody [HBsAb/anti-HBs],
  - HBV core antibody [HBcAb],
  - HBV surface antigen [HBsAg]
  - HCV antibody, EIA [HCVAb]

- HIV test;
- Serum pregnancy test (for women of childbearing potential);
- Urinalysis.

Test results were classified in relation to the parameter specific reference ranges. Results lower than the lower limit of the reference range were classified as 'Low' and results above the upper limit of the reference range were classified as 'High'. Results that are equal to or fall between the lower and upper limit of the reference range were classified as 'Normal'. The reference range indicator is left blank for parameters without a defined reference range. In addition, abnormal ('Low' or 'High') results were also assessed for clinical significance ('Abnormal Not Clinically Significant' or 'Abnormal Clinically Significant').

Laboratory data will be summarized and listed. Summary tables will not include visits where results are only available for a subset of patients (i.e., unscheduled visits, or visits where laboratory tests were only required if clinically indicated). All data collected at scheduled and unscheduled visits will be included in the listings.

The parameter names that will be used in the outputs will comprise of the test name and the standardized unit of measure, for example, 'Albumin (g/L)'. Parameters will be sorted in the order collected on the eCRF within tables and listings.

The change from Baseline to each post-baseline visit values will be calculated for all quantitative parameters with the exception of the urinalysis parameters.

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the reported results are reported. The results will be displayed to the same decimal precision in the listings.

The hematology, chemistry, coagulation and thyroid function shift tables will present summaries (frequencies and percentages) for the Baseline result categories ('Normal', 'Abnormal Not Clinically Significant', 'Abnormal Clinically Significant') and the 'shifts' from Baseline to the post-baseline visit within each Baseline category for each parameter within the specific test panel. The denominator for the percentage calculations will be the number of patients with non-missing data at the specific visit.

The listings of hematology, chemistry, coagulation, thyroid function and urinalysis results will include all the information (fields) that were reported on the laboratory eCRF pages as well as the relative study day of the sample collection (refer to Section 3.4). In addition, the observation that was used as the Baseline record (value) and nadir record for each parameter will be flagged, and the change from Baseline values at each post-baseline visit will be presented (where applicable). The reference range indicator and clinical significance flags will also be presented.

A separate listing that includes only the subset of patients that had at least one abnormal result ('Low' or 'High') will also be created for the hematology, chemistry, coagulation and thyroid function results. All of the patient's results for every parameter where at least one abnormal classification was observed will be included.

All microscopic examination results collected on the Urinalysis eCRF page will be listed.

All serology test result information collected on the Form: HIV, Hepatitis B and C1 eCRF page will be listed.

All pregnancy test result information collected on the Pregnancy Test eCRF page will be listed.

11.3.Vital Signs Assessments

The following vital signs will be assessed at the visits specified in the Time and Events Schedule (see Section 6.D of Protocol):

- Systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/minute), temperature (C°), weight (kg), height (cm), BMI (kg/m^2), and pulse oximetry.

The individual parameter results and the units of measure will be reported on the Vital Signs eCRF page.

The vital signs data will be summarized and listed. All data collected at scheduled and unscheduled visits will be included in the listings.

The parameter names that will be used in the outputs will comprise of the parameter name and the standardized unit of measure, for example 'Systolic Blood Pressure (mmHg)'. Parameters will be sorted in the order specified above within tables and listings.

The change from Baseline to each post-baseline visit values will be calculated for all parameters.

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the reported results are reported. The results will be displayed to the same decimal precision in the listings.

The listing of vital signs will include all the information (fields) that was collected on the Vital Signs eCRF page as well as the relative study day of the assessment (refer to Section 3.4). The observation that was used as the Baseline record (value) for each parameter will be flagged, and the change from Baseline values at each post-baseline visit will be presented.

11.4. Cardiac Function Assessment [Electrocardiogram (ECG) and Echocardiogram]

ECG and echocardiogram will be assessed at Screening and End of Treatment as specified in the Time and Events Schedule (see protocol). The results of Investigator Interpretation ('Normal', 'Abnormal Not Clinically Significant (NCS)', 'Abnormal Clinically Significant (CS)') will be reported on the ECG and Echocardiogram eCRF page.

ECG and echocardiogram findings will only be listed. All data collected at scheduled and unscheduled visits will be included in the listings.

