# STATISTICAL ANALYSIS PLAN
# FOR CLINICAL STUDY REPORT

## A PHASE 1/2 STUDY OF THE SAFETY AND EFFICACY OF ULOCUPLUMAB COMBINED WITH NIVOLUMAB IN SUBJECTS WITH ADVANCED OR METASTATIC SOLID TUMORS (CXCESSOR4: CLINICAL TRIAL OF THE ANTI-CXCR4 ANTIBODY ULOCUPLUMAB IN MALIGNANT TUMORS)

## PROTOCOL CA212115

## VERSION # 1.0

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

# 1 BACKGROUND AND RATIONALE

[redacted]

[redacted]

This study will clinically evaluate the combination of nivolumab with ulocuplumab to determine whether this combined novel mechanism will benefit metastatic cancers poorly treated by standard therapies.

**Research Hypothesis:**

Treatment with ulocuplumab in combination with nivolumab will be safe, tolerable and demonstrate clinically meaningful efficacy in subjects with advanced or metastatic solid tumors.

# 2 STUDY DESCRIPTION

Within each tumor type (Small Cell Lung Cancer, SCLC and Pancreatic Adenocarcinoma, PAC), the study is divided into different phases and the design of each phase generally depends on the results from earlier phases:

- The "Dose Evaluation Phase" (Stage 1) which is further divided into a dose limiting toxicity (DLT) "DLT evaluation period" and the "Dose Evaluation Phase" itself that, depending on the outcome of the DLT evaluation period, will consist either of a randomized design considering three cohorts or a single arm design considering one cohort. During that phase a unique "recommended dose and schedule" of ulocuplumab will be determined for use during the Dose Expansion Phase.

Using the recommended dose and schedule and, depending on the magnitude of the efficacy of that regimen during the Dose Evaluation Phase, the "Dose Expansion Phase" (Stage 2) will have the following form: in case of moderate efficacy (see Table 2.1.2-1), the form of this phase will be a single arm consisting of the second stage of a Simon 2-stage design; in case of high efficacy (see Table 2.1.2-1), it will have the form of a two-arm open label randomized Phase 2 design with a comparative arm.

The selected design and recommended dose and schedule may be different for each tumor type.

**Schedule of Analyses:**

The analyses presented in this Statistical Analysis Plan (SAP) are intended to take place independently for each tumor type (SCLC and PAC) and at the following time points for each phase of the study:

- Dose Evaluation Phase (note that data from the DLT evaluation period will be included in some of the below analyses):
  - An interim analysis (IA) will be conducted when all subjects in the Dose Evaluation Phase have a minimum of 3 months of treatment or discontinued prematurely. The objectives of this IA will be: 1) to determine if further study of ulocuplumab combined with nivolumab is warranted; 2) if further study is warranted, to select a recommended dose and schedule for the Dose Expansion Phase; and 3) if the Dose Expansion Phase is to be completed, to determine the design to be used.
  - The final analysis will take place when all subjects will have discontinued the study. In relation to this:
    - If the Dose Expansion Phase is of the form of a Simon 2-stage design, this analysis may be integrated into the Simon 2-stage analyses (IA or final).
    - If the Dose Expansion Phase is of the form of a Randomized Phase 2 design, a summary of the Dose Expansion Phase will take place, separately from the Randomized data.

- Dose Expansion Phase:
  - 2-stage design
    - An IA will be conducted when all subjects have a minimum of 3 months of treatment or discontinued prematurely. The objectives of this IA will be similar to item 1) and 2) of the Dose Evaluation Phase IA objectives.
    - The final analysis will take place when all subjects will have discontinued the study.
  - Randomized Phase 2
    - IAs will be conducted on a regular basis for the interim monitoring as specified in the Data Monitoring Committee (DMC) charter.
    - The final analysis will take place when all subjects will have discontinued the study.

At the time of finalizing this SAP, it is known that subjects reported more than 2 DLTs in the "ulocuplumab 400mg weekly combined with nivolumab" cohort (DL1, in PAC subjects). Therefore, and according to protocol, the DL-1 cohort (ulocuplumab 200mg weekly combined with nivolumab) has been initiated. Following this and, considering the current study design, there will be no randomization during the Dose Evaluation phase and no use of the DL3B regimen: "ulocuplumab at 1600mg every 2 weeks combined with nivolumab". The current version of this SAP is using this information and does not consider that randomization nor the DL3B regimen while describing the planned analyses. Also, as no ulocuplumab dose reduction were reported for the DL1 cohort and as the DL-1 cohort does not allow dose reduction no analysis related to ulocuplumab dose reduction will be planned.

Also, to streamline the document, any reference to the analysis of the potential "Randomized Phase 2" part of the study are not included at this time and may be added at a later time if warranted.

## 2.1 Study Design

This is an open-label, multicenter phase 1/2 study of ulocuplumab in combination with nivolumab designed to independently evaluate the safety and efficacy in subjects with SCLC and PAC. The study design consists of a Dose Evaluation Phase (Stage 1) that will include a DLT evaluation period to identify the maximum tolerated dose (MTD). If the maximum dose level (DL3) is identified as the MTD, a parallel evaluation of three cohorts will assess two dose levels (800 mg, 1600 mg) and an additional schedule for 1600 mg (every 2 weeks). If 2 or more DLT are seen with any dose during the DLT evaluation period, a lower dose will be evaluated as a single arm. Nivolumab will be administered every two weeks.

A recommended dose will be selected based on the safety and efficacy data from Stage 1 and will proceed to Dose Expansion in the form of a Simon optimal 2-stage like design or a randomized Phase 2 study with comparative arm if high efficacy is observed.

The treatment period will continue until disease progression or occurrence of unacceptable toxicity. The duration of the study is anticipated to be approximately 2 years.

The study design schematic is presented the Figure below.

**Figure 2.1-1: Dose Evaluation Phase (Stage 1)**

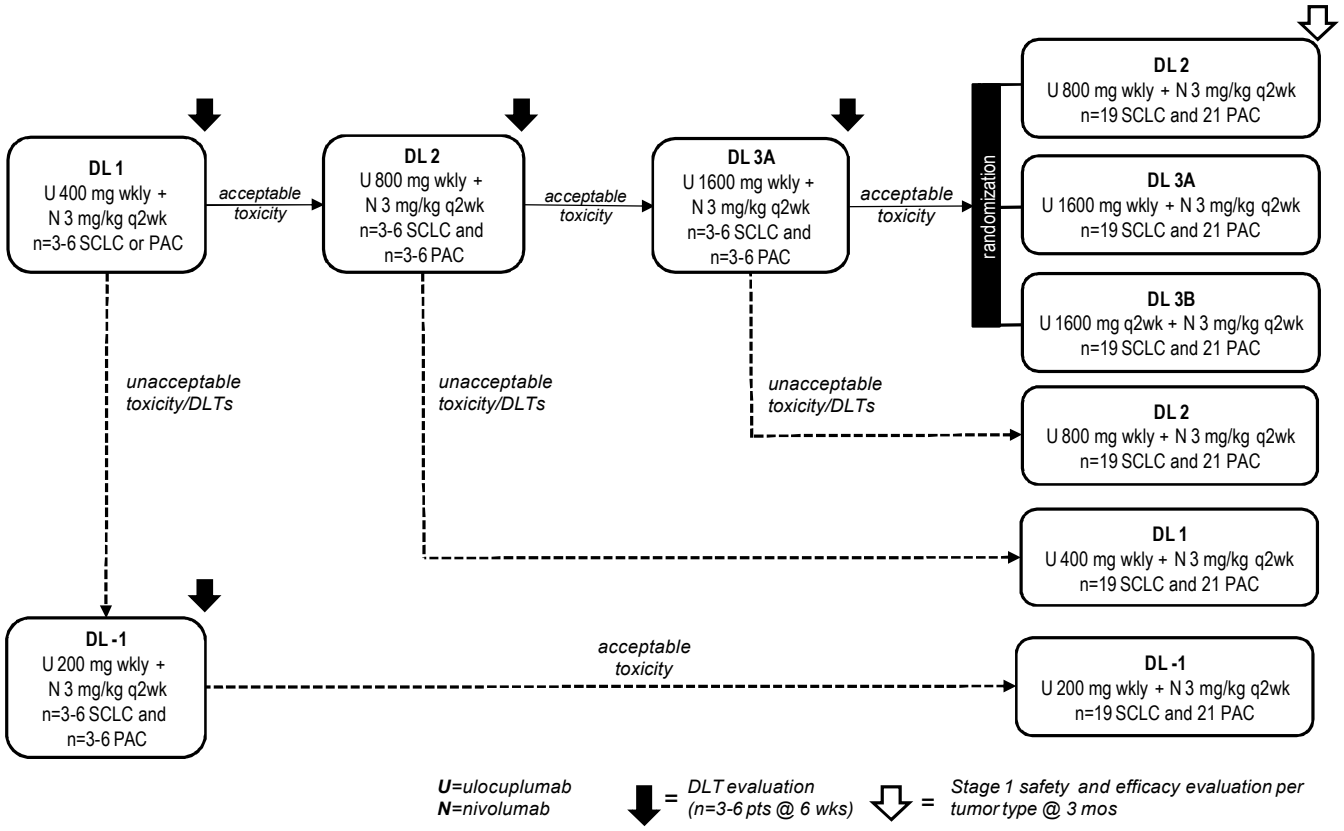
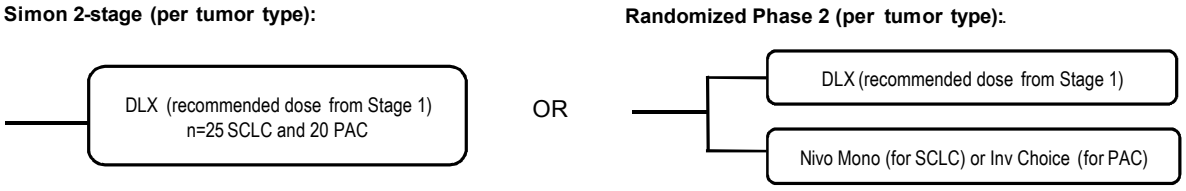



