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## Clinical Protocol CA212115

A Phase 1/2 Study of the Safety and Efficacy of Ulocuplumab Combined with Nivolumab in  
Subjects with Advanced or Metastatic Solid Tumors

(CXCessoR<sup>4</sup>: Clinical trial of the anti-CXCR4 antibody ulocuplumab in malignant tumors)

**Revised Protocol Number: 03**  
**Incorporates Amendment: 04**

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

## DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	13-Jan-2016	Incorporates Amendment 04
Amendment 04	13-Jan-2016	This amendment changes 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. Chest x-rays were added to monitor for pulmonary toxicity. Administrative edits and clarifications are also incorporated.
Revised Protocol 02	16-Sep-2015	Incorporates Amendment 03
Amendment 03	16-Sep-2015	This amendment changes dose delay, dose modification, discontinuation and dose limiting toxicity (DLT) criteria to account for the known toxicity profiles of ulocuplumab and nivolumab and correct internal inconsistencies in the management of toxicity. The major change is to remove the requirement to discontinue study therapy for grade 3 platelets > 7 days and replace it with the recommendation to hold study therapy for grade 3 platelets > 7 days.
Revised Protocol 01	20-May-2015	Incorporates Amendment 02
Amendment 02	20-May-2015	This amendment adds a sentinel 400 mg weekly ulocuplumab dose level in the dose evaluation phase at the request of regulatory authorities. It also incorporates administrative edits and minor clarifications to the study procedures.  This amendment applies to all subjects and is to be implemented after IRB/IEC/HA review.
Original Protocol	23-Mar-2015	Not applicable

## SYNOPSIS

### Clinical Protocol CA212115

**Protocol Title:** A Phase 1/2 Study of the Safety and Efficacy of Ulocuplumab Combined with Nivolumab in Subjects with Advanced or Metastatic Solid Tumors

**Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):**

- Ulocuplumab 200 mg, 400 mg, 800 mg or 1600 mg administered IV over 60 minutes every week combined with nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression
- Ulocuplumab 1600 mg administered IV over 60 minutes every 2 weeks combined with nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression

**Study Phase:** 1/2

**Research Hypothesis:** Treatment with ulocuplumab plus nivolumab will be safe, tolerable and demonstrate a clinically meaningful efficacy in subjects with advanced or metastatic solid tumors.

**Objectives:**

**Primary Objective:**

- Stage 1: To identify the recommended dose and schedule of ulocuplumab, based on safety and efficacy, 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 pancreatic adenocarcinoma (PAC) only), of ulocuplumab combined with nivolumab in subjects with advanced or metastatic tumors

**Secondary Objectives:**

- 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

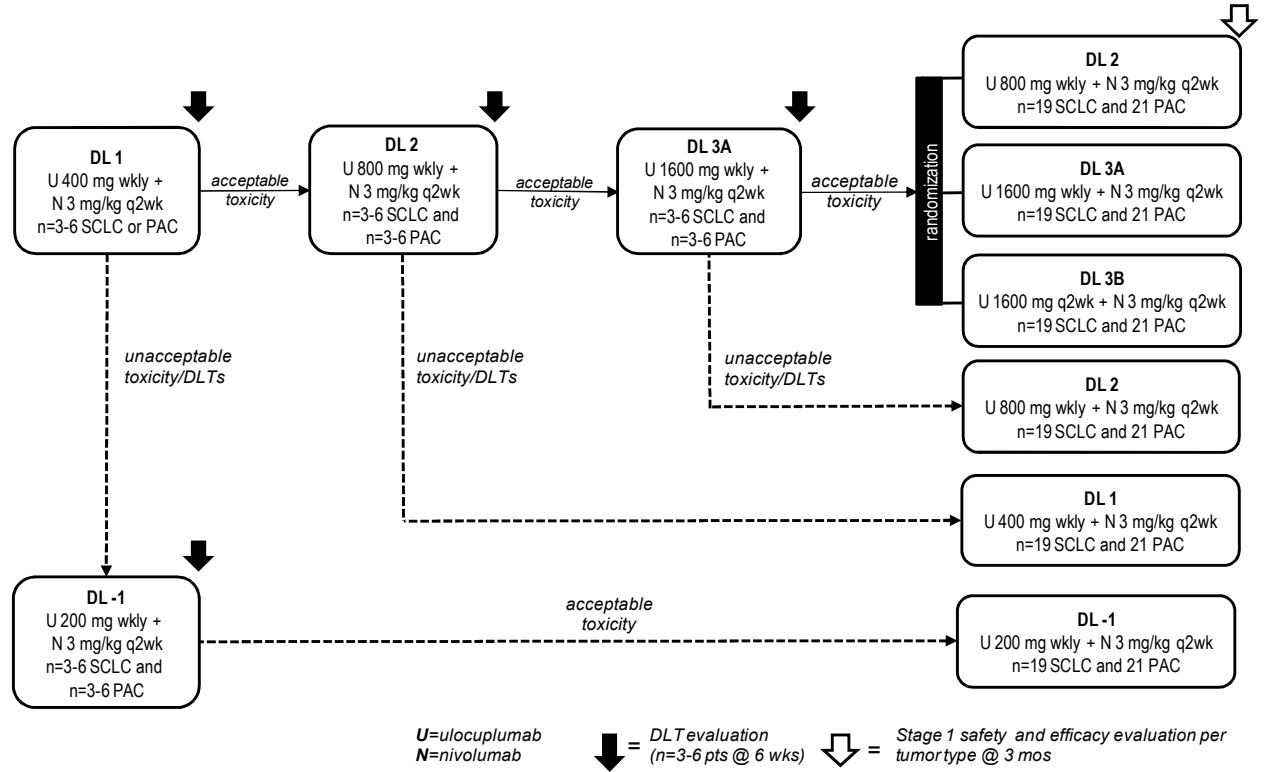
**Exploratory Objectives:**

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

**Study Design:** This is an open-label, multicenter phase 1/2 study to evaluate safety and efficacy of ulocuplumab in combination with nivolumab in subjects with small cell lung cancer (SCLC) and PAC. The study design allows for the testing of different doses and schedules of ulocuplumab in the Dose Evaluation Phase. In addition, the protocol

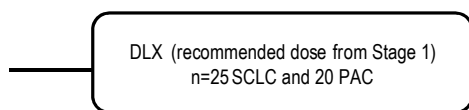
incorporates a flexible design to permit the initiation of a randomized Phase 2 study with comparative arm in the Dose Expansion Phase if high efficacy is observed. If high efficacy is not observed, the study continues as a single arm study for the Dose Expansion Phase.

**Dose Evaluation Phase (Stage 1)**

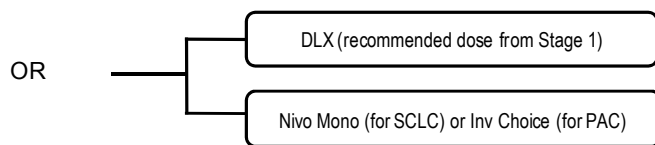


**Dose Expansion Phase (Stage 2)**

Simon 2-stage (per tumor type):



Randomized Phase 2 (per tumor type):



**Study Population:** Subjects with pathologically confirmed locally advanced or metastatic SCLC and PAC that have failed at least one prior line of chemotherapy are eligible. Subjects must have an ECOG score of 0-1. Subjects with active brain metastases are excluded.

**Study Drug:**

Study Drug for CA212115		
Medication	Potency	IP/Non-IP
Ulocuplumab (BMS-936564)	100 mg (10 mg/mL)	IP
Nivolumab (BMS-936558)	100 mg (10 mg/mL)	IP

**Study Assessments:** Radiographic tumor assessments will be performed at baseline, at 6 weeks from first dose and continue every 6 weeks for the first 24 weeks and every 12 weeks thereafter until disease progression or treatment discontinuation.

**Statistical Considerations:**

**Sample Size:** The sample size will start at dose level 1 (DL1) with a minimum of 3 treated subjects with either PAC or SCLC using a Rolling Six design for evaluation of dose limiting toxicity (DLT). Then, the sample size will be increased by the number of subjects separately by tumor type needed to continue the DLT evaluation at each dose level followed by the number of subjects separately by tumor type 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 selected for each tumor type.

For SCLC, up to approximately 175 treated subjects may be needed. This sample size considers 3-18 subjects for the DLT evaluation and 19 subjects per cohort (57 subjects for three randomized cohorts) of the Dose Evaluation Phase. The Dose Expansion Phase in the form of a second stage of a Simon 2-stage like design would require an additional 25 subjects OR in the form of a randomized Phase 2 study with a comparative arm would require an additional 50 subjects per arm (ie. 100 subjects for the two arms).

For PAC, up to approximately 331 treated subjects may be needed. This sample size considers 3-18 subjects for the DLT evaluation and 21 subjects per cohort (63 subjects for three randomized cohorts) for the Dose Evaluation Phase. The Dose Expansion Phase in the form of a second stage of a Simon 2-stage like design would require an additional 20 subjects OR in the form of a randomized Phase 2 study with a comparative arm would require an additional 125 subjects per arm (ie. 250 subjects for the two arms).

**Endpoints:** The primary efficacy endpoint will be ORR, as determined by the investigators, for the Dose Evaluation Phase and if a Simon 2-stage like design is continued for the Dose Expansion Phase. If a randomized Phase 2 study with a comparative arm is selected for the Dose Expansion Phase, the primary efficacy endpoint will be ORR for SCLC and OS for PAC. Secondary efficacy endpoints will consist of safety, tolerability and PFS. Safety and tolerability endpoints will consist of the incidence of DLT (primary safety endpoint during the DLT evaluation phase), adverse events (AE), serious adverse events (SAE) and specific laboratory abnormalities (worst grade). Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

**Analyses:** All analyses will be presented separately by tumor type. Within a tumor type, the Dose Evaluation Phase analyses will be presented by cohort. If a Simon 2-stage like design is completed, analyses of the Dose Evaluation Phase and the Dose Expansion Phase will be pooled and presented by cohort. If a randomized Phase 2 study with comparator arm is initiated, the analyses of this design will be presented by treatment arm.

Baseline characteristics and efficacy analyses will be summarized for the All Dose Evaluation Randomized Treated Subjects (primary population) and the All Treated Subjects population by cohort (and, if a randomized two-arm Phase 2 study is initiated, for the All Dose Expansion Randomized Subjects population by randomized treatment arm). ORR will be summarized by a binomial response rate and corresponding two-sided 95% exact CI using the Clopper and Pearson method. If a randomized Phase 2 study is initiated, ORR will be compared between the treatment arms using a one-sided alpha level of 0.10 with Cochran-Mantel-Haenszel (CMH) test stratified by the stratification factors defined for each tumor type. The primary analysis of OS as primary endpoint for PAC will be a comparison of the OS of subjects randomized to ulocuplumab plus nivolumab to that of subjects randomized to the investigator's choice chemotherapy using a one-sided alpha level of 0.10 log-rank test stratified by the stratification factors defined for each tumor type. PFS and OS will be summarized using the Kaplan-Meier (KM) product-limit method.