The listing of ECG and echocardiogram findings will include all the information (fields) that was collected on the ECG and Echocardiogram eCRF pages as well as the relative study day of the assessment (refer to Section 3.4).

11.5.Physical Examination Findings

A complete physical examination, including weight will be performed at the visits specified the schedule of Events (see Section 6.D of Protocol).

This will include examination of the heart, lungs, abdomen, skin and other organ systems as necessary, including injection sites, if applicable. All findings will be reported on the Physical Examination eCRF pages

Physical examination findings will only be listed. All data collected at scheduled and unscheduled visits will be included in the listings.

The listing of physical examination findings will include all the information (fields) that was collected on the Physical Examination eCRF pages as well as the relative study day of the examination (refer to Section 3.4). The listing will be sorted by body system (as specified above) and by visit within body system.

12.CHANGES TO THE PLANNED ANALYSIS

Not applicable.

13.INTERIM AND FINAL ANALYSIS

Not applicable for this study.

14.TABLES

Table number	Table Title	Population
	Demographic and Baseline Variables	
14.1.1	Patient Disposition and Analysis Populations – Part 1	ITT
14.1.2	Patient Disposition and Analysis Populations – Part 2	ITT
14.1.2.1	Demography and Baseline Characteristics Data - Part 1	ITT
14.1.2.2	Demography and Baseline Characteristics Data - Part 2	ITT
14.1.3.1	Baseline Disease Status - Part 1	ITT
14.1.3.2	Baseline Disease Status - Part 2	ITT
14.1.4.1	Prior RCC Therapies/Interventions - Part 1	ITT
14.1.4.2	Prior RCC Therapies/Interventions - Part 2	ITT
14.1.4.3	Prior RCC Medications - Part 1	ITT
14.1.4.4	Prior RCC Medications - Part 2	ITT
14.1.5.1	Medical History - Part 1	ITT
14.1.5.2	Medical History - Part 2	ITT
	PK/Efficacy	
14.2.1.1.1	Summary of Plasma Pexa-Vec Concentrations -Part 1	PK
14.2.1.1.2	Summary of Plasma Pexa-Vec Concentrations - Part 2	PK
14.2.1.2.1	Summary of Overall Response Rate based on RECIST v1.1 - Part 1	ITT
14.2.1.2.2	Summary of Overall Response Rate based on RECIST v1.1 - Part 2	ITT
14.2.1.2.3	Summary of Overall Response Rate based on RECIST v1.1 - Part 1	PP (Optional)
14.2.1.2.4	Summary of Overall Response Rate based on RECIST v1.1 - Part 2	PP (Optional)
14.2.1.2.5	Summary of Overall Response Rate based on RECIST v1.1 – Subgroup 1	ITT
14.2.1.2.6	Summary of Overall Response Rate based on RECIST v1.1 – Subgroup 2	ITT
14.2.1.2.7	Summary of Overall Response Rate based on RECIST v1.1 – Subgroup 3	ITT
14.2.1.2.8	Summary of Overall Response Rate based on RECIST v1.1 – Subgroup 4	ITT
14.2.1.2.9	Summary of Overall Response Rate based on RECIST v1.1 – Subgroup 1	PP (Optional)
14.2.1.2.10	Summary of Overall Response Rate based on RECIST v1.1 – Subgroup 2	PP (Optional)
14.2.1.2.11	Summary of Overall Response Rate based on RECIST v1.1 – Subgroup 3	PP (Optional)
14.2.1.2.12	Summary of Overall Response Rate based on RECIST v1.1 – Subgroup 4	PP (Optional)
14.2.1.2.13	Summary of Overall Response Rate based on irRECIST - Part 1	ITT
14.2.1.2.14	Summary of Overall Response Rate based on irRECIST - Part 2	ITT