**Figure 2.1-2: Dose Expansion Phase (Stage 2)**




### *2.1.1 Dose Evaluation Phase (Stage 1)*

The Dose Evaluation Phase will consist of a DLT evaluation period followed by an evaluation of up to three cohorts with various doses and schedules of ulocuplumab combined with nivolumab. The DLT evaluation period will be conducted in the first 3-6 subjects with either PAC or SCLC at dose level 1 (DL1; 400 mg weekly ulocuplumab combined with nivolumab), followed by 3-6 subjects each with PAC and SCLC at DL2 (800 mg weekly ulocuplumab combined with nivolumab), followed by 3-6 subjects each with PAC and SCLC at DL3A (1600 mg weekly ulocuplumab combined with nivolumab) for 6 weeks. For DL1, both tumor types will be combined for the safety evaluation. If 2 or more DLT are observed at DL1, de-escalation to DL-1 will occur (200 mg weekly ulocuplumab combined with nivolumab). For all other dose levels, each tumor

type will be evaluated for safety independently in the event that tumor specific AE may emerge. Enrollment during the DLT evaluation phase will allow for concurrent accrual of up to 6 subjects in each dose/tumor cohort (i.e., Rolling Six design[1]).

The incidence of DLT(s) assessed during the first 6 weeks of treatment will be used to initially determine whether a dose level is tolerable. DLT should not be adverse event (AE) considered by the investigator to be disease related. The following drug-related AE (whether related to one or both agents) will be considered a DLT:

- Any drug-related non-hematological AE of Grade ≥ 3, including the following laboratory abnormalities:
  - If a subject has baseline Grade ≤ 1 AST, ALT, or total bilirubin, a drug-related Grade ≥ 3 toxicity will be considered a DLT
  - If a subject has baseline Grade 2 AST or ALT, drug-related elevations in AST and/or ALT > 2x baseline or a maximum of > 8x ULN will be considered a DLT
- Any Grade 4 drug-related hematological AE or hematological or non-hematological laboratory abnormality with the following exceptions:
  - Grade 4 amylase or lipase not associated with symptoms or clinical manifestations
  - Grade 4 lymphocytopenia not associated with symptoms or clinical manifestations
- Any drug-related AE that results in dose reduction of ulocuplumab during the DLT period
- Any drug related AE that results in dose delay of ulocuplumab > 14 days during DLT period
- Any toxicity managed by discontinuation of ulocuplumab or nivolumab.

Depending on the number of DLT observed during the DLT evaluation period, escalation or de-escalation of ulocuplumab may be warranted. Dose escalation/de-escalation at the 800mg weekly and 1600mg weekly ulocuplumab dose levels will occur independently for each tumor type. No dose modification of nivolumab will be allowed in this study.

### *2.1.2 Decision Rules to Proceed with Dose Expansion Phase*

An interim analysis (IA) will be carried out when all subjects in the Dose Evaluation Phase in an individual tumor type have at least three months of treatment, or discontinued prematurely. This IA will be conducted independently for each tumor type. Investigator-assessed ORR will be used to guide the decision making for the Stage 2 portion of the study. However, all available efficacy and safety data will be used to select the recommended dose that will be further evaluated in the Dose Expansion Phase. Furthermore, if the level of efficacy observed at the recommended dose in the Dose Evaluation Phase does not warrant stopping evaluation of that tumor type, it will be used to select the appropriate Expansion Phase study design, either continuing with the second stage of a Simon 2-stage-like design or conducting a randomized Phase 2 study with comparative arm. The determination of low, moderate or high efficacy will be based primarily on the response rates observed with ulocuplumab and nivolumab (see Table 2.1.2-1), but the totality of available safety and efficacy data will be considered. For further information on the interim analysis and the efficacy thresholds used for decision rules, refer to Section 7.5.1.

- If the number of responders per tumor type at the recommended dose level is consistent with low efficacy, the evaluation of that tumor type will be placed on hold pending final review of the data.
- If the number of responders per tumor type at the recommended dose level is consistent with moderate efficacy, the Dose Expansion Phase will continue with a single-arm evaluation.
- If the number of responders per tumor type at the recommended dose level is consistent with high efficacy, the Dose Expansion Phase will be continue with a randomized Phase 2 study with comparative arm.

**Table 2.1.2-1: Stage 1 Efficacy Threshold For Each Tumor Type**

| Efficacy Threshold | SCLC | PAC |
|---|---|---|
| Low | 3 responders / 19 subjects | 1 responders / 21 subjects |
| Moderate | 4-8 responders / 19 subjects | 2-5 responders / 21 subjects |
| High | 9 responders / 19 subjects | 6 responders / 21 subjects |

### *2.1.3 Dose Expansion Phase (Stage 2)*

Based on the results of the IA, the Dose Expansion Phase will consist of a second stage of a Simon 2-stage single arm study (moderate efficacy) or a randomized Phase 2 study with comparative arm (high efficacy).

The second stage of a Simon 2-stage design will expand enrollment at the recommended dose level in a single arm study. The primary endpoint will be investigator-assessed ORR for both tumor types.

The randomized Phase 2 study will compare the combination therapy at the recommended dose level versus a comparative arm appropriate for that tumor type. The primary endpoint of this study will be dictated by the tumor type, where ORR is the endpoint for a randomized Phase 2 study in SCLC and OS for a randomized Phase 2 study in PAC. For ORR, independent radiology review committee (IRRC) will perform blinded independent review of the imaging per RECIST 1.1 criteria. Stratification factors will be used for this portion of the study and will include performance status (ECOG 0 vs. 1) and type of chemotherapy used in the first line setting (fluoropyrimidine-containing vs. gemcitabine-containing regimens). More details regarding the randomized Phase 2 for each tumor type are described in the protocol.

## 2.2 Treatment Assignment

A subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Enrolled subjects that have met all eligibility criteria will continue with treatment assignment and drug vial assignment through the IVRS.