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## 1.2 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.

## 1.3 Objectives(s)

### 1.3.1 Primary Objectives

- Stage 1: To identify the recommended dose and schedule of ulocuplumab, based on safety and efficacy, 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

### 1.3.2 Secondary Objectives

- 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

### 1.3.3 Exploratory Objectives

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## **2 ETHICAL CONSIDERATIONS**

### **2.1 Good Clinical Practice**

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

### **2.2 Institutional Review Board/Independent Ethics Committee**

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

### **2.3 Informed Consent**

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

- 1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood
- 2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
- 3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion
- 4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information
- 5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject
- 6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

### **3 INVESTIGATIONAL PLAN**

#### **3.1 Study Design and Duration**

This is an open-label, multi-center 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 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. A recommended dose will be selected based on the safety and efficacy data from Stage 1 and will

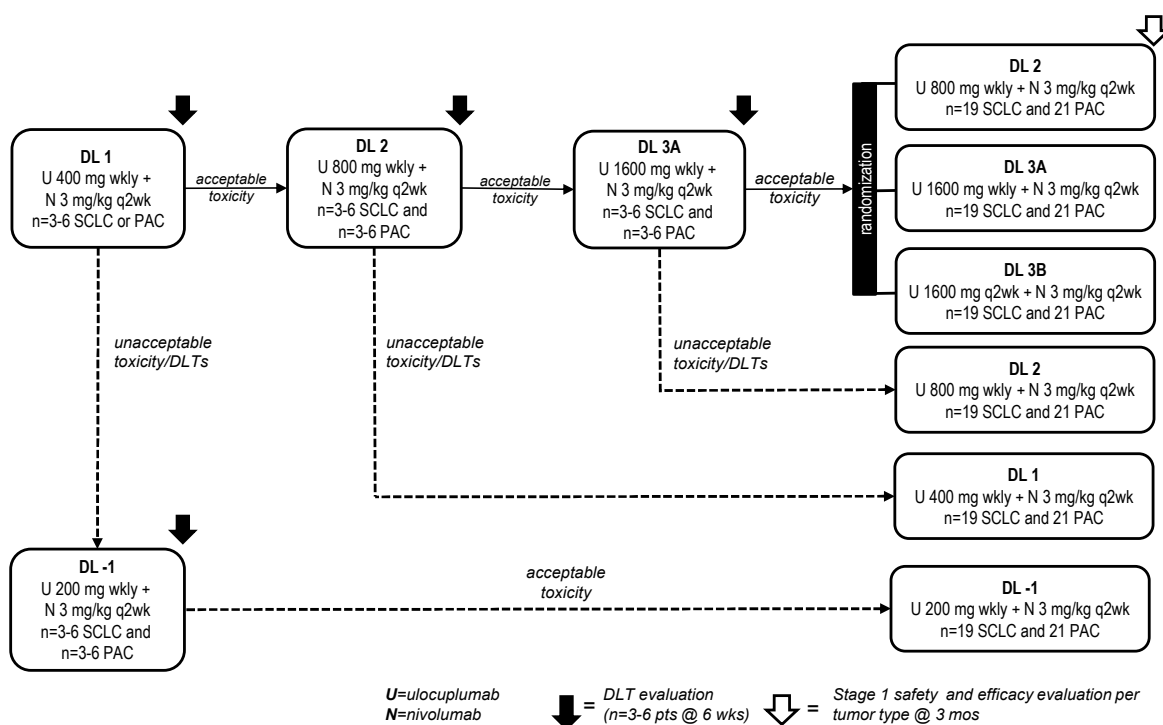
proceed to Dose Expansion in the form of a Simon optimal 2-stage like design or a randomized Phase 2 study with comparative arm if high efficacy is observed.<sup>40</sup>

The study will consist of Screening, Treatment, and Follow-up. All subjects will undergo a screening period to determine eligibility within 28 days prior to initial dosing. During the treatment phase, ulocuplumab will be administered weekly or every two weeks (1600 mg dose only) and nivolumab will be administered every two weeks. The treatment period will continue until disease progression or occurrence of unacceptable toxicity. During follow-up, subjects will be monitored for disease activity and safety. The duration of the study is anticipated to be approximately 2 years.

The study design schematic is presented in Figure 1.

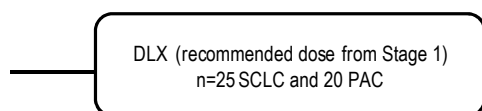
**Figure 1: Study Design Schematic**

**Dose Evaluation Phase (Stage 1)**



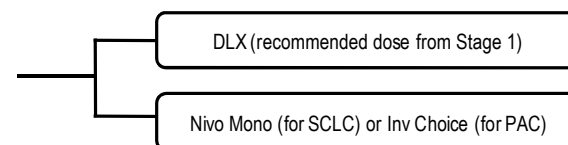
**Dose Expansion Phase (Stage 2)**

**Simon 2-stage (per tumor type):**



OR

**Randomized Phase 2 (per tumor type):**



### 3.1.1 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 (ie, Rolling Six design). This design allows for 3-6 evaluable subjects to contribute to the DLT evaluation depending upon how many are enrolled and still being evaluated during the DLT period. Decisions as to whether to enroll a new participant onto the current dose level or next highest dose level will be based on available data at the time of new participant enrollment. Study stopping rules for the DLT evaluation period and the decision to proceed with the Dose Evaluation Phase include the following:

- Enrollment in the active cohort will proceed if there are:
  - < 3 subjects enrolled, up to a maximum of 6 subjects
  - 1 DLT in 2 or up to 5 subjects evaluable for toxicity
- Enrollment in the active cohort will be paused if there are:
  - a maximum of 6 subjects enrolled (including evaluable and non-evaluable)
- Active cohort is deemed intolerable and enrollment will be stopped for evaluation if there are:
  - ≥ 2 DLT in up to 6 subjects evaluable for toxicity
- Active cohort is deemed tolerable and enrollment will proceed to next step if there are :
  - 0 DLT in 3 or up to 6 subjects evaluable for toxicity
  - 1 DLT in 6 subjects evaluable for toxicity
- Subjects who are not evaluable for DLT (ie, discontinuation due to disease progression) will be replaced with a concurrently enrolled subject

**Table 3.1.1-1: Dose Levels for Ulocuplumab and Nivolumab**

Dose Level	Ulocuplumab	Nivolumab
DL-1	200 mg weekly	3 mg/kg every 2 weeks
DL1	400 mg weekly	3 mg/kg every 2 weeks
DL2	800 mg weekly	3 mg/kg every 2 weeks
DL3A	1600 mg weekly	3 mg/kg every 2 weeks

DL3B	1600 mg every 2 weeks	3 mg/kg every 2 weeks
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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 800 mg weekly and 1600 mg weekly ulocuplumab dose levels will occur independently for each tumor type. No dose modification of nivolumab will be allowed in this study.

- If the toxicity at DL1 and DL2 and DL3A are acceptable, enrollment will proceed with three randomized cohorts (DL2, DL3A, and DL3B) to complete Stage 1
- If the toxicity at DL3A is unacceptable, enrollment will proceed at DL2 to complete Stage 1
- If the toxicity at DL2 is unacceptable, enrollment will proceed at DL1 to complete Stage 1
- If the toxicity at DL1 is unacceptable, a new DLT evaluation period will proceed at DL-1
- If the toxicity of DL-1 is unacceptable, enrollment will stop for that tumor type
- If the toxicity at DL-1 is acceptable, enrollment will proceed at DL-1 to complete Stage 1 at a single dose level

### **3.1.2 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 proceeding with a Simon 2-stage-like design or conducting a randomized Phase 2 study with comparative arm. The efficacy thresholds used for the IA analysis are based on the preliminary efficacy data from the ongoing Phase 1/2 study evaluating nivolumab monotherapy in SCLC and PAC and the level of activity reported for 2L options.<sup>12 41</sup> The determination of low, moderate or high efficacy will be based primarily on the response rates observed with ulocuplumab and nivolumab, 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, please refer to [section 8.5](#).

- 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 3.1.2-1: Stage 1 Efficacy Threshold For Each Tumor Type**

<b>Efficacy Threshold</b>	<b>SCLC</b>	<b>PAC</b>
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

### **3.1.3 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 like single arm study (moderate efficacy) or a randomized Phase 2 study with comparative arm (high efficacy).

The second stage of a Simon 2-stage like design will expand enrollment at the recommended dose level in a single arm study. An additional 25 SCLC subjects and 20 PAC subjects will be enrolled to complete this evaluation. The primary endpoint will be investigator-assessed ORR for both tumor types and PFS will be considered a secondary endpoint.

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. More details regarding the randomized Phase 2 for each tumor type are described below.

#### **SCLC**

A randomized Phase 2 study with comparative arm in SCLC will compare the recommended dose of ulocuplumab combined with nivolumab versus nivolumab monotherapy. The main goal of this comparison will be to determine whether the combination therapy is superior to nivolumab monotherapy. The primary endpoint of this study will be evaluation of IRRC assessed ORR. Safety, tolerability and PFS will be considered as secondary endpoints. A randomized Phase 2 study would require an additional 50 subjects per arm (ie. 100 for the two arms). The SCLC subjects included in the Dose Evaluation Phase will not be part of the efficacy analysis of the randomized Phase 2 study. A stratification factor will be used for this portion of the study to balance recruitment and will include performance status (ECOG 0 vs 1). For additional statistical considerations for the randomized Phase 2 study with comparative arm in SCLC subjects, please see [Section 8](#).

#### **PAC**

A randomized Phase 2 study with comparative arm in PAC will compare the recommended dose of ulocuplumab combined with nivolumab versus Investigator’s Choice 2L chemotherapy. The main goal of this comparison will be to determine if ulocuplumab plus nivolumab combination therapy is superior to 2L chemotherapy. The primary endpoint of this study will be OS. Safety,

tolerability and PFS will be considered as secondary endpoints. For PAC, a randomized Phase 2 study would require an additional 125 subjects per arm (ie. 250 for the two arms). [REDACTED]. The PAC subjects included in the Dose Evaluation Phase will not be considered in the analysis of the randomized Phase 2 study. Investigator's choice chemotherapy options in this study are based on NCCN guidelines for PAC and include the following.<sup>27</sup>

- Subjects that have failed FOLFIRINOX or other fluoropyrimidine based regimens can consider gemcitabine-based therapies for this study
- Subjects that have failed gemcitabine based regimens can consider fluoropyrimidine-based regimens for this study

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). For additional statistical considerations for the randomized Phase 2 study with comparative arm in PAC subjects, please see [Section 8](#).