Table number	Table Title	Population
14.2.1.2.15	Summary of Overall Response Rate based on irRECIST - Part 1	PP (Optional)
14.2.1.2.16	Summary of Overall Response Rate based on irRECIST - Part 2	PP (Optional)
14.2.1.3.1	Summary of Best Overall Response Rate based on RECIST v1.1 - Part 1	ITT
14.2.1.3.2	Summary of Best Overall Response Rate based on RECIST v1.1 - Part 1	PP (Optional)
14.2.1.3.3	Summary of Best Overall Response Rate based on irRECIST - Part 1	ITT
14.2.1.3.4	Summary of Best Overall Response Rate based on irRECIST - Part 1	PP (Optional)
14.2.1.3.5	Summary of Best Overall Response Rate based on RECIST v1.1 - Part 2	ITT
14.2.1.3.6	Summary of Best Overall Response Rate based on RECIST v1.1 - Part 2	PP (Optional)
14.2.1.3.7	Summary of Best Overall Response Rate based on irRECIST - Part 2	ITT
14.2.1.3.8	Summary of Best Overall Response Rate based on irRECIST - Part 2	PP (Optional)
14.2.2.2.1	Progression Free Survival Time based on RECIST v1.1 – Part 1	ITT
14.2.2.2.2	Progression Free Survival Time based on RECIST v1.1 – Part 2	ITT
14.2.2.2.3	Progression Free Survival Time based on RECIST v1.1 – Part 1	PP (Optional)
14.2.2.2.4	Progression Free Survival Time based on RECIST v1.1 – Part 2	PP (Optional)
14.2.2.2.5	Progression Free Survival Time based on RECIST v1.1 – Subgroup 1	ITT
14.2.2.2.6	Progression Free Survival Time based on RECIST v1.1 – Subgroup 2	ITT
14.2.2.2.7	Progression Free Survival Time based on RECIST v1.1 – Subgroup 3	ITT
14.2.2.2.8	Progression Free Survival Time based on RECIST v1.1 – Subgroup 4	ITT
14.2.2.2.9	Progression Free Survival Time based on RECIST v1.1 – Subgroup 1	PP (Optional)
14.2.2.2.10	Progression Free Survival Time based on RECIST v1.1 – Subgroup 2	PP (Optional)
14.2.2.2.11	Progression Free Survival Time based on RECIST v1.1 – Subgroup 3	PP (Optional)
14.2.2.2.12	Progression Free Survival Time based on RECIST v1.1 – Subgroup 4	PP (Optional)
14.2.2.3.1	Progression Free Survival Time based on irRECIST (Local) - Part 1	ITT
14.2.2.3.2	Progression Free Survival Time based on irRECIST (Central) - Part 1	ITT
14.2.2.3.3	Progression Free Survival Time based on irRECIST (Local) - Part 2 –	PP (Optional)
14.2.2.3.4	Progression Free Survival Time based on irRECIST (Central) - Part 2	PP (Optional)
14.2.2.4.1	Overall Survival Time - Part 1	ITT
14.2.2.4.2	Overall Survival Time - Part 2	ITT
14.2.2.4.3	Overall Survival Time - Part 1	PP (Optional)
14.2.2.4.4	Overall Survival Time - Part 2	PP (Optional)
14.2.2.4.5	Overall Survival Time – Subgroup 1	ITT
14.2.2.4.6	Overall Survival Time – Subgroup 2	ITT
14.2.2.4.7	Overall Survival Time – Subgroup 3	ITT