## 2.3 Blinding and Unblinding

Not applicable (open label study whatever the study phase).

## 2.4 Protocol Amendments

There are currently 5 approved amendments. The history of protocol amendments including the dates and changes to the protocol are summarized below.

- Amendment 1 (25-Mar-2015, all sites in the USA): The objective of this amendment was to initiate a biopsy sub-study that will allow to explore the changes in cellular architecture and localization of immune cell populations before and during treatment with ulocuplumab and nivolumab for use in future exploratory research (e.g., to validate the hypothesis that the refractory nature of SCLC and PAC results from an immunosuppressive environment surrounding the tumor that prevents activated lymphocytes from accessing the tumor site).
- Amendment 2 (20-May-2015, all sites): The objective of this amendment was to add a sentinel 400mg weekly ulocuplumab dose level in the dose evaluation phase at the request of regulatory authorities. It also incorporated administrative edits and minor clarifications to the study procedures.
- Amendment 3 (30-Sep-2015, all sites): This amendment changed dose delay, dose modification, discontinuation and DLT criteria to account for the known toxicity profiles of ulocuplumab and nivolumab and corrected internal inconsistencies in the management of toxicity. The major change was to remove the requirement to discontinue study therapy for > 7 days of grade 3 thrombocytopenia and replace it with a recommendation to delay therapy for > 7 days of grade 3 thrombocytopenia that occurs in the absence of bleeding. Discontinuation is still required for grade 4 thrombocytopenia lasting longer than 5 days.
- Amendment 4 (13-Jan-2016, all sites): This amendment changed DLT, dose delay, dose modification and dose discontinuation criteria to align with nivolumab program standard language. Additional changes have been made to platelet inclusion criteria and prohibited medications. Also, chest x-rays were added to monitor for potential early pulmonary toxicity.
- Amendment 5 (13-Jan-2016, all sites in the USA): The objective of this amendment was to add optional peripheral blood DNA sample to the biopsy sub study.

# 3 OBJECTIVES

## 3.1 Primary

- Stage 1: To identify the recommended dose and schedule, based on safety and efficacy, of ulocuplumab in combination with nivolumab in subjects with advanced or metastatic tumors.
- Stage 2: To evaluate the efficacy, separately by tumor type, based on objective response rate (ORR) or overall survival (OS; randomized Phase 2 study in PAC only), of ulocuplumab combined with nivolumab in subjects with advanced or metastatic tumors.

## 3.2 Secondary

- To assess the safety and tolerability of ulocuplumab combined with nivolumab, in subjects with advanced or metastatic tumors.

- To assess progression-free survival (PFS) with ulocuplumab combined with nivolumab, separately by tumor type, in subjects with advanced or metastatic tumors.

### 3.3 Exploratory

[redacted]

## 4 ENDPOINTS

Dose Evaluation Phase:

- DLT evaluation period: the primary endpoint (safety) is the incidence of DLTs.
- Dose Evaluation Phase: the primary endpoint is the investigator assessed ORR. Secondary endpoint is PFS.

Dose Expansion Phase:

- 2-stage design: the primary endpoint is the investigator assessed ORR. Secondary endpoint is PFS.

Common exploratory endpoints are duration of response, disease control rate, and the magnitude of reduction in tumor volume. For all tumor types and phases secondary endpoints will include the safety parameters as described in Section 4.2.

Disease progression will primarily be determined using RECIST 1.1 criteria but "clinical progression" will be considered when RECIST 1.1 criteria cannot be evaluated and only clinical progression data is available (e.g., for some PAC subjects).

Timing of evaluation of the efficacy and safety endpoints is detailed in protocol Table 5.1-1 (Screening), 5.1-2 (On-Study Assessments for Dose Evaluation Phase, Stage 1: Ulocuplumab

Weekly Dosing), 5.1-4 (On-Study Assessments for Dose Expansion Phase, Stage 2) and 5.1-5 (Follow-up Assessments).

## 4.1 Efficacy Endpoints

### *4.1.1 Primary Endpoint*

Investigator assessed ORR is defined as the number of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects. The BOR is defined as the best response designation, as determined by the investigator, recorded between the first dosing date and the date of objectively documented progression or the date of subsequent anti-cancer therapy (systemic medication, surgery or radiotherapy for cancer), whichever occurs first. CR or PR determinations included in the BOR assessment must be confirmed by a second scan no less than 4 weeks after the criteria for response are first met. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial progression.

### *4.1.2 Secondary Endpoints*

Progression-free survival is defined as the time from first dosing date to the date of the first documented tumor progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable (i.e., with non-missing tumor data) tumor assessment. Subjects who did not have any baseline or on-study tumor assessments and did not die will be censored on the date of their first dose. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

### *4.1.3 Exploratory Endpoints*

[redacted]

[redacted]

## 4.2 Safety Endpoints

Beside the evaluations used to address the primary endpoint of the DLT evaluation period (the incidence of DLTs), safety endpoints include deaths, SAEs and AEs, select AEs, immune-mediated AEs (IMAEs), and other events of special interest, laboratory evaluations, electrocardiograms (ECG), and reasons off treatment.

### *4.2.1 Select Adverse Events*

The select Adverse Events (select AEs) consist of a list of preferred terms grouped by specific category that are of relevance for understanding the risks of immune therapies such as nivolumab. To date, 7 categories of select AEs have been identified see Table 4.2.1-1.

**Table 4.2.1-1: Select Adverse Events**

| Category | Subcategory |
|---|---|
| Endocrine Adverse Events | Adrenal Disorder |
| | Diabetes |
| | Pituitary Disorder |
| | Thyroid Disorder |
| Hypersensitivity/Infusion Reactions | |
| Gastrointestinal Adverse Events | |
| Hepatic Adverse Events | |
| Pulmonary Adverse Events | |
| Renal Adverse Events | |
| Skin Adverse Events | |

AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity are included as select AEs. The select AEs and the categories are defined by the Sponsor and the list that is the most current at the time of analysis will be used. Changes may be made to this list with each new version of the Medical Dictionary for Regulatory Activities (MedDRA), prior to database lock. Categories of select AEs may include subcategories (e.g. adrenal disorders, diabetes, pituitary disorders, and thyroid disorders are subcategories of the endocrine event category). Other categories could be created during the conduct of the study. If so, similar table/listing will be produced for these

additional categories. Similarly, some category can be removed or regrouped and corresponding table/listing will be updated accordingly.

The analysis of select adverse events will be conducted using the 30-day safety window.

### *4.2.2 Immune-mediated Adverse Events*

In order to further characterize the safety profile of immune therapies such as nivolumab, an analysis of immune-mediated AEs (IMAE) will be conducted. IMAEs are specific events (or groups of PTs describing specific events) that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency). In addition, hypersensitivity/infusion-related reactions will be analyzed along with the IMAE categories because multiple event terms may be used to describe such events and pooling of terms is therefore necessary for full characterization. Hypersensitivity/infusion-related reactions do not otherwise meet criteria to be considered IMAEs.

IMAE analyses include events, regardless of causality, occurring within 100 days of the last dose. Related analyses are limited to subjects who received immunosuppressive medication for treatment of the event, with the exception of endocrine events which will be included regardless of treatment since these events are often managed without immunosuppression. IMAE categories will be populated using the list that is the most current at the time of analysis.

### *4.2.3 Other Events of Special Interest*

The other events of special interest (OESI) consist of a list of preferred terms grouped by specific category (i.e.: myasthenic syndrome, demyelination, Guillain-Barre syndrome, pancreatitis, uveitis and encephalitis). The OESI categories and terms are defined by the Sponsor and the list that is the most current at the time of analysis will be used.

[redacted]

[redacted]

[redacted]

[redacted]

# 5 SAMPLE SIZE AND POWER

Within each tumor type, the sample size will start with a minimum of 3 treated subjects using a Rolling Six design for evaluation of DLT. Then, the sample size will be increased by the number of subjects needed to continue the DLT evaluation then, by the number of subjects needed for one or three randomized cohort(s) to complete the Dose Evaluation Phase. Finally, the sample size will be increased by the number of subjects needed for the Dose Expansion Phase.