### **3.1.4 Dose Limiting Toxicity**

The incidence of DLT(s) assessed in the first 3-6 evaluable subjects per tumor type (if applicable) during the first 6 weeks will be used to initially determine whether a dose level is tolerable. A subject will be considered evaluable for DLT if they have received at least 5 out of 6 ulocuplumab doses and at least 2 out of 3 nivolumab doses in a 6 week dosing period or experienced a DLT. DLT should not be 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 Grade  $\geq 3$  drug-related non-hematological AE, including the following laboratory abnormalities
  - If a subject has baseline Grade  $\leq 1$  AST, ALT, or total bilirubin, a drug-related Grade  $\geq 3$  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 (see [section 4.5.3.1](#))
- Any toxicity managed by discontinuation of nivolumab (see [section 4.5.3.2](#))



### **3.2 Post Study Access to Therapy**

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

### **3.3 Study Population**

For entry into the study, the following criteria **MUST** be met.

#### **3.3.1 Inclusion Criteria**

##### **1. Signed Written Informed Consent**

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, potential tumor biopsies, and other requirements of the study.

##### **2. Target Population**

a) Subjects with pathologically confirmed metastatic disease of the following tumor types:

i) Subjects with histologically confirmed pancreatic ductal adenocarcinoma (PDAC) who must meet the following:

(1) Subjects must have had progression, refractory disease or best response of stable disease during or after at least 1 chemotherapy regimen for the treatment of metastatic (Stage IV) disease.

Note: For DLT evaluation phase only, subjects may have had progression, refractory disease or best response of stable disease during or after at least 1 chemotherapy regimen for the treatment of locally advanced or metastatic (Stage IV) disease.

AND

- (2) Subjects must not have clinically relevant ascites at baseline, such as ascites in need of paracentesis.
- ii) Subjects with histologically or cytologically confirmed SCLC. Subjects must have progression or refractory disease to most recent therapy. Subjects must have had at least 1 platinum based chemotherapy regimen for the treatment of limited or extensive stage disease.
- b) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment must be performed within 28 days prior to first dose).
- c) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- d) All baseline laboratory requirements will be assessed and should be obtained within 14 days of first dose. Screening laboratory values must meet the following criteria:
- WBCs  $\geq 2000/\mu\text{L}$
  - Neutrophils  $\geq 1500/\mu\text{L}$
  - Platelets  $\geq 120 \times 10^3/\mu\text{L}$
  - Hemoglobin  $\geq 9.0 \text{ g/dL}$
  - Creatinine serum creatinine  $\leq 1.5 \times \text{ULN}$  or creatinine clearance (CrCl)  $\geq 40 \text{ mL/minute}$  (using Cockcroft/Gault formula)
  - AST and ALT levels  $\leq 3 \times \text{ULN}$  or  $\leq 5 \times \text{ULN}$  if liver metastases are present
  - Total Bilirubin  $\leq 1.5 \times \text{ULN}$  (except subjects with Gilbert Syndrome who can have total bilirubin  $< 3.0 \text{ mg/dL}$ )
  - Albumin  $\geq 3 \text{ g/dL}$
  - Lipase  $\leq 1.5 \text{ ULN}$ . Subjects with Lipase  $> 1.5 \text{ ULN}$  may enroll if there are neither clinical nor radiographic signs of a pancreatitis.
  - Amylase  $\leq 1.5 \text{ ULN}$ . Subjects with Amylase  $> 1.5 \text{ ULN}$  may enroll if there are neither clinical nor radiographic signs of a pancreatitis.
- e) Prior focal radiotherapy to an isolated bony or soft tissue metastasis must be completed at least 2 weeks before study drug administration.

### 3. Age and Reproductive Status

- a) Men and women  $\geq 18$  years of age
- b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug
- c) Women must not be breastfeeding
- d) WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug (s) plus 5 half-lives of nivolumab plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post

treatment completion. (note: nivolumab half-life is approximately 25 days and is greater than ulocuplumab half-life)

- e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of study drug (s) plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion
- f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

#### **HIGHLY EFFECTIVE METHODS OF CONTRACEPTION**

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy
- Complete Abstinence\*

\*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

#### **LESS EFFECTIVE METHODS OF CONTRACEPTION**

- Diaphragm with spermicide
- Cervical cap with spermicide

- Vaginal sponge
- Male Condom without spermicide
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom\*

\* A male and female condom must not be used together

### **3.3.2 Exclusion Criteria**

#### **1. Target Disease Exceptions**

- a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

#### **2. Medical History and Concurrent Diseases**

- a) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.
- b) Other prior malignancy active within the previous 3 years except for local or organ confined early stage cancer that has been definitively treated with curative intent, does not require ongoing treatment, has no evidence of residual disease, and has a negligible risk of recurrence and is therefore unlikely to interfere with the primary and secondary endpoints of the study, including response rate and safety.
- c) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- d) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose. Inhaled or topical steroids, and adrenal replacement steroid doses are permitted in the absence of active autoimmune disease.

- e) Prior therapy with 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.
- f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enroll.
- g) Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 21 days of first administration of study treatment (subjects with prior cytotoxic or investigational products < 3 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to CTC grade 1 level).

### **3. Physical and Laboratory Test Findings**

- a) Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBV sAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection.
- b) Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
- c) Subjects must not be dependent on continuous supplemental oxygen use.

### **4. Allergies and Adverse Drug Reaction**

- a) History of allergy to study drug components.
- b) History of severe hypersensitivity reaction to any monoclonal antibody.

### **5. Other Exclusion Criteria**

- a) Prisoners or subjects who are involuntarily incarcerated
- b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

#### **3.3.3 Women of Childbearing Potential**

A Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40 mIU/mL to confirm menopause.

\*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

Other parenteral products may require washout periods as long as 6 months.

### **3.4 Concomitant Treatments**

#### **3.4.1 Prohibited and/or Restricted Treatments**

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event, see also [Section 3.4.2.3](#))
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except to treat a drug-related adverse event, see also Section 3.4.2.3)
- Any concurrent antineoplastic therapy (ie, surgery [exception described in [Section 3.4.2.2](#)], chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy described in Section 3.4.2.1)
- Medications that Durably Inhibit Platelet Function:
  - With the exception of low-dose aspirin, warfarin (coumadin) and heparin (including unfractionated and low molecular weight), subjects enrolled in this study should not take concomitant medications that durably inhibit platelet function. For such medications, a wash-out period of  $\geq 7$  days is required prior to starting treatment. Agents that inhibit platelet function transiently or inhibit coagulation by other mechanisms should be used with caution.
  - Medications that directly and durably inhibit platelet function include aspirin containing combinations, clopidogrel, dipyridamole, tirofiban, dipyridamole, epoprostenol, eptifibatide, cilostazol, abciximab, ticlopidine, cilostazol
- Supportive care for disease-related symptoms may be offered to all subjects on the trial.

#### **3.4.2 Other Restrictions and Precautions**

##### **3.4.2.1 Palliative Radiation Therapy**

Palliative (limited-field) radiation therapy is permitted, but only for pain control to sites of bone disease present at baseline and only if all of the following criteria are met:

- 1) Repeat imaging (mandatory) demonstrates no new sites of bone metastases
- 2) The lesion being considered for palliative radiation is not a target lesion

- 3) The case is discussed with the BMS Medical Monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met

### **3.4.2.2 Surgical Resection Following Initial Response**

Investigators may choose to resect solitary lesions in subjects with residual disease and render the subject free of macroscopic disease. Subjects enrolled in this study may have lesions surgically resected only following consultation with the Medical Monitor and following the Week 24 tumor assessments. If additional tumor shrinkage is noted compared to the tumor assessments at Week 18, it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage. Subjects with a confirmed PR who go on to have surgical resection of remaining disease will be considered a PR. Subjects with SD who go on to have surgical resection of remaining disease will be considered a SD. Patients may continue treatment after surgery. Tumor tissue of any resected solitary lesion should be submitted to BMS (see [Section 5.6.1](#)). Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of these specimens will be provided in a separate Procedure Manual at the time of study initiation.

### **3.4.2.3 Corticosteroid Treatment**

The use of corticosteroids for the management of related AE in accordance with the algorithms in the IB and this protocol is permitted. Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents are needed. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted. However, the use of systemic corticosteroids at baseline, before starting ulocuplumab or nivolumab, should be avoided because of their potential interference with the PD activity and efficacy of checkpoint inhibitors. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose are not eligible.

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

### **3.4.2.4 Imaging Restrictions**

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m<sup>2</sup>) are at increased risk of nephrogenic systemic fibrosis. MRI

contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

### **3.5 Discontinuation of Subjects following any Treatment with Study Drug**

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Pregnancy
- Additional protocol specific reasons for discontinuation (see [Sections 4.5.3.1](#) and [4.5.3.2](#))

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in [Section 5](#). The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

### **3.6 Post Study Drug Study Follow up**

In this study, ORR and OS are key endpoints of the study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (See [Section 5.1](#)). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.



### **3.6.1      *Withdrawal of Consent***

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

### **3.6.2      *Lost to Follow-Up***

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

## **4            *STUDY DRUG***

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

**Table 4-1: Study Drugs for CA212115**

<b>Product Description / and Dosage Form</b>	<b>Potency</b>	<b>IP/Non-IMP</b>	<b>Blinded or Open Label</b>	<b>Packaging/ Appearance</b>	<b>Storage Conditions (per label)</b>
BMS-936564 (ulocuplumab) Solution for Injection	100 mg (10 mg/mL)	IP	Open-label	Primary packaging: 10 mL per vial/Open-label Secondary packaging: carton containing 10 mg/mL kitted vials/ Open-label Colorless, clear to slightly opalescent solution, essentially free of particles.	Store at 2°C to 8°C. Protect from light
BMS-936558 (nivolumab) Solution for Injection	100 mg (10 mg/mL)	IP	Open-label	Primary packaging: 10 mL per vial/Open-label Secondary packaging: carton containing 10 mg/mL kitted vials/Open-label Clear to opalescent colorless to pale yellow liquid. May contain particles	Store at 2°C to 8°C. Protect from light and freezing

#### **4.1 Investigational Product**

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are: BMS-936564 (ulocuplumab) and BMS-936558 (nivolumab).