Table number	Table Title	Population
14.2.2.4.8	Overall Survival Time – Subgroup 4	ITT
14.2.2.4.9	Overall Survival Time – Subgroup 1	PP (Optional)
14.2.2.4.10	Overall Survival Time – Subgroup 2	PP (Optional)
14.2.2.4.11	Overall Survival Time – Subgroup 3	PP (Optional)
14.2.2.4.12	Overall Survival Time – Subgroup 4	PP (Optional)
14.2.3.1	Tumor Measurements based on RECIST V1.1 - Part 1	ITT
14.2.3.2	Tumor Measurements based on RECIST V1.1 – Part 2	ITT
14.2.3.3	Tumor Measurements based on RECIST V1.1 – Part 1	PP (Optional)
14.2.3.4	Tumor Measurements based on RECIST V1.1 – Part 2	PP (Optional)
14.2.3.5	Tumor Measurements based on irRECIST (Central) - Part 1	ITT
14.2.3.6	Tumor Measurements based on irRECIST (Central) – Part 2	ITT
14.2.3.7	Tumor Measurements based on irRECIST (Central) – Part 1	PP (Optional)
14.2.3.8	Tumor Measurements based on irRECIST (Central) – Part 2	PP (Optional)
14.2.3.9	Tumor Measurements based on irRECIST (Local) – Part 1	ITT
14.2.3.10	Tumor Measurements based on irRECIST (Local) – Part 2	ITT
14.2.3.11	Tumor Measurements based on irRECIST (Local) – Part 1	PP (Optional)
14.2.3.12	Tumor Measurements based on irRECIST (Local) – Part 2	PP (Optional)
	Safety	
14.3.1.1	Summary of Concomitant Medications - Part 1	SAF
14.3.1.2	Summary of Concomitant Medications - Part 2	SAF
14.3.1.3	Summary of Subsequent Anti-cancer Therapies - Part 1	SAF
14.3.1.4	Summary of Subsequent Anti-cancer Therapies - Part 2	SAF
14.3.2.1.1	Exposure - Part 1	SAF
14.3.2.1.2	Exposure - Part 2	SAF
14.3.2.1.3	Exposure by Cycle and Visit - Part 1	SAF
14.3.2.1.4	Exposure by Cycle and Visit - Part 2	SAF
	Adverse Events	
14.3.3.1.1	Overall Summary of Adverse Events - Part 1	SAF
14.3.3.1.2	Overall Summary of Adverse Events - Part 2	SAF
14.3.3.2.1	Summary of Treatment-Emergent Adverse Events – Part 1	SAF
14.3.3.2.2	Summary of Treatment-Emergent Adverse Events - Part 2	SAF
14.3.3.3.1	Summary of Treatment-Emergent Adverse Events Considered as Dose-Limiting Toxicity (DLT) - Part 1	SAF
14.3.3.4.1	Summary of Serious Treatment-Emergent Adverse Events - Part 1	SAF

Table number	Table Title	Population
14.3.3.4.2	Summary of Serious Treatment-Emergent Adverse Events - Part 2	SAF
14.3.3.5.1	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events - Part 1	SAF
14.3.3.5.1	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events - Part 2	SAF
14.3.3.6.1	Summary of Treatment Emergent Adverse Events by Maximum Severity Grade (according to CTCAE v.5.0) - Part 1	SAF
14.3.3.6.2	Summary of Treatment Emergent Adverse Events by Maximum Severity Grade (according to CTCAE v.5.0) - Part 2	SAF
14.3.3.7.1	Summary of Treatment-Emergent Adverse Events by Relationship to Pexa-Vec IV Infusion - Part 1	SAF
14.3.3.7.2	Summary of Treatment-Emergent Adverse Events by Relationship to Pexa-Vec IV Infusion - Part 2	SAF
14.3.3.7.3	Summary of Treatment-Emergent Adverse Events by Relationship to Pexa-Vec IT Injection - Part 2	SAF
14.3.3.7.4	Summary of Treatment-Emergent Adverse Events by Relationship to Cemiplimab IV Infusion - Part 1	SAF
14.3.3.7.5	Summary of Treatment-Emergent Adverse Events by Relationship to Cemiplimab IV Infusion - Part 2	SAF
14.3.3.8.1	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events Related to Pexa-Vec IV Infusion - Part 1	SAF
14.3.3.8.2	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events Related to Pexa-Vec IV Infusion - Part 2	SAF
14.3.3.8.3	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events Related to Pexa-Vec IT Injection - Part 2	SAF
14.3.3.8.4	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events Related to Cemiplimab IV Infusion – Part 1	SAF
14.3.3.8.5	Summary of Grade 3 or 4 Treatment-Emergent Adverse Events Related to Cemiplimab IV Infusion - Part 2	SAF
14.3.3.9.1	Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation - Part 1	SAF
14.3.3.9.2	Summary of Treatment-Emergent Adverse Events Leading to Study Discontinuation - Part 2	SAF
14.3.3.10.1	Summary of Treatment-Emergent Adverse Events Resulting in Interruption of Pexa-Vec IV Infusions - Part 1	SAF
14.3.3.10.2	Summary of Treatment-Emergent Adverse Events Resulting in Interruption of Pexa-Vec IV Infusions - Part 2	SAF
14.3.3.10.3	Summary of Treatment-Emergent Adverse Events Resulting in Interruption of Pexa-Vec IT Injections - Part 2	SAF
14.3.3.10.4	Summary of Treatment-Emergent Adverse Events Resulting in Interruption of Cemiplimab IV Injections - Part 1	SAF
14.3.3.11.1	Summary of Treatment-Emergent Adverse Events Resulting in Withdrawal of Pexa-Vec IV Infusions - Part 1	SAF
14.3.3.11.2	Summary of Treatment-Emergent Adverse Events Resulting in Withdrawal of Pexa-Vec IV Infusions - Part 2	SAF
14.3.3.11.3	Summary of Treatment-Emergent Adverse Events Resulting in Withdrawal of Pexa-Vec IT Infusions - Part 2	SAF
14.3.3.11.4	Summary of Treatment-Emergent Adverse Events Resulting in Withdrawal of Cemiplimab IV Infusions - Part 1	SAF
14.3.3.11.5	Summary of Treatment-Emergent Adverse Events Resulting in Withdrawal of Cemiplimab IV Infusions - Part 2	SAF
14.3.3.12.1	Summary of Adverse Event of Special Interest - Part 1	SAF
14.3.3.12.2	Summary of Adverse Event of Special Interest - Part 2	SAF
14.3.3.13.1	Summary of Treatment Emergent Adverse Event Leading to Death - Part 1	SAF
14.3.3.13.2	Summary of Treatment Emergent Adverse Event Leading to Death - Part 2	SAF
	Laboratory parameters	
14.3.4.1.1	Summary of Chemistry, Thyroid and Troponin Function - Part 1	SAF
14.3.4.1.2	Summary of Chemistry, Thyroid, and Troponin Function- Part 2	SAF