## 5.1 SCLC Sample Size

For SCLC, up to approximately 175 treated subjects may be needed. This sample size considers the following:

- Up to 18 subjects for the DLT evaluation
- 19 subjects per cohort for the Dose Evaluation Phase (57 subjects for three randomized cohorts)
- A second stage of a Simon 2-stage like design in the Dose Expansion Phase that would require an additional 25 subjects

OR

- A randomized Phase 2 study with comparative arm in the Dose Expansion Phase that would require an additional 50 subjects per arm (i.e. 100 for the two arms)

These numbers are obtained using the following methods and assumptions:

- A Simon optimal 2-stage design will test the null hypothesis that the true response rate is less than or equal to 15% versus the alternative hypothesis that it exceeds 15%. The type I error rate will be 5% (one-sided) and the design will have 90% power to reject the null hypothesis when the true response rate is 35%. The Simon design in this tumor type will require 19 treated subjects for the first stage and at least 4 responders to initiate Stage 2. An additional 25 treated subjects will be needed for the second stage and the drug will be considered of potential clinical interest if, at the end of the second stage, there are 11 or more responders out of the total of 44 treated subjects. Subjects who were assigned treatment but never treated will not count towards the total of 19 treated subjects for the first stage or the 44 treated subjects in a cohort and will be replaced.
- If an open label randomized Phase 2 with comparative arm study is initiated (1:1 ratio), the primary measurement for efficacy will be IRRC assessed ORR. Considering one-sided alpha level of 0.10 a sample size of 50 subjects per arm would provide approximately 80% power to detect a difference of 20% in the response rates between the two arms (based on a Fisher's exact test) assuming an ORR of 35% for the combination arm of ulocuplumab plus nivolumab and an ORR of 15% for the nivolumab monotherapy arm.

## 5.2 PAC Sample Size

For PAC, up to approximately 331 treated subjects may be needed. This sample size considers the following:

- Up to 18 subjects for the DLT evaluation
- 21 subjects per cohort for the Dose Evaluation Phase (63 subjects for three randomized cohorts)
- A second stage of a Simon 2-stage like design in the Dose Expansion Phase that would require an additional 20 subjects

OR

- A randomized Phase 2 study with comparative arm in the Dose Expansion Phase that would require an additional 125 subjects per arm (i.e. 250 for the two arms)

These numbers are obtained using the following methods and assumptions:

- A Simon optimal 2-stage design will test the null hypothesis that the true response rate is less than or equal to 5% versus the alternative hypothesis that it exceeds 5%. The type I error rate will be 5% (one-sided) and the design will have 90% power to reject the null hypothesis when the true response rate is 20%. The Simon design in this tumor type will require 21 treated subjects for the first stage and at least 2 responders to initiate Stage 2. An additional 20 treated subjects will be needed for the second stage and the drug will be considered of potential clinical interest if, at the end of the second stage, there are 5 or more responders out of the total of 41 treated subjects. Subjects who were assigned treatment but never treated will not count towards the total of 21 treated subjects for the first stage or the total of 41 subjects in a cohort and will be replaced.
- If an open label randomized Phase 2 study with comparative arm is initiated (1:1 ratio), the primary measurement for efficacy will be OS. A one-sided alpha level of 0.10log-rank test will be used to compare the OS of subjects randomized to the combination arm of ulocuplumab plus nivolumab to that of subjects randomized to the investigator's choice chemotherapy arm. In order for the test to have at least 80% power to reject the null hypothesis of no difference in OS among treatment groups when the hazard ratio of the experimental arm to the control arm is 0.75, the study will require 218 events (deaths) to complete. The analysis of OS will take place when the following two conditions have been met: 218 events have been observed and all subjects have been on study for at least 6 months. The requirement that subjects be on study for at least 6 months is meant to ensure adequate follow-up. A total of 250 subjects are to be randomized. Assuming an accrual rate of 20 subjects per month, the accrual will last approximately 13 months. Assuming exponentially distributed OS and median OS times in the control and experimental arms of 4.5 months and 6.0 months, respectively, it is expected that the requisite number of events (deaths) will occur approximately 10 months after all subjects have been randomized.

# 6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

## 6.1 Study Periods

### *6.1.1 Baseline Period*

- Baseline AEs will be defined as AEs with an onset date prior to but not including the first day of treatment.

- For infusion related events, baseline will be defined as AEs with an onset date and time prior to but not including the first day and time of treatment.
- For all other evaluations (ECOG, laboratory data, ECGs, vital signs, etc.) baseline will be defined as evaluations with an onset date on or prior to the first day of treatment.

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected on the same date (and time, if collected), the assessment with the latest database entry date (and time, if collected) will be considered as baseline.

### *6.1.2 Post Baseline Period*

- On-treatment AEs will be defined as AEs with an onset date on or after the first day of treatment.
- For infusion related events, on-treatment will be defined as AEs with an onset date and time on or after the first day and time of treatment.
- For all other evaluations (ECOG, laboratory data, ECGs, vital signs, etc.) on-treatment will be defined as evaluations taken after the first day of treatment.
- If a subject is still on study treatment, any AE/evaluation post baseline is considered as on-treatment. For subjects off study treatment, AEs/evaluations will be counted as on-treatment if the event occurred within 30 days or 100 days (depending on the analysis) after the last dose of ulocuplumab or nivolumab, whichever is later.
- Late-emergent drug-related AEs will be defined as drug-related AEs with an onset date greater than 100 days after the last dose of study treatment in subjects who are off study treatment.

## 6.2 Treatment Regimens

As indicated at the end of Section 3, the current version of this SAP does not consider any randomization nor the DL3B regimen while describing the planned analyses.

The cohorts are defined by the ulocuplumab regimen only. The nivolumab regimen will always be 3mg/kg every 2 weeks (no nivolumab dose modification is allowed).

The cohort “as allocated” will be retrieved from the IVRS.

The cohort “as treated” will be the same as the cohort “as allocated” by IVRS. However, if a subject received an incorrect drug for the entire period of treatment, the subject’s cohort will be defined by the incorrect drug the subject actually received.

For the Dose Evaluation Phase and the 2-stage design, all analysis will be presented “as-treated”.

## 6.3 Populations for Analyses

All populations will be defined separately by tumor type.

- Dose Evaluation Phase:
  - All DLT-evaluable Subjects: All subjects who completed the DLT evaluation period (i.e., received at least 5 out of 6 doses of ulocuplumab and at least 2 out of 3 doses of nivolumab in a 6 week dosing period or experienced a DLT).
  - All Dose Evaluation Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS during the Dose Evaluation Phase (this population includes subjects from the DLT evaluation period).
  - All Dose Evaluation Treated Subjects: All subjects who received at least one dose of any study medication during the Dose Evaluation Phase (this population includes subjects from the DLT evaluation period).
  - All Dose Evaluation Excluding DLT Treated Subjects: All subjects who were allocated to a unique cohort during the Dose Evaluation Phase and were treated (this population excludes subjects from the DLT evaluation period).
- Dose Expansion Phase:
  - All Dose Expansion Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS during the Dose Expansion Phase.
  - All Dose Expansion Treated Subjects: All subjects who were allocated to a unique cohort during the Dose Expansion Phase and were treated (this population correspond to the second stage of a 2-stage design and it will not be used as such for reporting, see "Both Phases combined" below).
- Both Phases combined:
  - All 2-stage Enrolled Subjects: This population consists of the pooling of the "All Dose Evaluation Enrolled Subjects" with the "All Dose Expansion Enrolled Subjects".
  - All 2-stage Treated Subjects: This population consists of the pooling of the "All Dose Evaluation Excluding DLT Treated Subjects" with the "All Dose Expansion Treated Subjects".
  - All 2-stage Including DLT Treated Subjects: This population consists of the pooling of the "All Dose Evaluation Treated Subjects" with the "All Dose Expansion Treated Subjects".
- Other populations (note that the PK and the immunogenicity are study drug specific as these populations are defined for ulocuplumab or for nivolumab, separately):
  - All Dose Evaluation PK Evaluable Subjects: All subjects who received at least one dose of study medication and have available serum concentration data during the Dose Evaluation Phase.