#### **4.2 Non-investigational Product**

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

In this protocol, non-investigational product(s) is/are the following:

- Dose Evaluation Phase (Stage 1): Not applicable
- Dose Expansion (Stage 2): For PAC subjects, if Stage 1 results in a decision to move to a randomized Phase 2 study with comparative arm in Dose Expansion Phase, Investigator's Choice for advanced or metastatic PAC subjects will be the comparator arm. The treatment options for 2L PAC include the following:
  - Gemcitabine with or without albumin-bound paclitaxel
  - Capecitabine and other fluoropyrimidine based regimens

#### **4.3 Storage and Dispensing**

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Please refer to the current version of the Investigator Brochures and/or pharmacy manual or reference sheets for complete storage, handling, dispensing and infusion information for BMS-936564 (ulocuplumab) and BMS-936558 (nivolumab).

#### **4.3.1 Ulocuplumab (BMS-936564)**

Ulocuplumab (BMS-936564) vials must be stored refrigerated 2°C to 8°C in a tightly closed container and must be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Once the ulocuplumab injection is transferred to the IV bag, it can be stored for a maximum of 12 hours at room temperature/under ambient light at 15°C - 25°C. If the solution in the IV bag cannot be used for infusion within the 12 hours at room temperature, it must be refrigerated at 2°C - 8°C, not to exceed 12 hours maximum in the refrigerator. The solution is stable for a total storage combination time of 24 hours.

Following transfer to the IV bag, preparation time of dilution to the end time of infusion should not exceed 24 hours as the diluted solution of BMS-936564 once prepared, must be infused within a 24 hour timeframe.

Any temperature deviations from the recommended storage conditions would require the site to contact the Sponsor for further instruction and disposition.

#### **4.3.2 Nivolumab (BMS-936558)**

Nivolumab (BMS-936558) vials must be stored at a temperature of 2°C to 8°C and should be protected from light, freezing and shaking. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

#### Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Bag

The dosing calculations should be based on the body weight. Nivolumab injection is to be administered as an IV infusion over 60 minutes at 3 mg/kg.

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C) for up to 24 hours and a maximum of 4 hours of the total 24 hours can be at room temperature and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the nivolumab Investigator Brochure sections 3.2.2 and 3.2.3 and/or pharmacy reference sheets.<sup>13</sup>

#### **4.3.3 Ulocuplumab and Nivolumab Combination**

When both ulocuplumab and nivolumab are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Ulocuplumab is to be administered first. The ulocuplumab infusion must be promptly followed by a saline flush to clear the line of ulocuplumab before starting the nivolumab infusion.

#### **4.4 Method of Assigning Subject Identification**

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. Specific instructions for using IVRS will be provided in a separate document.

Enrolled subjects that have met all eligibility criteria will continue with treatment assignment and drug vial assignment through the IVRS.

There will be two requirements for IVRS randomization in this study. The first one will occur in the Dose Evaluation Phase (Stage 1) after the DLT evaluation period. In this instance, the IVRS will be used to assign subjects to one of three cohorts for the dose evaluation (DL2, DL3A, DL3B). Additionally, if a randomized Phase 2 study with comparative arm is initiated in the Dose Expansion Phase (Stage 2), IVRS will be used to assign subjects to one of the two treatment arms.

#### **4.5 Selection and Timing of Dose for Each Subject**

Ulocuplumab will be administered every week or every two weeks depending on the cohort being evaluated. Nivolumab will be administered every two weeks for all cohorts. On the day of study drug administration, ulocuplumab is to be administered first. The second infusion will always be nivolumab, and will start no sooner than 30 minutes after completion of the ulocuplumab infusion.

For weekly ulocuplumab dosing, subjects may be dosed +/-1 day from their scheduled dosing date, but no less than 6 days between doses. For every 2 week dosing (ulocuplumab or nivolumab), subjects may be dosed  $\pm 2$  days from their scheduled dosing date, but no less than 12 days between doses. If dosing cannot be administered within the window of the scheduled dosing date, the dose will be considered a missed dose and the subject should come in for their next regular visit relative to Day 1. If the next regular visit is less than 6 days from the last ulocuplumab dose for weekly dosing, nivolumab may be administered alone for that visit.

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

##### **4.5.1 Dose Delays and Interruptions**

###### **4.5.1.1 Ulocuplumab Dose Delay**

Investigators should, whenever possible, determine which medication is causing the toxicity and delay or dose reduce ulocuplumab and/or delay nivolumab, as applicable. If ulocuplumab is delayed due to an AE, nivolumab dosing may continue at the discretion of the Investigator. Ulocuplumab should be delayed for the following:

- Any Grade  $\geq 3$  drug-related AE, including laboratory abnormalities except for Grade 3 AEs that do not require nivolumab dose delay (see [section 4.5.1.2](#))

If the decision is to resume ulocuplumab dosing, the subject should restart treatment on the next regularly scheduled ulocuplumab dosing visit. Skipped doses are not to be replaced. If treatment is delayed > 6 weeks, the subject must be permanently discontinued from ulocuplumab therapy.

#### **4.5.1.2 Nivolumab Dose Delay**

Investigators should, whenever possible, determine which medication is causing the toxicity and delay or dose reduce ulocuplumab and/or delay nivolumab, as applicable. If nivolumab is delayed due to an AE, ulocuplumab dosing should also be delayed. Nivolumab should be delayed for the following:

- Any Grade  $\geq 2$  non-skin, drug-related AE, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin drug-related AE
- Any Grade  $\geq 3$  drug-related laboratory abnormality, with the following exceptions for thrombocytopenia, lymphocytopenia, AST, ALT, total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 thrombocytopenia  $< 7$  days (not associated with Grade  $\geq 2$  hemorrhage) does not require dose delay
  - Grade 3 lymphocytopenia not associated with symptoms or clinical manifestations does not require dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 lymphocytopenia.
  - Grade 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities
  - If a subject has baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade  $\geq 2$  toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade  $\geq 3$  toxicity
  - If a subject has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for drug-related elevations in AST and/or ALT  $> 2x$  baseline or a maximum of  $> 8x$  ULN
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication

If the decision is to resume nivolumab dosing, the subject should restart treatment on the next regularly scheduled nivolumab dosing visit. Skipped doses are not to be replaced. If treatment is delayed  $> 6$  weeks, the subject must be permanently discontinued from all study therapy, except as specified in [Section 4.5.3.2](#).

Because of the potential for nivolumab-related AE requiring early recognition and prompt intervention, management algorithms have been developed and are included for suspected pulmonary toxicity, GI toxicity, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity. In order to standardize the management of AEs for all subjects, recommended treatment management algorithms are included in [Appendix 2](#). Adverse event treatment management algorithms included in the nivolumab IB might be considered for individual cases.

### **4.5.1.3 Criteria to Resume Nivolumab Treatment**

Subjects may resume treatment with nivolumab when the drug-related AE resolves to Grade  $\leq$  1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of a Grade 2 toxicity
- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 or 2 toxicity range who require dose delays for reasons other than a 1 or 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
  - Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters ([Section 4.5.3.2](#)) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

### **4.5.1.4 Ulocuplumab or Nivolumab Dose Interruptions**

If an ulocuplumab infusion is interrupted or an ulocuplumab-related infusion reaction prevents subsequent infusion of nivolumab on the same day, the dose of nivolumab should be replaced as soon as possible. In such instances, at least 12 days must elapse between the replacement dose of nivolumab and the administration of the next dose of ulocuplumab combined with nivolumab to maintain a 2 week period (+/-2 days) in between nivolumab dosing.

## **4.5.2 Dose Modifications**

### **4.5.2.1 Ulocuplumab Dose Modification Criteria**

Investigators should, whenever possible, determine which medication is causing the toxicity and delay or dose reduce ulocuplumab and/or delay nivolumab, as applicable. Depending on the nature of the AE, inpatient ulocuplumab dose modifications may occur according to [Table 4.5.2.1-1](#). The following rules apply when modifying the dose of ulocuplumab:

- Assessment of causality must be determined and documented by the Investigator and also discussed by the BMS Medical Monitor
- Following implementation of a dose reduction for ulocuplumab, the dose should not be re-escalated
- If the same AE recurs despite a dose reduction, a second dose reduction versus discontinuation of the subject from ulocuplumab will be discussed and agreed upon by the Investigator and BMS Medical Monitor

**Table 4.5.2.1-1: Ulocuplumab Dose Modification Criteria**

Adverse Event	Dose Delay (refer to section 4.5.1.1)	Criteria to Resume Ulocuplumab Treatment			
		For DL-1	For DL1	For DL2	For DL3A/3B
Any Gr ≥ 3 drug-related AE, including laboratory abnormalities, except for Grade 3 hematologic AEs listed below or other exceptions listed in section 4.5.1	Hold ulocuplumab until return to baseline or Grade ≤ 1, whichever is lower	1st event: Discontinue ulocuplumab	1st event: Resume at 200 mg weekly	1st event: Resume at 400 mg weekly	1st event: Resume at 800 mg weekly
			2nd event: Discontinue ulocuplumab	2nd event: Resume at 200 mg weekly	2nd event: Resume at 400 mg weekly
				3rd event: Discontinue ulocuplumab	3rd event: Discontinue ulocuplumab
Any Gr3 drug-related neutropenia, Gr3 thrombocytopenia > 7 days	Hold ulocuplumab until return to baseline or Grade ≤ 1, whichever is lower	2nd event: Discontinue ulocuplumab	1st event: Resume at 200 mg weekly	1st event: Resume at 400 mg weekly	1st event: Resume at 800 mg weekly
			3rd event: Discontinue ulocuplumab	2nd event: Resume at 200 mg weekly	2nd event: Resume at 400 mg weekly
				3rd event: Discontinue ulocuplumab	3rd event: Discontinue ulocuplumab
Gr4 asymptomatic lipase or amylase elevations	Hold ulocuplumab until return to baseline or Grade ≤ 1, whichever is lower	All events: Resume at same dose. Consult with BMS Medical Monitor if recurrent or sustained.			

**4.5.2.2 Nivolumab Dose Modification Criteria**

Inpatient dose modifications of nivolumab for the management of toxicities are not permitted. Dose delay criteria for nivolumab can be found in section 4.5.1.2.