Table number	Table Title	Population
14.3.4.1.3	Summary of Chemistry, Thyroid, and Troponin Function Shifts from Baseline - Part 1	SAF
14.3.4.1.4	Summary of Chemistry, Thyroid, and Troponin Function Shifts from Baseline - Part 2	SAF
14.3.4.2.1	Summary of Hematology - Part 1	SAF
14.3.4.2.2	Summary of Hematology - Part 2	SAF
14.3.4.2.3	Summary of Hematology Shift from Baseline - Part 1	SAF
14.3.4.2.4	Summary of Hematology Shift from Baseline – Part 2	SAF
14.3.4.3.1	Summary of Coagulation - Part 1	SAF
14.3.4.3.2	Summary of Coagulation - Part 2	SAF
14.3.4.3.3	Summary of Coagulation Shift from Baseline - Part 1	SAF
14.3.4.3.4	Summary of Coagulation Shift from Baseline – Part 2	SAF
	Other Safety	
14.3.5.2.1	Karnofsky Performance Status - Part 1	SAF
14.3.5.2.2	Karnofsky Performance Status - Part 2	SAF
14.3.5.3.1	Vital signs – Part 1	SAF
14.3.5.3.2	Vital signs – Part 2	SAF
14.3.5.4.1	Cardiac function - Part 1	SAF
14.3.5.4.1	Cardiac function - Part 2	SAF

15.LISTINGS

Listing Number	Listing Title	Population
16.2.1.1.1	Analysis Populations – Part 1	ITT
16.2.1.1.2	Analysis Populations – Part 2	ITT
16.2.1.2.1	Patient Disposition – Part 1	ITT
16.2.1.2.2	Patient Disposition – Part 2	ITT
16.2.2.1.1	Protocol Deviations – Part 1	ITT
16.2.2.1.2	Protocol Deviations – Part 2	ITT
16.2.4.1.1	Demography and Baseline Characteristics Data – Part 1	ITT
16.2.4.1.2	Demography and Baseline Characteristics Data – Part 2	ITT
16.2.4.2.1	Medical History – Part 1	ITT
16.2.4.2.2	Medical History – Part 2	ITT
16.2.4.3.1	Serology – Part 1	ITT
16.2.4.3.2	Serology – Part 2	ITT
16.2.4.4.1	Pregnancy Test – Part 1	ITT
16.2.4.4.2	Pregnancy Test – Part 2	ITT
16.2.4.5.1	RCC History – Part 1	ITT
16.2.4.5.2	RCC History – Part 2	ITT
16.2.4.6.1	Prior RCC Medications – Part 1	ITT
16.2.4.6.2	Prior RCC Medications – Part 2	ITT
16.2.4.7.1	Prior Local-Regional Therapy for RCC – Part 1	ITT
16.2.4.7.2	Prior Local-Regional Therapy for RCC – Part 2	ITT
16.2.4.8.1	Prior Radiotherapy for RCC – Part 1	ITT
16.2.4.8.2	Prior Radiotherapy for RCC – Part 2	ITT
16.2.4.9.1	Prior Surgical Intervention – Part 1	ITT
16.2.4.9.2	Prior Surgical Intervention – Part 2	ITT
16.2.4.10.1	Prior and Concomitant Medications – Part 1	ITT
16.2.4.10.2	Prior and Concomitant Medications – Part 2	ITT