    All Dose Expansion PK Evaluable Subjects: All subjects who received at least one dose of study medication and have available serum concentration data during the Dose Expansion Phase.
  - All Dose Evaluation Biomarker Evaluable Subjects: All subjects who received at least one dose of study medication and have baseline and at least one post-baseline biomarker assessment during the Dose Evaluation Phase.

- All Dose Expansion Biomarker Evaluable Subjects: All subjects who received at least one dose of study medication and have baseline and at least one post-baseline biomarker assessment during the Dose Expansion Phase.
- All Dose Evaluation Immunogenicity Evaluable Subjects: All subjects who received at least one dose of study medication and have baseline and at least one post-baseline immunogenicity assessment during the Dose Evaluation Phase.
- All Dose Expansion Immunogenicity Evaluable Subjects: All subjects who received at least one dose of study medication and have baseline and at least one post-baseline immunogenicity assessment during the Dose Expansion Phase.

# 7 STATISTICAL ANALYSES

## 7.1 General Methods

All analyses will be presented separately by tumor type.

Descriptive summaries of continuous and other numeric variables will at least consist of the following summary statistics: median, minimum and maximum values. Categorical variables will be summarized by the frequency and proportion of subjects falling into each category. Unless otherwise indicated, percentages in tables will be column percentages, using the total number of observations in the population, grouped by cohort, as the denominator. Percentages will be rounded to one decimal place, and thus may not always add up to exactly 100%.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the most recent version of the dictionary at the time of the database lock will be used. AEs and laboratory tests will be graded using the National Cancer Institute - Common Toxicity Criteria for Adverse Event (NCI-CTCAE) Version 4.03. Clinical laboratory values will be first reported in using International System of Units (SI). Analyses will be repeated using US conventional units. Medications will be coded using the most recent version of the BMS WHO Drug Dictionary.

Time-to event variables (e.g., PFS, OS, DOR, etc.) will be analyzed using the Kaplan-Meier product limit method (KM). When specified, the median will be reported along with 95% confidence interval (CI) using Brookmeyer and Crowley methodology[4] (using the log-log transformation for construction of CI). Rates at fixed timepoints (e.g., PFS at 6 months) will be derived from the Kaplan-Meier estimate along with their corresponding log-log transformed CIs. Exact confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[5].

## 7.2 Study Conduct

### *7.2.1 Accrual*

For the Dose Evaluation Phase the analyses on accrual will be using the All Dose Evaluation Enrolled Subjects population. For the Dose Expansion Phase the analyses will be using the All 2-stage Enrolled Subjects population.

For each phase, the number of subjects enrolled and treated will be provided for the following:

- Enrollment summary by country and site.
- Enrollment summary by month.

A subject listing of accrual (informed consent date, first dose date, country, investigational site, and as treated dose level) will also be produced.

For the Dose Evaluation Phase, a distribution of the number of subjects by cohort will be provided for the DLT Period (number enrolled, treated and DLT-evaluable) and for the Dose Evaluation Phase itself (number enrolled and treated).

### *7.2.2 Relevant Protocol Deviations*

For the Dose Evaluation Phase, the relevant protocol deviations will be summarized by cohort using the All Dose Evaluation Excluding DLT Treated Subjects population.

For the Dose Expansion Phase, the relevant protocol deviations will be summarized by cohort using the All 2-stage Treated Subjects population.

The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At Entrance:

- Subjects without histologically or cytologically-documented SCLC or without histologically-documented PAC.
- For PAC, subjects without current disease stage of IV.
- Subjects without measurable disease at baseline.
- Subject with baseline ECOG performance status > 1.
- For PAC, subjects without at least one prior line of chemotherapy for metastatic disease.
- For SCLC, subjects without at least one prior platinum therapy.
- Subject with prior therapy including any T cell co-stimulation or checkpoint pathways such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, including ipilimumab and nivolumab; or other medicines specifically targeting T cells.

On-study:

- Subjects receiving concurrent anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, non-palliative radiation therapy, standard or investigational agents for treatment of SCLC or PAC).

For each summary, a subject listing will also be produced.

## 7.3 Study Population

### *7.3.1 Subject Disposition*

For the Dose Evaluation Phase, the enrolment will be summarized using the All Dose Evaluation Enrolled Subjects population.

For the Dose Expansion Phase, the enrolment will be summarized using the All 2-stage Enrolled Subjects population.

For each phase, the following enrolment summary will be provided (supporting listing will be supplied):

- Number of subjects enrolled, entering or not the treatment period,
- Reason for not entering the treatment period.

For the Dose Evaluation Phase, the discontinuation will be summarized by cohort using the All Dose Evaluation Treated Subjects population.

For the Dose Expansion Phase, the discontinuation will be summarized using the All 2-stage Treated Subjects population.

The following discontinuation summary will be provided (supporting listing will be supplied):

- Number of subjects who discontinued treatment,
- Reason for treatment discontinuation,
- Number of subjects who discontinued the study,
- Reason for study discontinuation.

For the tabulation of discontinuations during the Dose Evaluation Phase, if more than one cohort is to be reported pooled data across cohorts will also be presented.

### *7.3.2 Demographics and Other Baseline Characteristics*

For the Dose Evaluation Phase, demographics and other baseline characteristics will be summarized by cohort using the All Dose Evaluation Treated Subjects population.

For the Dose Expansion Phase, demographics and other baseline characteristics will be summarized by cohort using the All 2-stage Treated Subjects population.

For the Dose Evaluation Phase, if more than one cohort is to be reported pooled data across cohorts will also be presented.

#### *7.3.2.1 Demographics and Baseline Disease Characteristics*

The following characteristics will be summarized. All baseline presentations will identify subjects with missing measurements. Demographic data will be listed.

- Age (in years, descriptive statistics),
- Age category ($< 65$, $\geq 65$ and $< 65$, $65$ - $< 75$, $\geq 75$ years),

- Gender, Race, Ethnicity,
- Weight (kg),
- ECOG performance status (0, 1),
- Time from initial disease diagnosis to start of treatment (in years, descriptive statistics and by categories of: < 6 months, 6 months - < 1 year, 1 - < 2 years, 2 - < 3 years, ≥ 3 years),
- Disease stage at initial diagnosis (stage I, stage II, stage III, stage IIIA, stage IIIB, stage IIIC, stage IV),
- Cell type at initial diagnosis (adenocarcinoma, small cell carcinoma, other),
- For SCLC, disease classification at initial diagnosis (limited disease, extensive disease),
- Disease stage at current diagnosis (stage III, stage IV),
- Smoking status (current or former, never smoker, unknown),
- Alcohol Use (prior use, current use and, for each of these "none", "average ≤ 2 drinks/day", "average ≥ 3 drinks/day"),
- For PAC, family history of PAC (parent, grandparent, sibling),
- All lesions: presence of lesion, site of lesion, number of sites with at least one lesion (1, 2, 3, 4, ≥ 5),
- Target lesions: presence of target lesion, site of target lesion, number of sites with at least one target lesion (1, 2, 3, 4, ≥ 5), sum of reference diameters of target lesions (in mm, descriptive statistics and by categories of: < 20, 20 - 50, > 50 - 100, > 100).

#### *7.3.2.2 Prior Cancer Therapy*

Agents and medication will be reported using the generic name. The following prior cancer therapy will be summarized:

- Line of therapy (first, second, third, other - note: the intent is for a line of therapy for metastatic disease. Adjuvant therapy for PAC subjects should not be considered to define line of therapy),
- Best response to most recent prior systemic therapy regimen (CR or PR, SD, PD, unknown or not reported),
- Primary reason regimen was discontinued (disease progression, maximum clinical benefit, toxicity, completed treatment, other),
- Time from completion of most recent prior systemic therapy regimen to start of treatment (< 1, 1 - <3, 3 - 6, > 6 months),
- For SCLC, prior medication response on platinum based therapy (resistant/refractory, sensitive, unknown or not reported),
- Prior surgery related to cancer (yes or no),
- Prior radiotherapy (yes or no),
- Prior systemic cancer therapy classified by therapeutic class and generic name.