**4.5.3 Discontinuation Criteria**

**4.5.3.1 Ulocuplumab Discontinuation Criteria**

Discontinuation criteria apply for all drug-related AE attributed to ulocuplumab and consist of the following:

- Grade ≥ 3 thrombocytopenia associated with bleeding (occurring concomitant with ≥ Grade 2 hemorrhage)



- Grade  $\geq 3$  drug-related infusion reaction of any duration
- Any Grade 4 drug-related AE or laboratory abnormality except for Grade 4 AE listed as exceptions to the nivolumab discontinuation criteria (see section 4.5.3.2)
- Any recurring drug-related Grade  $\geq 3$  AE or laboratory abnormality that requires multiple dose reductions of ulocuplumab (see specific criteria in [section 4.5.2.1](#))
- Any drug-related AE resulting in dose delay of ulocuplumab  $> 6$  weeks
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued ulocuplumab dosing

#### **4.5.3.2 Nivolumab Discontinuation Criteria**

Discontinuation criteria apply for all drug-related AE attributed to nivolumab and consist of the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting  $> 7$  days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurological toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - ◆ Grade 3 drug-related thrombocytopenia associated with bleeding requires discontinuation
    - ◆ Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - If a subject has a baseline AST or ALT within normal limits:
        - AST or ALT  $> 5-8x$  ULN for  $> 2$  weeks
        - AST or ALT  $> 8x$  ULN, irrespective of duration
        - Concurrent AST or ALT  $> 3x$  ULN and total bilirubin  $> 2x$  ULN
      - If a subject has a baseline AST or ALT within Grade 1 or 2 toxicity range:
        - AST or ALT  $> 10x$  ULN for  $> 2$  weeks
        - AST or ALT  $> 15x$  ULN, irrespective of duration
        - Total bilirubin  $> 5x$  ULN
        - Concurrent AST or ALT  $> 3x$  ULN and total bilirubin  $> 2x$  ULN

- Any Grade 4 non-skin drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 thrombocytopenia or neutropenia < 5 days
  - Grade 4 lymphocytopenia or leukopenia not associated with symptoms or clinical manifestations. It is recommended to consult with the BMS Medical Monitor for Grade 4 lymphocytopenia.
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical/radiographic manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities.
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor.
- Any dosing delay lasting > 6 weeks with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
  - Dosing delays > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued ulocuplumab or nivolumab dosing

#### **4.5.4 Treatment of Ulocuplumab- or Nivolumab-Related Infusion Reactions**

Infusion reactions have been reported in subjects treated with ulocuplumab and nivolumab. If an infusion reaction was to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

**For Grade 1 symptoms** (Mild reaction; infusion interruption not indicated; intervention not indicated):

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab or ulocuplumab administrations.

**For Grade 2 symptoms** (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for  $\leq 24$  hours):

Stop the nivolumab or ulocuplumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ulocuplumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ulocuplumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

**For Grade 3 or Grade 4 symptoms** (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]; Grade 4: (life threatening; pressor or ventilatory support indicated):

Immediately discontinue infusion of ulocuplumab or nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Ulocuplumab or nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or

generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

#### **4.5.5 Treatment Beyond Disease Progression**

As described in [Section 1.1.10](#) accumulating evidence indicates that subjects treated with immunotherapy may derive clinical benefit despite evidence of progressive disease (PD).

Subjects will be permitted to continue with treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Subject is tolerating study drugs
- Subject has provided written informed consent prior to receiving additional study treatment

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond progression must be discussed with the BMS Medical Monitor and documented in the study records.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event. Subjects who have tumor shrinkage following RECIST 1.1-defined progression will also be descriptively summarized separately since these immune responses may be used in decision rules for selecting Dose Expansion Phase (Stage 2) study design.

#### **4.5.6 Antiemetic Premedications**

Antiemetic medications should not be routinely administered prior to dosing of drugs. See [Section 4.5.4](#) for subsequent premedication recommendations following ulocuplumab- or nivolumab-related infusion reaction.

#### **4.6 Blinding/Unblinding**

Not applicable.

#### **4.7 Treatment Compliance**

The investigator or designated study personnel will maintain a drug accountability log of all study drug(s); received, dispensed, destroyed and the amount returned to the Sponsor or supply depot. The investigator and study personnel will ensure that each subject receives the calculated dose of the study drug, dependent on either fixed dosing (ulocuplumab) or body weight (nivolumab).

Drug supplies will be inventoried and accounted for throughout the study. The drug accountability log will be reviewed by the study monitor during site visits and at the completion of the study.

#### **4.8 Destruction of Study Drug**

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

#### **4.9 Return of Study Drug**

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Arrangements for the return of study drug will be made by the responsible Study Monitor.

#### **4.10 Retained Samples for Bioavailability / Bioequivalence**

Not applicable.

## 5 STUDY ASSESSMENTS AND PROCEDURES

### 5.1 Flow Chart/Time and Events Schedule

**Table 5.1-1: Screening Procedural Outline (CA212115)**

Procedure	Screening Visit <sup>a</sup>	Notes
Call IVRS	X	To obtain subject number
<b><u>Eligibility Assessments</u></b>		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to first dose.
Medical History	X	
Screening/Baseline Tumor Assessment	X	MRI brain, CT chest, CT/MRI abdomen, pelvis and all other known sites of disease within 28 days prior to first dose. Baseline MRI is required to rule out active brain metastasis (SCLC only).
<b><u>Safety Assessments</u></b>		
Physical Examination	X	Within 14 days prior to first dose
Vital Signs and oxygen saturation	X	Including BP, HR, respiratory rate, temperature and oxygen saturation by pulse oximetry (at rest). Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Physical Measurements (including performance status)	X	Height, Weight and ECOG status. Within 14 days prior to first dose
ECG (12-lead)	X	Within 14 days prior to first dose
Chest X-ray	X	Within 14 days prior to first dose
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Concomitant Medication Collection	X	Within 14 days prior to first dose

**Table 5.1-1: Screening Procedural Outline (CA212115)**

Procedure	Screening Visit <sup>a</sup>	Notes
Laboratory Tests	X	CBC w/differential, Chemistry panel including: total protein, LDH, AST, ALT, ALP, total bilirubin, BUN or serum urea level, uric acid, creatinine, albumin, Ca, Mg, Na, P, K, Cl, glucose, amylase, lipase, TSH, Free T4, Free T3, hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA), within 14 days prior to first dose. Screening labs done within 72 hours prior to first dose can also be used for on treatment lab purposes at Day 1 dosing.
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours of first dose
FSH	X	If needed to document post-menopausal status as defined in <a href="#">Section 3.3.3</a> .
Tumor Tissue Samples	X	Sufficient tumor tissue obtained in the metastatic setting or from an unresectable site (block or minimum of 15 slides, obtained from fresh core biopsy, punch biopsy, excisional biopsy or surgical specimen). Archival sample within 6 months of screening is permitted.

<sup>a</sup> Within 28 days of treatment



**Table 5.1-2: On-Study Assessments for Dose Evaluation Phase (Stage 1): Ulocuplumab Weekly Dosing (CA212115)**

Procedure	Ulocuplumab administered every week Nivolumab administered every 2 weeks		Notes
	Week 1, 3, 5, 7, 9, etc Ulocuplumab + Nivolumab dosing visits	Week 2, 4, 6, 8, 10, etc Ulocuplumab dosing visits	
<b><u>Safety Assessments</u></b>			
Targeted Physical Examination	X	X	Within 72 hours prior to dosing.
Vital Signs and Oxygen Saturation	X	X	Including BP, HR, respiratory rate, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing.
Weight	X		Nivolumab dosing calculations should be based on body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.
ECOG Status	X		
ECG (12-lead)	See Notes		Every 6 weeks from first dose for the first 12 weeks, then every 12 weeks ( $\pm$ 1 wk)
Adverse Events Assessment	Continuous		
Review of Concomitant Medications	X	X	
Chest X-Ray		X	Week 2 only (monitor for pulmonary toxicity)
Laboratory Tests	X	X	On-study local laboratory assessments should be done within 72 hours prior to each dose: total protein, CBC w/differential, ALT, AST, total bilirubin, direct bilirubin (reflex testing when total bilirubin is elevated), alkaline phosphatase, BUN or serum urea level, uric acid, creatinine, albumin, Ca, Mg, Na, K, P, Cl, LDH, glucose, amylase, lipase, TSH (Free T4 and Free T3 reflex testing if TSH result abnormal).

**Table 5.1-2: On-Study Assessments for Dose Evaluation Phase (Stage 1): Ulocuplumab Weekly Dosing (CA212115)**

Procedure	Ulocuplumab administered every week Nivolumab administered every 2 weeks		Notes
	Week 1, 3, 5, 7, 9, etc Ulocuplumab + Nivolumab dosing visits	Week 2, 4, 6, 8, 10, etc Ulocuplumab dosing visits	
CRP	See Notes		Day 1, then every 6 weeks from first dose for the first 12 weeks, then every 12 weeks ( $\pm 1$ wk)
CA19.9 tumor marker	See Notes		PAC subjects only. Day 1, then every 6 weeks from first dose for the first 12 weeks, then every 12 weeks ( $\pm 1$ wk)
Immunogenicity blood sample	See Notes		Samples will be collected at time points per <a href="#">Section 5.5</a>
Pregnancy Test ( <i>WOCBP only</i> )	See Notes		Serum or urine within 24 hours prior to first dose and then every 4 weeks.
<b><u>Pharmacokinetic Assessments</u></b>			
PK Samples	See Notes		Samples will be collected at time points per Section 5.5
<b><u>Biomarker Testing</u></b>			
[REDACTED]	[REDACTED]		
[REDACTED]	[REDACTED]		

**Table 5.1-2: On-Study Assessments for Dose Evaluation Phase (Stage 1): Ulocuplumab Weekly Dosing (CA212115)**

Procedure	Ulocuplumab administered every week Nivolumab administered every 2 weeks		Notes
	Week 1, 3, 5, 7, 9, etc Ulocuplumab + Nivolumab dosing visits	Week 2, 4, 6, 8, 10, etc Ulocuplumab dosing visits	
<b><u>Efficacy Assessment</u></b>			
Tumor Assessment			<ul style="list-style-type: none"> <li>• Every 6 weeks (<math>\pm</math> 1 wk) from first dose for the first 24 weeks, then every 12 wks (<math>\pm</math> 1 wk) until disease progression or treatment is discontinued (whichever occurs later).</li> <li>• CT chest, CT/MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.</li> <li>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated</li> </ul>
<b><u>Outcomes Research Assessment</u></b>			
EQ-5D	See notes		Assessments should be collected on day 1 and at the same time as tumor assessments. Questionnaires should be completed prior to study drug administration and before any clinical activities.
<b><u>Clinical Drug Supplies</u></b>			
IVRS call for vial assignment and randomization	X	X	Randomization call will be implemented after the DLT period, if applicable
Administer Ulocuplumab treatment	X	X	Ulocuplumab will be administered first on days where both therapies are given. See <a href="#">section 4.5</a> .
Administer Nivolumab treatment	X		See section 4.5

**Table 5.1-3: On-Study Assessments for Dose Evaluation Phase (Stage 1): Ulocuplumab Dosing Every 2 Weeks (CA212115)**

Procedure	Ulocuplumab administered every 2 weeks Nivolumab administered every 2 weeks	Notes
	Week 1, 3, 5, 7, 9, etc Ulocuplumab + Nivolumab dosing visits	
<b><u>Safety Assessments</u></b>		
Targeted Physical Examination	X	Within 72 hours prior to dosing.
Vital Signs and Oxygen Saturation	X	Including BP, HR, respiratory rate, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing.
Weight	X	Nivolumab dosing calculations should be based on body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram.
ECOG Status	X	
ECG	See Notes	Every 6 weeks from first dose for the first 12 weeks, then every 12 weeks ( $\pm$ 1 wk)
Adverse Events Assessment	X	
Review of Concomitant Medications	X	
Laboratory Tests	X	On-study local laboratory assessments should be done within 72 hours prior to each dose: total protein, CBC w/differential, ALT, AST, total bilirubin, direct bilirubin (reflex testing when total bilirubin is elevated), alkaline phosphatase, BUN or serum urea level, uric acid, creatinine, albumin, Ca, Mg, Na, K, P, Cl, LDH, glucose, amylase, lipase, TSH (Free T4 and Free T3 reflex testing if TSH result abnormal).