Listing Number	Listing Title	Population
16.2.4.11.1	Patient Eligibility and Inclusion/Exclusion Violations – Part 1	ITT
16.2.4.11.2	Patient Eligibility and Inclusion/Exclusion Violations – Part 2	ITT
16.2.4.12.1	Cemiplimab Re-treatment Eligibility – Part 1	ITT
16.2.4.12.2	Cemiplimab Re-treatment Eligibility – Part 2	ITT
16.2.4.13.1	Pexa-Vec Re-treatment Eligibility – Part 1	ITT
16.2.4.13.2	Pexa-Vec Re-Treatment Eligibility – Part 2	ITT
16.2.4.14.1	Cardiac Consultation and Clearance – Part 1	ITT
16.2.4.14.2	Cardiac Consultation and Clearance – Part 2	ITT
16.2.5.1.1.1	Study Drug Administration – Pexa-Vec IV Infusion – Part 1	ITT
16.2.5.1.1.2	Study Drug Administration – Pexa-Vec IV Infusion – Part 2	ITT
16.2.5.1.1.3	Study Drug Administration – Pexa-Vec IT Injection – Part 2	ITT
16.2.5.1.2.1	Study Drug Administration – Cemiplimab IV Infusion – Part 1	ITT
16.2.5.1.2.2	Study Drug Administration – Cemiplimab IV Infusion – Part 2	ITT
16.2.5.1.3	Pexa-Vec IT Injection Procedure – Part 2	SAF
16.2.5.1.4.1	Post-Study Cancer Treatment – Part 1	SAF
16.2.5.1.4.2	Post-Study Cancer Treatment – Part 2	SAF
16.2.5.2.1	Exposure – Part 1	SAF
16.2.5.2.2	Exposure – Part 2	SAF
16.2.6.1.1	Individual Plasma Pexa-Vec Concentrations – Part 1	PK
16.2.6.1.2	Individual Plasma Pexa-Vec Concentrations – Part 1	PK
16.2.6.1.3.1	Tumor Measurements based on RECIST V1.1 - Part 1	ITT
16.2.6.1.3.2	Tumor Measurements based on RECIST V1.1 – Part 2	ITT
16.2.6.1.3.3	Tumor Measurements based on irRECIST (Central) - Part 1	ITT
16.2.6.1.3.4	Tumor Measurements based on irRECIST (Central) - Part 2	ITT
16.2.6.1.3.5	Tumor Measurements based on irRECIST (Local) - Part 1	ITT
16.2.6.1.3.6	Tumor Measurements based on irRECIST (Local) - Part 2	ITT
16.2.6.1.4.1	Tumor Measurements based on RECIST V1.1– Sum of Longest Diameters (cm)- Part 1	ITT
16.2.6.1.4.2	Tumor Measurements based on RECIST V1.1– Sum of Longest Diameters (cm)- Part 2	ITT