#### 7.3.2.3 Other Baseline Medical Evaluations

General medical history and pretreatment events will be tabulated. Prior/current non-study medication classified by anatomic class, therapeutic class and generic name will be tabulated and listed.

### 7.3.3 Baseline Laboratory Examinations

Baseline laboratory data needed for the CSR will be extracted from the on-treatment shift tables in toxicity grading from baseline (see Section 7.6.12.1).

## 7.4 Extent of Exposure

For the Dose Evaluation Phase, extent of exposure will be summarized by cohort using the All Dose Evaluation Treated Subjects population.

For the Dose Expansion Phase, extent of exposure will be summarized by cohort using the All 2-stage Treated Subjects population.

Extent of exposure will be presented separately for ulocuplumab and for nivolumab. A listing of study medication dosing (infusion details and dose modification) and a listing of batch number will also be provided.

### 7.4.1 Study Therapy

Below table summarizes the key parameters that will be used to calculate dosing data.

**Table 7.4.1-1: Administration of Study Therapy: Definition of Parameters**

| | Ulocuplumab | Nivolumab |
|---|---|---|
| Assigned Starting Dose | DL-1: 200mg weekly<br>DL1: 400mg weekly<br>DL2: 800mg weekly<br>DL3A: 1600mg weekly | 3mg/kg every 2 weeks |
| Dose | Dose (mg) is defined as total dose administered at each dosing date | Dose (mg/kg) is defined as total dose administered at each dosing date (mg) divided by the most recent weight (kg). Dose administered and weight are collected from the CRF |
| Cumulative Dose | Cumulative dose (mg) is the sum of the doses administered to a subject during the treatment period | Cumulative dose (mg/kg) is the sum of the doses administered to a subject during the treatment period |
| Relative Dose Intensity (%) | Cumulative dose divided by [(Last dose date - Start dose date + 7) × assigned starting dose in mg / 7] × 100 | Cumulative dose divided by [(Last dose date - Start dose date + 14) × 3 / 14] × 100 |
| Duration of Treatment (days) | Last dose date - Start dose date + 1 | Last dose date - Start dose date + 1 |

The following parameters will be summarized:

- Number of doses received (descriptive statistics),
- Cumulative dose (descriptive statistics),
- Relative dose intensity (≥ 110%, 90 - < 110%, 70 - < 90%, 50 - < 70%, < 50%),
- Duration of study therapy (months) using:
  - A Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off treatment. Subjects who are still on-treatment will be censored on their last dose date.
  - Descriptive statistics (minimum, maximum, KM median with 95% CI and by categories of: > 3 months, > 6 months, > 9 months, > 12 months as well as number off treatment).

### *7.4.2 Modifications of Study Therapy*

#### *7.4.2.1 Infusion Interruption and Infusion with IV Rate Reduction*

Each ulocuplumab or nivolumab infusion can be interrupted and/or the IV infusion rate can be reduced. The following parameters will be summarized using CRF data:

- Number of subjects with at least one infusion interrupted,
- Number of infusion interrupted per subject (0, 1, 2, 3, ≥ 4),
- Total number of infusions interrupted / total number of infusions received,
- Reason for infusion interrupted (any).

Similar summaries will be provided for infusion with IV rate reduction.

#### *7.4.2.2 Dose Delay*

Derived data will be used for reporting dose delay. Starting from the second dose, a dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date) for nivolumab or 2 days (i.e., greater than or equal to 3 days from scheduled dosing date) for ulocuplumab. It is defined as “duration since previous administration in days -7” for ulocuplumab or as “duration since previous administration in days -14” for nivolumab. The following parameters will be summarized:

- Number of subjects with at least one dose delayed,
- Number of dose delayed per subject (0, 1, 2, 3, ≥ 4),
- Total number of doses delayed / total number of doses received,
- Reason for dose delayed,
- Length of delay (4 - 7 days, 8 - 14 days, 15 - 42 days, > 42 days; for ulocuplumab, the first class is 3 - 7 days).

The reason for dose delayed will be any reasons supplied by the investigator for the period during which a dose delay was determined. If the reason corresponding to the dose delay (as defined by above algorithm) is missing then 'Not reported' will be provided.

#### *7.4.2.3 Ulocuplumab Partial Dose Discontinuation*

Ulocuplumab can be discontinued while the subject is continuing on nivolumab alone. The following parameters will be summarized using CRF data:

- Number of subjects with ulocuplumab discontinuation,
- Reason for ulocuplumab discontinuation.

### *7.4.3 Concomitant Medications*

Concomitant medications are medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy). Concomitant medication classified by anatomic class, therapeutic class and generic name will be tabulated and listed.

### *7.4.4 Immune Modulating Medications*

Concomitant IMM classified by anatomic class, therapeutic class and generic name will be tabulated as a whole and separately for the following use:

- AE management,
- Immunomodulating treatment for AE,
- Infusion-related
- Premedication,
- Other use.

Concomitant IMM will be listed.

## 7.5 Efficacy

Except where indicated, for the Dose Evaluation Phase, efficacy parameters will be summarized by cohort using the All Dose Evaluation Excluding DLT Treated Subjects population.

For the Dose Expansion Phase, efficacy parameters will be summarized by cohort using the All 2-stage Treated Subjects population.

Supportive listing will be provided for response, time to response, duration of response, PFS and OS.

### *7.5.1 Objective Response Rate*

BOR will be summarized by response category and ORR will be computed along with an exact 90% CI (primary analysis for ORR as primary endpoint, see Section 4).

The primary population for estimating the ORR will be the All Dose Evaluation Excluding DLT Treated Subjects population. Additionally, the parameters will be summarized using the All Dose Evaluation Treated Subjects population (supportive analyses). All analyses will be presented as-treated.

For the Dose Evaluation Phase, the decision to further study ulocuplumab combined with nivolumab in each tumor type will primarily be based on the pre-defined Simon 2-stage design thresholds (at least 4 responders for SCLC and at least 2 responders for PAC), using data from the IA. In addition, the selection of the recommended dose will be based on all available safety and efficacy data from both tumor types. The decision to proceed from the Dose Evaluation Phase to the Dose Expansion Phase will be conducted for each tumor type independently. Consideration may be given for evaluating final data before decision is reached to stop further study of the combination to ensure that the full characterization of the response pattern is evaluated.

The decision to proceed with an open label randomized two-arm Phase 2 design rather than completing the second stage of a Simon 2-stage design for the Expansion Phase will be taken if, among the treated subjects in the recommended dose selected during the Dose Evaluation Phase, a "high" frequency of responders is observed. For SCLC, this "high" number will be at least 9 responders and, for PAC, at least 6 responders. This number of responders has been defined considering clinical input but, ensuring that the related proportion of responders also presents with a 90% exact CI lower limit above 25% for SCLC or above 12% for PAC. These percentages correspond to the minimum proportion of responders that would be needed at the end of a Simon 2-stage design in order to further evaluate the drug (for SCLC, 11 responders among the 44 subjects is 25% and, for PAC, 5 responders among the 41 subjects is 12%).

For the Dose Expansion Phase, the primary population will be the All 2-stage Treated Subjects population (as-treated analyses).

### *7.5.2 Overall Survival*

OS will be estimated using KM methodology. Median values along with two-sided 95% CIs will be calculated. KM based OS rates at 3, 6, 9, 12, 18, and 24 months will be estimated and associated two-sided 95% CIs will be provided.

### *7.5.3 Progression-free Survival*

PFS will be estimated using KM methodology. Median values along with two-sided 95% CIs will be calculated. KM based PFS rates at 3, 6, 9, 12, and 18 months will be estimated and associated two-sided 95% CIs will be provided.