**Table 5.1-3: On-Study Assessments for Dose Evaluation Phase (Stage 1): Ulocuplumab Dosing Every 2 Weeks (CA212115)**

Procedure	Ulocuplumab administered every 2 weeks Nivolumab administered every 2 weeks	Notes
	Week 1, 3, 5, 7, 9, etc Ulocuplumab + Nivolumab dosing visits	
CRP	See Notes	Day 1, then every 6 weeks from first dose for the first 12 weeks, then every 12 weeks ( $\pm 1$ wk)
CA19.9 tumor marker	See Notes	PAC subjects only. Day 1, then every 6 weeks from first dose for the first 12 weeks, then every 12 weeks ( $\pm 1$ wk)
Immunogenicity blood sample	See Notes	Samples will be collected at time points per <a href="#">Section 5.5</a>
Pregnancy Test ( <i>WOCBP only</i> )	See Notes	Serum or urine within 24 hours prior to first dose and then every 4 weeks.
<b><u>Pharmacokinetic Assessments</u></b>		
PK Samples	See Notes	Samples will be collected at time points per Section 5.5
<b><u>Biomarker Testing</u></b>		
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	

**Table 5.1-3: On-Study Assessments for Dose Evaluation Phase (Stage 1): Ulocuplumab Dosing Every 2 Weeks (CA212115)**

Procedure	Ulocuplumab administered every 2 weeks Nivolumab administered every 2 weeks	Notes
	Week 1, 3, 5, 7, 9, etc Ulocuplumab + Nivolumab dosing visits	
<b><u>Efficacy Assessment</u></b>		
Tumor Assessment		<ul style="list-style-type: none"> <li>• Every 6 weeks (<math>\pm</math> 1 wk) from first dose for the first 24 weeks, then every 12 wks (<math>\pm</math> 1 wk) until disease progression or treatment is discontinued (whichever occurs later).</li> <li>• CT chest, CT/MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.</li> <li>• Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated</li> </ul>
<b><u>Outcomes Research Assessments</u></b>		
EQ-5D	See notes	Assessments should be collected on day 1 and at the same time as tumor assessments. Questionnaires should be completed prior to study drug administration and before any clinical activities.
<b><u>Clinical Drug Supplies</u></b>		
IVRS call for vial assignment and randomization	X	Randomization call will be implemented after the DLT period, if applicable
Administer Ulocuplumab treatment	X	Ulocuplumab will be administered first on days where both therapies are given. See <a href="#">section 4.5</a>
Administer Nivolumab treatment	X	See section 4.5

**Table 5.1-4: On-Study Assessments for Dose Expansion Phase (Stage 2) (CA212115)**

Procedure	Ulocuplumab administered weekly or every 2 weeks Nivolumab administered every 2 weeks <sup>a</sup>		Notes
	Week 1, 3, 5, 7, 9, etc ulocuplumab + nivolumab dosing visits	Week 2, 4, 6, 8, 10, etc ulocuplumab dosing visits <sup>b</sup>	
<b><u>Safety Assessments</u></b>			
Targeted Physical Examination	X	X	Within 72 hours prior to dosing
Vital Signs and Oxygen Saturation	X	X	Including BP, HR, respiratory rate, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest within 72 hours prior to dosing.
Weight	X		The nivolumab dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated.
ECOG Status	X		
ECG (12-lead)	See notes		Every 6 weeks from first dose for the first 12 weeks, then every 12 weeks ( $\pm$ 1 wk)
Adverse Events Assessment	Continuous		
Review of Concomitant Medications	X	X	
Laboratory Tests	X	X	Local laboratory assessments should be done within 72 hours prior to each dose through Week 24 and every alternate dose thereafter and include total protein, CBC w/differential, ALT, AST, total bilirubin, direct bilirubin (reflex testing when total bilirubin is elevated), alkaline phosphatase, BUN or serum urea level, uric acid, creatinine, albumin, Ca, Mg, Na, K, P, Cl, LDH, glucose, amylase, lipase, TSH (Free T4 and Free T3 reflex test if TSH result abnormal).





**Table 5.1-4: On-Study Assessments for Dose Expansion Phase (Stage 2) (CA212115)**

Procedure	Ulocuplumab administered weekly or every 2 weeks Nivolumab administered every 2 weeks <sup>a</sup>		Notes
	Week 1, 3, 5, 7, 9, etc ulocuplumab + nivolumab dosing visits	Week 2, 4, 6, 8, 10, etc ulocuplumab dosing visits <sup>b</sup>	
<b><u>Efficacy Assessment</u></b>			
Tumor Assessment	See Notes		Every 6 weeks ( $\pm$ 1 wk) from first dose for the first 24 weeks, then every 12 wks ( $\pm$ 1 wk) until disease progression or treatment is discontinued (whichever occurs later). CT chest, CT/MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated
<b><u>Clinical Drug Supplies</u></b>			
IVRS call for vial assignment and randomization	X	X	Randomization call will be implemented if a phase 2 randomized study design is initiated
Administer Ulocuplumab treatment (See section 4.5)	X	X	Ulocuplumab will be administered first on days where both therapies are given. For 1600mg every 2 week dosing, ulocuplumab doses will be given Week 1, 3, 5, etc. <sup>b</sup>
Administer Nivolumab treatment (See section 4.5)	X		If a randomized phase 2 design is initiated for SCLC, the comparator will be nivolumab monotherapy every 2 weeks
Investigator choice chemotherapy treatment	X	X	If a randomized phase 2 design is initiated for PAC, the comparator will be investigator choice chemotherapy

<sup>a</sup> If a randomized phase 2 design is initiated for SCLC, the comparator will be nivolumab monotherapy following the every 2 week visit schedule (eg, week 1, 3, 5, 7, etc.). If a randomized phase 2 design is initiated for PAC, the comparator will be investigator choice chemotherapy following the weekly visit assessments, as applicable.

<sup>b</sup> For ulocuplumab every 2 week dosing, ulocuplumab doses will be given Week 1, 3, 5, etc. Visits at Week 2, 4, 6, etc. will not be required.

<b>Table 5.1-5: Follow-up Assessments (CA212115) - All Subjects</b>			
<b>Procedure</b>	<b>Follow Up,<sup>a</sup> Visits 1 and 2</b>	<b>Survival,<sup>b</sup> Follow up Visits</b>	<b>Notes</b>
<b>Safety Assessments</b>			
Targeted Physical Examination	X		
Adverse Event Assessments	X	X	AEs during the survival follow up visits considered study drug-related should be followed until resolution, stabilization, or returned to baseline.
Laboratory Tests	X		CBC w/differential, total protein, ALT, AST, total bilirubin, direct bilirubin (reflex testing when total bilirubin is elevated), alkaline phosphatase, BUN or serum urea level, uric acid, creatinine, albumin, Ca, Mg, Na, K, P, Cl, LDH, glucose, amylase, lipase, TSH (Free T4 and Free T3 reflex testing if TSH result abnormal).
Pregnancy Test (WOCBP Only)	X		Serum or urine
Review of Concomitant Medications	X		
PK Samples	X		See <a href="#">section 5.5</a>
Immunogenicity blood sample	X		See section 5.5
<b>Survival Status</b>			
Subject Status	X	X	Every 3 months, may be accomplished by visit, phone contact or email, to assess subsequent anti-cancer therapy
<b>Efficacy Assessments</b>			
Tumor Assessment		See Notes	<p>Only for subjects without progression on study therapy and even if they receive subsequent treatment.</p> <p>Every 6 weeks (<math>\pm</math> 1 wk) from first dose for the first 24 weeks, then every 12 wks (<math>\pm</math> 1 wk) until disease progression or treatment is discontinued (whichever occurs later).</p> <p>CT chest, CT/MRI abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.</p> <p>Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated</p>

<b>Table 5.1-5: Follow-up Assessments (CA212115) - All Subjects</b>			
<b>Procedure</b>	<b>Follow Up,<sup>a</sup> Visits 1 and 2</b>	<b>Survival,<sup>b</sup> Follow up Visits</b>	<b>Notes</b>
<b>Outcomes Research Assessments</b>			
EQ-5D	X	X	The EQ-5D can be done via a phone contact when a clinic visit is not feasible (ie, follow up scans are being done at another facility or department) in order to not miss the assessment.
Cancer-specific questionnaire* LCSS (SCLC) EORTC-QLQ-C30 (PAC)	X	X	*Only for Stage 2 Randomized study subjects

<sup>a</sup> Follow-up visit 1 (FU1) = 35 days ( $\pm$  7 days) from the last dose or coincide with the date of discontinuation ( $\pm$  7 days) if date of discontinuation is greater than 42 days after last dose, Follow-up visit 2 (FU2) = 80 days ( $\pm$  7 days) from follow-up visit 1

<sup>b</sup> Survival visits = every 3 months from FU2. Regardless of any subsequent treatment, all subjects will remain on study follow-up for disease progression and survival assessment.

### **5.1.1 Retesting During Screening or Lead-in Period**

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value). Any new result will override the previous result (ie, the most current result prior to start of therapy) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

## **5.2 Study Materials**

- NCI CTCAE Grading Criteria
- BMS-936564 (ulocuplumab) Investigator Brochure
- BMS-936558 (nivolumab) Investigator Brochure
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Manual for operation of interactive voice response system
- Manual for entry of local laboratory data
- Pregnancy surveillance forms
- RECIST 1.1 pocket guide
- Questionnaires: EQ-5D, LCSS (for SCLC) and EORTC-QLQ-C30 (for PAC)

## **5.3 Safety Assessments**

Safety assessments should be performed per tables in [Section 5.1](#).

Physical examinations are to be performed per tables in Section 5.1 and as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug and at time points specified in Section 5.1. Chest X-ray is to be performed for monitoring of pulmonary toxicity per tables in Section 5.1.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug-related toxicities resolve, return to baseline or are deemed irreversible.