Listing Number	Listing Title	Population
16.2.6.1.4.3	Tumor Measurements based on irRECIST (Central) – Sum of Longest Diameters (cm)- Part 1	ITT
16.2.6.1.4.4	Tumor Measurements based on irRECIST (Central) - Sum of Longest Diameters (cm)- Part 2	ITT
16.2.6.1.4.5	Tumor Measurements based on irRECIST (Local) - Sum of Longest Diameters (cm)- Part 1	ITT
16.2.6.1.4.6	Tumor Measurements based on irRECIST (Local) - Sum of Longest Diameters (cm)- Part 2	ITT
16.2.6.1.3.1	Medical Imaging - Part 1	ITT
16.2.6.1.3.2	Medical Imaging - Part 2	ITT
16.2.6.2.1	Overall Response - RECIST v1.1 – Part 1	ITT
16.2.6.2.2	Overall Response - RECIST v1.1 – Part 2	ITT
16.2.6.2.3	Overall Response – irRECIST (Central) – Part 1	ITT
16.2.6.2.4	Overall Response – irRECIST (Central) – Part 2	ITT
16.2.6.2.5	Overall Response – irRECIST (Local) – Part 2	ITT
16.2.6.2.6	Overall Response – irRECIST (Local) – Part 2	ITT
16.2.6.3.1.1	Progression Free Survival Time based on RECIST v1.1 – Part 1	ITT
16.2.6.3.1.2	Progression Free Survival Time based on RECIST v1.1 – Part 1	ITT
16.2.6.3.1.3	Progression Free Survival Time based on irRECIST (Central) – Part 1	ITT
16.2.6.3.1.4	Progression Free Survival Time based on irRECIST (Central) – Part 2	ITT
16.2.6.3.1.5	Progression Free Survival Time based on irRECIST (Local) – Part 1	ITT
16.2.6.3.1.6	Progression Free Survival Time based on irRECIST (Local) – Part 2	ITT
16.2.6.3.2.1	Overall Survival Time – Part 1	ITT
16.2.6.3.2.2	Overall Survival Time – Part 2	ITT
16.2.6.4.1	Tumor Biopsies – Part 1	ITT
16.2.6.4.2	Tumor Biopsies – Part 2	ITT
16.2.6.4.3	Blood Immune Correlates – Part 1	ITT
16.2.6.4.4	Blood Immune Correlates – Part 2	ITT
16.2.7.1.1	Adverse Events – Part 1	SAF
16.2.7.1.2	Adverse Events – Part 2	SAF
16.2.7.2.1	Serious Adverse Events – Part 1	SAF
16.2.7.2.2	Serious Adverse Events – Part 2	SAF

Listing Number	Listing Title	Population
16.2.7.3.1	Adverse Events of Special Interest – Part 1	SAF
16.2.7.3.2	Adverse Events of Special Interest – Part 2	SAF
16.2.7.4.1	Adverse Events Considered as Dose-Limiting Toxicity (DLT) - Part 1	SAF
16.2.7.5.1	Adverse Events Leading to Study Discontinuation– Part 1	SAF
16.2.7.5.2	Adverse Events Leading to Study Discontinuation – Part 2	SAF
16.2.7.6.1	Adverse Events Resulting in Withdrawal of Pexa-Vec IV Infusions - Part 1	SAF
16.2.7.6.2	Adverse Events Resulting in Withdrawal of Pexa-Vec IV Infusions - Part 2	SAF
16.2.7.6.3	Adverse Events Resulting in Withdrawal of Pexa-Vec IT Injection – Part 2	SAF
16.2.7.7.1	Adverse Events Resulting in Withdrawal of Cemiplimab IV Infusions – Part 1	SAF
16.2.7.7.2	Adverse Events Resulting in Withdrawal of Cemiplimab IV Infusions – Part 2	SAF
16.2.7.8.1	Deaths - Part 1	SAF
16.2.7.8.2	Deaths - Part 2	SAF
16.2.8.1.1.1	Chemistry, Thyroid, and Troponin Function Results – Part 1	SAF
16.2.8.1.1.2	Chemistry, Thyroid, and Troponin Function Results – Part 2	SAF
16.2.8.1.2.1	Abnormal Chemistry, Thyroid, and Troponin Function Results – Part 1	SAF
16.2.8.1.2.2	Abnormal Chemistry, Thyroid, and Troponin Function Results – Part 2	SAF
16.2.8.2.1.1	Hematology Results – Part 1	SAF
16.2.8.2.1.2	Hematology Results – Part 2	SAF
16.2.8.2.2.1	Abnormal Hematology Results – Part 1	SAF
16.2.8.2.2.2	Abnormal Hematology Results – Part 2	SAF
16.2.8.3.1.1	Coagulation Results – Part 1	SAF
16.2.8.3.1.2	Coagulation Results – Part 2	SAF
16.2.8.3.2.1	Abnormal Coagulation Results – Part 1	SAF
16.2.8.3.2.2	Abnormal Coagulation Results – Part 2	SAF
16.2.8.5.1	Urinalysis – Part 1	SAF
16.2.8.5.2	Urinalysis – Part 2	SAF
16.2.9.1	Vital Signs Results – Part 1	SAF
16.2.9.2	Vital Signs Results – Part 2	SAF