The following information will also be summarized:

- Number and type of events (progression: RECIST 1.1 or clinical, death),
- Number of subjects censored on first dosing date (number with no baseline tumor assessment and no death, number with no on-study tumor assessment and no death)

- Number of subjects censored on date of last tumor assessment on-study (number received subsequent anti-cancer therapy, still on-treatment, in follow-up, off study [lost to follow-up, withdraw consent, other]).

### *7.5.4 Duration of Objective Response*

Duration of response will be estimated using KM methodology for subjects who achieve PR or CR. Median values along with two-sided 95% CIs will be calculated.

For the responders only, the time course of the following events of interest will graphically be displayed (swimmers plot): tumor response, progression, last dose received and death.

### *7.5.5 Disease Control Rate*

Analyses on disease control rate will be similar to the ones conducted on the ORR.

### *7.5.6 Magnitude of Reduction in Tumor Volume*

The magnitude of reduction in tumor volume will be summarized descriptively using the following subject-level graphics:

- A bar plot (waterfall plot) showing the best reduction in target lesion (excluding assessment after PD and assessments after start of subsequent anti-cancer therapy).
- A plot (spider plot) of individual time course of tumor burden change.

### *7.5.7 Subsequent Therapy*

The number of subjects with any of the following subsequent cancer therapy will be summarized:

- Radiotherapy,
- Surgery,
- Systemic cancer therapy.

The number of subjects with any allowed on-treatment radiotherapy or surgery will also be reported. Systemic cancer therapy will further be reported by therapeutic class and generic name.

A supportive listing will be provided.

## 7.6 Safety

Dose limiting toxicities will specifically be reported for the DLT Evaluation period. Other safety parameters will be reported according to the different phases of the trial. These parameters will consist of the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose modification, select adverse events, IMAEs, other adverse events of special interest, ECGs and specific laboratory abnormalities (worst grade) for each cohort.

For the Dose Evaluation Phase, safety parameters (excluding DLTs) will be summarized by cohort using the All Dose Evaluation Treated Subjects population.

For the Dose Expansion Phase, safety parameters will be summarized by cohort using the All 2-stage Including DLT Treated Subjects population.

For the Dose Evaluation Phase, if more than one cohort is to be reported pooled data across cohorts will also be presented.

### *7.6.1 DLT Evaluation Period / Maximum Tolerated Dose*

During the DLT Evaluation period, data and Study Team considerations that led to the determination (or not) that the dose levels of 200mg and/or 400mg and/or 800 mg and/or 1600 mg weekly are tolerable and can be used during the Dose Evaluation Phase will be described in-text. This will be based on the incidence of DLTs during the first 6 weeks of treatment with both agents for the DLT-evaluable Subjects but other available safety and efficacy data may also be considered.

### *7.6.2 Deaths*

The number of deaths and primary reason for death will be summarized for the following:

- All deaths,
- Deaths within 30 days of last dose,
- Deaths within 100 days of last dose.

Listing of deaths will be provided. In addition, to supply some safety information in subjects that were not treated, listing on deaths will be provided considering only the subjects who never started treatment.

### *7.6.3 Serious Adverse Events*

For SAEs the following will be summarized:

- Overall summary of SAEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT,
- Overall summary of drug-related SAEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT,

The analysis will be conducted using the 100-day safety window.

Listing of SAEs will be provided. In addition, to supply some safety information in subjects that were not treated, listing on SAEs will be provided considering only the subjects who never started treatment.

### *7.6.4 Adverse Events Leading to Discontinuation of Study Therapy*

For AEs leading to discontinuation the following will be summarized:

- Overall summary of AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT,

- Overall summary of drug-related AEs leading to discontinuation by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT,

The analysis will be conducted using the 100-day safety window.

Listing of AEs leading to discontinuation will be provided.

### *7.6.5 Adverse Events Leading to Dose Modification*

Dose modification consists of dose delay of either drug and the following will be summarized:

- Overall summary of AEs leading to study therapy dose delay by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT.

The analysis will be conducted using the 100-day safety window.

Listing of AEs leading to study therapy dose delay will be provided.

### *7.6.6 All Adverse Events*

For AEs the following will be summarized:

- Overall summary of any AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT,
- Overall summary of any AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT,
- Overall summary of drug-related AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT,
- Overall summary of any non-serious AEs presented by SOC/PT. For the Dose Evaluation Phase, only the population of All Dose Evaluation Treated Subjects will be used.
- Overall summary of late-emergent drug-related AEs by worst CTC grade (grade 1, 2, 3, 4, 5, unknown) presented by SOC/PT,
- Overall summary of any AEs that required IMM by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT.

The analyses will be conducted using the 100 days safety window.

Listing of AEs and listing of AEs requiring concomitant IMM will be provided.

### *7.6.7 Infusion-related Events*

For AEs reported as “Infusion-related Event = Yes” on the AE/SAE CRF page, a by-subject listing will be provided:

This analysis will be conducted using the 30-day safety window only.

### 7.6.8 Select Adverse Events

#### 7.6.8.1 Incidence of Select Adverse Events

For select AEs (see categories and subcategories definition in Table 4.2.1-1) each of the following analysis will be repeated for each category of select AE (excluding the endocrine event category). Analyses of the endocrine event category will be presented separately by subcategories.

- Overall summary of any select AEs by worst CTC grade presented by Category or Subcategory (any grade, grade 3-4, grade 5),
- Overall summary of drug-related select AEs by worst CTC grade presented by Category or Subcategory (any grade, grade 3-4, grade 5),
- Overall summary of any serious select AEs by worst CTC grade presented by Category or Subcategory (any grade, grade 3-4, grade 5),
- Overall summary of drug-related serious select AEs by worst CTC grade presented by Category or Subcategory (any grade, grade 3-4, grade 5),
- Overall summary of any select AEs leading to discontinuation by worst CTC grade presented by Category or Subcategory (any grade, grade 3-4, grade 5),
- Overall summary of drug-related select AEs leading to discontinuation by worst CTC grade presented by Category or Subcategory (any grade, grade 3-4, grade 5).

These analyses will be conducted using the 30-day safety window only.

The list of PTs used for analysis will be provided. Listing of select AEs (any, serious and leading to discontinuation) will be provided.

#### 7.6.8.2 IMM Received for Management of Select Adverse Events

Analysis of concomitant IMM received for management of any select AE among subjects who experienced at least one select AE will be provided separately for each category of select AEs (including the endocrine event category, as a whole) for the following specific events:

- Any grade select AEs,
- Any grade drug-related select AEs,

For these analyses, the following will be provided:

- Concomitant IMM received classified by anatomic class, therapeutic class and generic name,
- Number of subjects who received IMM,
- Total duration of IMM (in weeks, descriptive statistics),
- Number of subjects who received corticosteroid at a dose ≥ 40mg prednisone or equivalent,
- Duration of corticosteroid at a dose ≥ 40mg or equivalent (in weeks, descriptive statistics),
- Initial dose (mg/kg) of corticosteroid at a dose ≥ 40mg prednisone or equivalent (descriptive statistics),
- Number of subjects who underwent corticosteroid taper,
- Duration of corticosteroid taper (in weeks, descriptive statistics).

The analyses will be conducted using the 30-day safety window only.

### 7.6.9 Immune-mediated Adverse Events

For IMAEs (see categories and PT definition in Section 4.2.2) a listing will be provided. Immune-modulating medications used for IMAE management will be tabulated. The list of PTs used for analysis will be provided.

These analyses will be conducted using the 100-day safety window only.

### 7.6.10 Other Events of Special Interest

For other events of special interest (see categories definition in Section 4.2.3) a listing will be provided. Immune-modulating medications used for other events of special interest will be tabulated. The list of PTs used for analysis will be provided.

### 7.6.11 Multiple Adverse Events

For multiple adverse events, the following will be summarized:

- Total number and exposure adjusted AEs summary,
- Frequency of unique adverse events summary (for select AEs only and presented for each category, including the endocrine event category, as a whole),

The analyses will be conducted using the 30-day safety window.

Listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event (i.e. same PT) have been collapsed will be provided. No formal comparisons will be made between cohorts.

### 7.6.12 Clinical Laboratory Evaluations

#### 7.6.12.1 Hematology, Serum Chemistry, and Electrolytes

Thrombocytopenia will mainly be examined using laboratory data. Analyses on hematology, serum chemistry, and electrolytes will consist of the followings:

- Worst CTC grade on-treatment per subject,
- Shift table of worst on-treatment CTC grade compared to baseline CTC grade per subject.

For each analysis, the following laboratory tests will be summarized:

- Hematology: hemoglobin (HB), platelets, white blood counts (WBC), absolute neutrophils count (ANC) and absolute lymphocyte count (LYMPA).
- Serum chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin and creatinine.

- Electrolytes: sodium (high and low), potassium (high and low), calcium (high and low), magnesium (high and low).
- Other: amylase (AMYL) and lipase (LIPA and LIPAC, lipase by colorimetric assay).

The analyses will be conducted using the 100-day safety window.

Listing of these laboratory parameters will be provided.

#### *7.6.12.2 Abnormal Hepatic Function Tests*

The number of subjects with the following abnormalities vs. lower limit of normal (LLN) or vs. upper limit of normal (ULN) will be summarized:

- ALT or AST > 3 x ULN, > 5 x ULN, > 10 x ULN and > 20 x ULN.
- Total bilirubin > 2 x ULN.
- Concurrent (within 1 day) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN.
- Concurrent (within 30 days) ALT or AST > 3 x ULN and total bilirubin > 2 x ULN.

The analyses will be conducted using the 100-day safety window.

Listing of these specific abnormalities will be provided.

#### *7.6.12.3 Abnormal Thyroid Function Tests*

The number of subjects with the following laboratory abnormalities will be summarized:

- Thyroid specific test (TSH) > ULN:
  - Any,
  - With TSH <= ULN at baseline,
  - With at least one FT3/FT4 test value < LLN,
  - With all other FT3/FT4 test values >= LLN,
  - With FT3/FT4 test missing.
- Thyroid specific test (TSH) < LLN:
  - Any,
  - With TSH >= LLN at baseline,
  - With at least one FT3/FT4 test value > ULN,
  - With all other FT3/FT4 test values ≤ ULN,
  - With FT3/FT4 test missing.

The analyses will be conducted using the 100-day safety window.

Listing of these specific abnormalities will be provided.

### 7.6.13 Electrocardiograms

Frequency distribution of maximal QTc(F) intervals and QTc(F) changes from baseline (> 30msec, > 60msec, etc.) will be tabulated. This analysis will be conducted using the 30-day safety window. A listing of Electrocardiogram parameters will be provided.

### 7.6.14 Vital Signs and Physical Findings

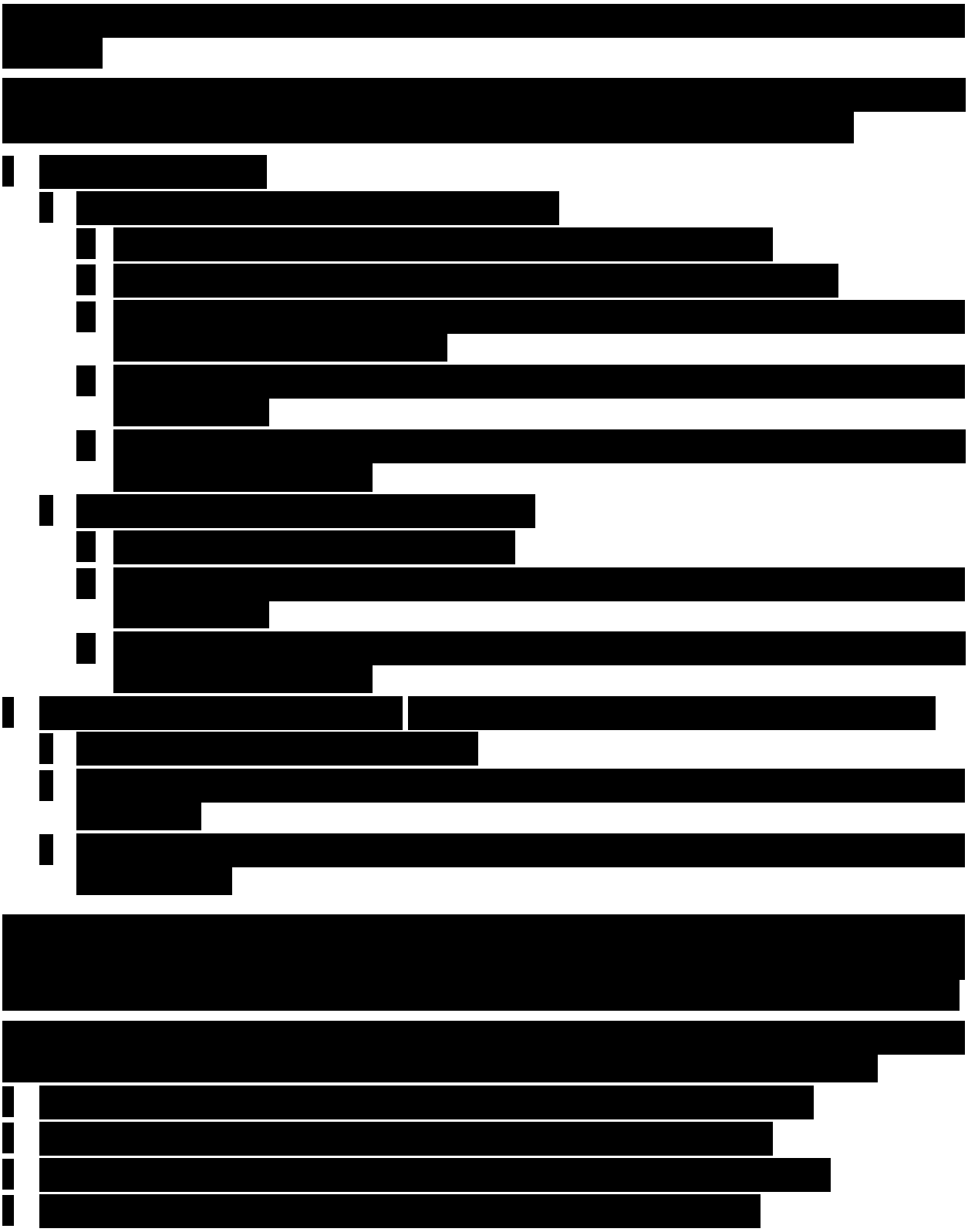
Vital signs and pulse oximetry (i.e. percentage of oxygen saturation) will be provided in separate listing.

### 7.6.15 Clinical Safety Program (CSP)

A listing with the following data from the infusion-related events CSP CRF pages will be provided.

- Prophylactic medications,
- Infusion-related event onset date and symptoms,
- Diagnostic procedure and date,
- Relevant risk factors and suspect medications,
- Therapeutic medications and therapeutic procedures.

[redacted]



[redacted]

[redacted]

## 8 CONVENTIONS

Refer to Section 3.3 of the Data Presentation Plan (DPP) for the details of the conventions to be used.

## 9 CONTENT OF REPORTS

Refer to Section 1.2 of the DPP for the list of outputs that will be produced.

# 10 REFERENCES

1 Skolnik JM, Barrett JS, Jayaraman B, Patel D and PC Adams. Shortening the Timeline of Pediatric Phase 1 Trials: The Rolling Six Design. Journal of Clinical Oncology (2007); 26 (2): 190-195

2 Shankar G, Arkin S, Cocea L, et al. Assessment and Reporting of the Clinical Immunogenicity of the Therapeutic Proteins and Peptides - Harmonized Terminology and Tactical Recommendations. The AAPS Journal 2014;DOI:10.1208/s12248-014-9599-2

3 Guidance for Industry, Immunogenicity Assessment Therapeutic Protein Products, 2013

4 Brookmeyer R. and Crowley J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982

5 Clopper, CJ and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413, 1934