Vital signs should be assessed at each on-study visit prior to dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. Oxygen saturation by pulse oximetry should be obtained prior to dosing and at any time a subject has any new or worsening respiratory symptoms. A reading at rest should be obtained at each time point. If a subject shows changes on pulse oximetry or other pulmonary related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the patient

subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in [Appendix 2](#).

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

### **5.3.1 Imaging Assessment for the Study**

For details on the imaging assessments for response evaluation, refer to [Appendix 3](#).

#### **5.3.1.1 CT/MRI**

Contrast-enhanced Computed Tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. CT with contrast of the chest, abdomen and pelvis are to be performed for tumor assessments every 6 weeks for the first 24 weeks, then every 12 wks until disease progression or treatment is discontinued. CT scans should be acquired with 5mm slices with no intervening gap (contiguous).

Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast enhanced MRI of the abdomen and pelvis may be obtained. MRI's should be acquired with slice thickness of 5 mm with no gap (contiguous).

Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

- Note: Use of CT component of a PET/CT scanner:

Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST 1.1 measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

#### **5.3.1.2 MRI Brain**

MRI of brain is required at screening for subjects with SCLC in order to rule out active metastatic disease. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

MRI brain scans during on-study treatment and follow up periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the investigator as per standard medical/clinical judgment.

#### **5.4 Efficacy Assessments**

Study evaluations will take place in accordance with the flow charts in [Section 5.1](#). Baseline tumor assessments should be performed within 28 days prior to the first dose utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning 6 weeks ( $\pm 1$  week) from first dose and continuing every 6 weeks ( $\pm 1$  week) for the first 24 weeks and every 12 weeks ( $\pm 1$  week) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST 1.1 criteria. For details on the efficacy assessments of overall tumor burden including baseline documentation of “target” and “non-target” lesions and RECIST 1.1 criteria, please see [Appendix 3](#).

##### **5.4.1 Primary Efficacy Assessment**

The primary efficacy endpoint will be ORR, as determined by the investigators, for the Dose Evaluation Phase and if a Simon 2-stage like design is selected for the Expansion Phase. If an open label randomized Phase 2 with a comparative arm is selected for the Expansion Phase, the primary efficacy endpoint will be ORR for SCLC and OS for PAC. If a randomized Phase 2 study is initiated for either tumor type, a blinded independent review of all imaging scans will be used to determine ORR, best overall response (BOR) and the magnitude of reduction in tumor volume. Refer to [Section 8.3](#) for the definition of these endpoints. For OS, every effort should be made to collect survival date on all treated subjects including withdrawal from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported every date collected in this study representing a date of subject contact will be used in determining the subject's last known alive date.















[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**5.6.5.5 Tumor Sample Collection Details**

Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of specimens will be provided in a separate Procedure Manual at the time of study initiation.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**5.7.2 LCSS- SCLC subjects only**

The LCSS is designed as a lung-cancer specific measure of QoL, specifically for use in clinical trials. It consists of 9 visual analogue scales that are administered in a fixed order and completed by the subject. The LCSS evaluates 6 major symptoms associated with lung malignancies and their effect on overall symptomatic distress, functional activities and global QoL. For subjects with SCLC, the LCSS will be administered only if a randomized Phase 2 study with comparative arm is initiated.



## 5.8 Other Assessments

Not applicable.

## 5.9 Results of Central Assessments

### 5.9.1 Evaluation of Scans

In addition to investigator assessed response, the protocol contains a plan to use an independent radiology review committee (IRRC) to also assess ORR if a randomized Phase 2 study is initiated. For instance, investigator assessed ORR will be the primary endpoint for subjects enrolled in the Dose Evaluation Phase or in the Dose Expansion Phase (Simon 2-stage single arm study only). For SCLC subjects enrolled in the Randomized Phase 2 with comparative arm, IRRC-assessed ORR will be the primary endpoint and an exploratory endpoint for PAC subjects. BMS may request the transfer of de-identified scans for internal or external evaluation through a third party.

## 6 ADVERSE EVENTS

An *Adverse Event (AE)* is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all AE. The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

## 6.1 Serious Adverse Events

A *Serious Adverse Event (SAE)* is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See [Section 6.6](#) for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See [Section 6.1.1](#) for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see [Section 6.1.1](#) for reporting details).

### **NOTE:**

The following hospitalizations are not considered SAE in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)

- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

### **6.1.1 Serious Adverse Event Collection and Reporting**

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. Subjects who are randomized and never treated with study drug must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

**SAE Email Address:** Refer to Contact Information list.

**SAE Facsimile Number:** Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.



**SAE Telephone Contact** (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report must be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

## **6.2 Nonserious Adverse Events**

A *nonserious adverse event* is an AE not classified as serious.

### **6.2.1 Nonserious Adverse Event Collection and Reporting**

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see [Section 6.1.1](#)). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

## **6.3 Laboratory Test Result Abnormalities**

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or delayed
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

## **6.4 Pregnancy**

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS

Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in [Section 6.1.1](#).

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in [Section 6.1.1](#).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

## **6.5 Overdose**

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs (see [Section 6.1.1](#) for reporting details).

## **6.6 Potential Drug Induced Liver Injury (DILI)**

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

- 1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

- 2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

- 3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

## **6.7 Other Safety Considerations**

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

## **7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES**

Ulocuplumab has demonstrated a manageable safety profile in over 140 subjects enrolled in two Phase 1 clinical trials at exposures that are related to the recommended starting dose proposed in CA212115. Nivolumab has demonstrated a manageable safety profile in more than 4000 patients in numerous early and late stage clinical trials. The AE profile of nivolumab appears to be independent of tumor type. Adverse events observed at 3 mg/kg nivolumab were manageable and generally reversible with the use of existing treatment algorithms. When comparing the toxicity profile of ulocuplumab and nivolumab in solid tumor indications, there is little overlap of AE profiles. Therefore, a data monitoring committee (DMC) will not be utilized for the open label, Dose Expansion Phase (Stage 1) of this study.

The subjects' safety will be monitored on an ongoing basis. Safety conference calls with investigators and representatives of the sponsor will be held regularly during the DLT evaluation period. The BMS Medical Monitor is a physician responsible for reviewing, on a systematic and continuous basis, the safety of patients on this study. This includes a review of serious and non serious adverse events, which includes all hematological and non-hematological events.

In addition, separate BMS medical safety teams (MST) routinely review safety signals across the nivolumab and ulocuplumab programs. The MST is independent from the BMS Medical Monitor. The MST has the primary responsibility within BMS for assessing emerging safety trends, identifying potential safety signals, notifying appropriate stakeholders of relevant findings, and implementing risk management plans.

The MST is responsible for reviewing data from all sources including non-clinical studies and clinical trials, monitoring the progress of various nivolumab and ulocuplumab safety support activities, and recommending and implementing necessary changes to the safety plan and any other specific safety-related activities.

If a randomized Phase 2 study with comparative arm is initiated, a DMC will be established to provide oversight of safety and efficacy evaluation and to provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the randomized Phase 2 study with comparative arm. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for ulocuplumab plus nivolumab and nivolumab monotherapy (for SCLC) or Investigator's Choice chemotherapy (for PAC). The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has

primary responsibility for design and conduct of the study. A separate charter will provide further guidance and describe the activities of this committee.

## **8 STATISTICAL CONSIDERATIONS**

### **8.1 Sample Size Determination**

The sample size will start at DL1 with a minimum of 3 treated subjects with either SCLC or PAC using a Rolling Six design for evaluation of DLT. Then, the sample size will be increased by the number of subjects, separately by tumor type, needed to continue the DLT evaluation at each dose level followed by the number of subjects, separately by tumor type, 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 for each tumor type.

#### **8.1.1 SCLC Sample Size**

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

- 3 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 (ie. 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.

### **8.1.2 PAC Sample Size**

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

- 3 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 (ie, 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 0.10 log-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 arms 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<sup>28,41</sup> 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.

## 8.2 Populations for Analyses

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS
- All Treated Subjects: All subjects who received at least one dose of any study medication
- All DLT-evaluable Subjects: All subjects who completed the DLT evaluation phase (ie. 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 Randomized Subjects: All subjects who were randomized to a cohort (DL2, DL3A, DL3B) or allocated to an unique DL2, DL1 or DL-1 cohort during the Dose Evaluation Phase
- All Dose Evaluation Randomized Treated Subjects: All subjects who were randomized to a cohort (DL2, DL3A, DL3B) or allocated to an unique DL2, DL1 or DL-1 cohort during the Dose Evaluation Phase and were treated
- All Dose Expansion Phase Randomized Subjects: All subjects who were randomized to a treatment arm during the Dose Expansion Phase

Where applies, the above populations will be defined for each phase individually or pooled across phases (eg. for the analysis of the 2-stage design).

## 8.3 Endpoints

### 8.3.1 Primary Endpoint(s)

The incidence of DLTs is the primary safety endpoint during the DLT evaluation phase.

In terms of efficacy, the primary endpoint for SCLC is investigator assessed ORR for the Dose Evaluation Phase and the single arm Dose Expansion Phase. If the randomized Phase 2 study in SCLC subjects is triggered, an IRRC will perform blinded independent review of the imaging per RECIST 1.1 criteria for the assessment of ORR. The 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 number of randomized subjects for the randomized Phase 2 study with comparative arm). The BOR is defined as the best response designation, as determined by the investigator, recorded between the first dosing date (randomization date for the randomized Phase 2 study with comparative arm) and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, 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 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 RECIST 1.1-defined progression.

For PAC, the primary endpoint is investigator assessed ORR for the Dose Evaluation Phase and the single arm Dose Expansion Phase. Overall survival (OS) is the primary endpoint for the randomized two-arm Phase 2 study. The ORR is defined as above and OS is defined as the time between the randomization date and the date of death due to any cause. A subject who has not died will be censored at the last known alive date.

### **8.3.2 Secondary Endpoint(s)**

Safety and tolerability will be analyzed through the incidence of DLTs, adverse events, serious adverse events, and specific laboratory abnormalities (worst grade). Toxicities will be graded using the NCI CTCAE version 4.0.

PFS is defined as the time from first dosing date (randomization date for the randomized Phase 2 study with comparative arm) to the date of the first documented tumor progression, as determined by the investigator (per RECIST 1.1), 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 tumor assessment. Subjects who did not have any on-study tumor assessments and did not die will be censored on the date of their first dosing date (randomization date for the randomized Phase 2 study with comparative arm). 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.

### **8.3.3 Exploratory Endpoint(s)**

[Redacted]

[Redacted]

[Redacted]

[Redacted]

## **8.4 Analyses**

All analyses will be presented separately by tumor type.