Listing Number	Listing Title	Population
16.2.10.1	Physical Examination Findings – Part 1	SAF
16.2.10.2	Physical Examination Findings – Part 2	SAF
16.2.11.1	Karnofsky Performance Status – Part 1	SAF
16.2.11.2	Karnofsky Performance Status – Part 2	SAF
16.2.13.1	Cardiac function (ECG and Echo) – Part 1	SAF
16.2.13.2	Cardiac function (ECG and Echo) – Part 2	SAF

16.FIGURES

Figure Number	Figure Title	Population
14.2	**PK/Efficacy**	
14.2.2.1.1	Individual Plasma Pexa-Vec Concentrations (Linear) - Part 1	PK
14.2.2.1.2	Individual Plasma Pexa-Vec Concentrations (Linear) - Part 2	PK
14.2.2.1.3	Individual Plasma Pexa-Vec Concentrations (Semi-Log) - Part 1	PK
14.2.2.1.4	Individual Plasma Pexa-Vec Concentrations (Semi-Log) - Part 2	PK
14.2.2.1.5	Mean Plasma Pexa-Vec Concentrations (Linear) - Part 1	PK
14.2.2.1.6	Mean Plasma Pexa-Vec Concentrations (Linear) - Part 2	PK
14.2.2.1.7	Mean Plasma Pexa-Vec Concentrations (Semi-Log) - Part 1	PK
14.2.2.1.8	Mean Plasma Pexa-Vec Concentrations (Semi-Log) - Part 2	PK
14.2.2.1.9	Progression Free Survival Time based on RECIST v1.1 – Part 1	ITT
14.2.2.1.10	Progression Free Survival Time based on RECIST v1.1 – Part 2	ITT
14.2.2.1.11	Progression Free Survival Time based on irRECIST (Central) – Part 1	ITT
14.2.2.1.12	Progression Free Survival Time based on irRECIST (Local) – Part 1	ITT
14.2.2.1.13	Progression Free Survival Time based on irRECIST (Central) – Part 1	ITT
14.2.2.1.14	Progression Free Survival Time based on irRECIST (Local) – Part 2	ITT
14.2.2.1.15	Overall Survival Time – Part 1	ITT
14.2.2.1.16	Overall Survival Time – Part 2	ITT
14.2.2.1.17	Spider Plot of Percent Change in Tumor Size from Baseline (RECIST V1.1) – Part 1	ITT
14.2.2.1.18	Spider Plot of Percent Change in Tumor Size from Baseline (RECIST V1.1) – Part 2	ITT
14.2.2.1.19	Spider Plot of Percent Change in Tumor Size from Baseline (irRECIST -Central) – Part 1	ITT
14.2.2.1.20	Spider Plot of Percent Change in Tumor Size from Baseline (irRECIST -Local) – Part 1	ITT
14.2.2.1.21	Spider Plot of Percent Change in Tumor Size from Baseline (irRECIST -Central) – Part 2	ITT
14.2.2.1.22	Spider Plot of Percent Change in Tumor Size from Baseline (irRECIST -Local) – Part 2	ITT
14.2.2.1.23	Waterfall Plot of Best Percent Change in Tumor Size from Baseline (RECIST V1.1) – Part 1	ITT
14.2.2.1.24	Waterfall Plot of Best Percent Change in Tumor Size from Baseline (RECIST V1.1) – Part 2	ITT
14.2.2.1.25	Waterfall Plot of Best Percent Change in Tumor Size from Baseline (irRECIST -Central) – Part 1	ITT

Figure Number	Figure Title	Population
14.2.2.1.26	Waterfall Plot of Best Percent Change in Tumor Size from Baseline (irRECIST -Local) – Part 1	ITT
14.2.2.1.27	Waterfall Plot of Best Percent Change in Tumor Size from Baseline (irRECIST -Central) – Part 2	ITT
14.2.2.1.28	Waterfall Plot of Best Percent Change in Tumor Size from Baseline (irRECIST -Local) – Part 2	ITT

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