### **8.4.1 Demographics and Baseline Characteristics**

Demographic and baseline characteristics will be summarized using descriptive statistics.

### **8.4.2 Efficacy Analyses**

For the Dose Evaluation Phase, efficacy analyses will be summarized using the All Dose Evaluation Randomized Treated Subjects by randomized cohort (primary population). Additionally, analyses including all efficacy data collected during that Phase using the All Treated Subjects population will be provided by regimen. Analyses will be presented as-treated.

If the form of the Expansion Phase is a Simon 2-stage like design, efficacy analyses will be summarized for the regimen recommended for the Dose Expansion Phase, pooling data from the related randomized cohort from the All Dose Evaluation Randomized Treated Subjects during Stage 1 with the Stage 2 data (primary population). Additionally, analyses using the All Treated Subjects and including all efficacy data collected for that regimen during the Dose Evaluation and the Dose Expansion Phases will be provided. Analyses will be presented as-treated.

If a randomized Phase 2 study with comparative arm is initiated, efficacy analyses will be presented separately by treatment arm using the All Expansion Phase Randomized Subjects. Analyses will be presented as-randomized.

#### **8.4.2.1 Primary Endpoint Methods**

ORR will be summarized by a binomial response rate and corresponding two-sided 90% exact CI using the Clopper and Pearson method. If a randomized Phase 2 study with comparative arm is initiated, ORR will be compared between the treatment arms using a one-sided alpha level of 0.10 with Cochran-Mantel-Haenszel (CMH) test stratified by the stratification factors defined for each tumor type. A two-sided, 80% CI for the difference in response rates will also be computed, adjusting for the stratification factors.

The primary analysis of OS as primary endpoint for PAC will be a comparison of the OS of subjects randomized to ulocuplumab plus nivolumab to that of subjects randomized to the investigator's choice chemotherapy using a one-sided alpha level of 0.10 log-rank test stratified by the stratification factors defined for each tumor type. The hazard ratio and associated two-sided 80% confidence interval will be computed using an univariate Cox proportional hazards model with treatment as the sole covariate. Further analyses of OS will be summarized descriptively using Kaplan-Meier methodology. Median values of OS, along with two-sided 95% CIs using the Brookmeyer and Crowley method considering a log-log transformation, will be calculated. OS rates at 3, 6, 9, 12, 18 and 24 months will be estimated as well as associated two-sided 95% CIs considering a log-log transformation.



#### **8.4.2.2 Secondary Endpoint Methods**

PFS as a secondary endpoint will be descriptively summarized as for OS above. PFS rates at 3, 6, 9, 12, and 18 months will be estimated as well as associated two-sided 95% CIs considering a log-log transformation.

#### **8.4.2.3 Exploratory Endpoint Methods**

[REDACTED]

#### **8.4.3 Safety Analyses**

Except where indicated, safety analyses will be using the All Treated Subjects population and will be presented as-treated.

During the DLT evaluation Phase, the primary analysis will consist of the incidence of DLTs among DLT-evaluable Subjects but all available safety and tolerability data will be used to assess the safety of the regimens.

For the Dose Evaluation Phase, safety analyses will be summarized by randomized cohort. Additionally, analyses including all safety data collected during that Phase will be provided by regimen.

If the form of the Expansion Phase, is a Simon 2-stage like design, safety analyses will be summarized for the regimen recommended for the Dose Expansion, pooling data from both stages of the study. Additionally, analyses including all safety data collected for that regimen during the Dose Evaluation and the Dose Expansion Phases will be provided.

If a randomized Phase 2 study with comparative arm is initiated, safety analyses will be presented separately by treatment arm.

Events (AEs or laboratory) will be counted as on-study if the event occurred within 100 days of the last dose of ulocuplumab or within 100 days of the last dose of nivolumab, whichever is later. All on-study AEs, treatment-related AEs, SAEs, treatment-related SAEs, AEs leading to discontinuation and treatment-related AEs leading to discontinuation will be tabulated (All Grades and Grade 3-4) using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study laboratory abnormalities including hematology, chemistry,

liver function, and renal function will be summarized (All Grades and Grade 3-4) using worst grade NCI CTCAE v 4.0 criteria.

[REDACTED]

[REDACTED]


[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



Baseline and change from baseline in EORTC-QLQ-C30 global health status/QoL composite scale data and the remaining EORTC QLQ-C30 scale data will be summarized by time point using descriptive statistics for each cohort (N, mean, standard deviation, median, first and third quartiles, minimum, maximum). In addition, the percentage of subjects demonstrating a clinically meaningful change (defined as a 10 point change from baseline) will be presented for each scale at each subsequent time point. Percentages will be based on number of subjects assessed at assessment time point.

#### **8.4.8 Other Analyses**

Not applicable.

#### **8.5 Interim Analyses**

Within each tumor type, 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 in the tumor type; 2) if further study is warranted, to select a recommended dose for the Dose Expansion Phase; and 3) if the Dose Expansion Phase is to be completed, to determine whether to conduct a single arm second stage of a Simon optimal 2 stage like design or an open label randomized Phase 2 design with a comparative arm.

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 for the Dose Evaluation Phase (at least 4 responders for SCLC and at least 2 responders for PAC). In addition, the selection of the recommended dose will be based on all available safety and efficacy data for that IA 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 to evaluating final data before decision is reached to stop further study the combination to ensure 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 optimal 2-stage like 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%).

During the Expansion phase, an IA will be conducted when all subjects of the second stage of the Simon 2-stage like design have a minimum of 3 months of treatment or discontinued prematurely. If a randomized Phase 2 study with comparative arm is initiated, IA will be conducted for the DMC as specified in the DMC charter on a regular basis.

## **9 STUDY MANAGEMENT**

### **9.1 Compliance**

#### **9.1.1 Compliance with the Protocol and Protocol Revisions**

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

#### **9.1.2 Monitoring**

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

#### **9.1.2.1 Source Documentation**

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

#### **9.1.3 Investigational Site Training**

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

### **9.2 Records**

#### **9.2.1 Records Retention**

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

#### **9.2.2 Study Drug Records**

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s): For PAC subjects, if Stage 1 results in a decision to move to a randomized Phase 2 study with comparative arm in Dose Expansion Phase,

Investigator's Choice for advanced or metastatic PAC subjects will be the comparator arm. The treatment options for 2L PAC include the following:

- Gemcitabine with or without albumin-bound paclitaxel
- Capecitabine and other fluoropyrimidine containing regimens

Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

### **9.2.3 Case Report Forms**

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

### **9.3 Clinical Study Report and Publications**

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- Subject recruitment (eg, among the top quartile of enrollers)
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

## 10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	<p>If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.</p> <p>If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.</p> <p><b>Expanded definition</b> Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence</p>



## 11 LIST OF ABBREVIATIONS

<b>Term</b>	<b>Definition</b>
ACTH	Adrenocorticotrophic hormone
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALP	Alkaline Phosphatase
ALT	alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	Area Under the Curve
BMS	Bristol-Myers Squibb
BOR	Best Overall Response
BP	blood pressure
BUN	Blood Urea Nitrogen
Ca <sup>++</sup>	Calcium
CAF	Cancer Associated Fibroblast
CA19.9	Cancer Antigen 19.9
CBC	complete blood count
CI	confidence interval
CLL	Chronic Lymphocytic Leukemia
C <sub>max</sub> , C <sub>MAX</sub>	maximum observed concentration
C <sub>min</sub> , C <sub>MIN</sub>	trough observed concentration
CR	Complete response
CrCl	Creatinine Clearance
CRF	Case Report Form, paper or electronic
CRP	C Reactive Protein
CT	Computed tomography
CTA	Clinical Trial Agreement

<b>Term</b>	<b>Definition</b>
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CV	coefficient of variation
CXCR4	CXC Chemokine Receptor 4
DCR	Disease control rate
DILI	Drug Induced Liver Injury
DL	Dose Level
DLBCL	Diffuse Large B Cell Leukemia
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ED-SCLC	Extensive Disease Small Cell Lung Cancer
EQ-VAS	EQ visual analog scale
EMR	Electronic Medical Records
EHR	Electronic Health Records
EOI	End of Infusion
EQ-5D	EuroQol 5 Dimensions Questionnaire
FAP	Fibroblast Activating Protein
FDA	Food and Drug Administration
FDG/PET	18-Fluoro-deoxyglucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
FL	Follicular Lymphoma
FOLFIRINOX	combination of 5-FU, leucovorin, irinotecan, oxaliplatin
FSH	follicle stimulating hormone
FU1	Follow-up 1
FU2	Follow-up 2
GCP	Good Clinical Practice
GEM	Gemcitabine

<b>Term</b>	<b>Definition</b>
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	Hormonal Replacement Therapy
IRB	Institutional Review Board
IA	Interim Analysis
IB	Investigator Brochure
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRRC	Independent Radiology Review Committee
IV	Intravenous
IVRS	interactive voice response system
KM	Kaplan-Meier
LD-SCLC	Limited Disease - Small Cell Lung Cancer
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
MEC	mitoxantrone, etoposide, and cytarabine
MM	Multiple Myeloma
MST	medical safety team
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
N	Nivolumab
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

<b>Term</b>	<b>Definition</b>
NIMP	non-investigational medicinal products
NK	Natural Killer
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PAC	Pancreatic adenocarcinoma
PD	Pharmacodynamics
PDAC	Pancreatic ductal adenocarcinoma
PD-1	Programmed death 1
PD-L1	Programmed cell death 1 ligand 1
PE	Physical Exam
PE	Platinum plus etoposide
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial response
Q2W	Every two weeks
QC	quality control
RCC	Renal Cell Carcinoma
RNA	Ribonucleic Acid
RBC	red blood cell
RO	Receptor Occupancy
RECIST	Response Evaluation Criteria in Solid Tumors
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	serious adverse event
SCLC	Small cell lung cancer
SD	stable disease
SDF-1	stromal cell-derived factor 1
SOC	Standard of care

<b>Term</b>	<b>Definition</b>
T3, T4	triiodothyronine (T3), thyroxine (T4)
TSH	Thyroid Stimulating Hormone
U	Ulocuplumab
ULN	Upper Limit of Normal
US	United States
VGPR	Very Good Partial Response
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
2L	Second Line

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**APPENDIX 1 PERFORMANCE STATUS SCALES**

STATUS	SCALES		STATUS
	KARNOFSKY	ZUBROD- ECOG-WHO	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal activity or to do active work	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40	3	
Severely disabled. Hospitalization indicated though death non imminent	30	3	
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Unable to get out of bed
Moribund	10	4	
Dead	0	5	Dead

## **APPENDIX 2           MANAGEMENT ALGORITHMS**

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology (I-O) agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

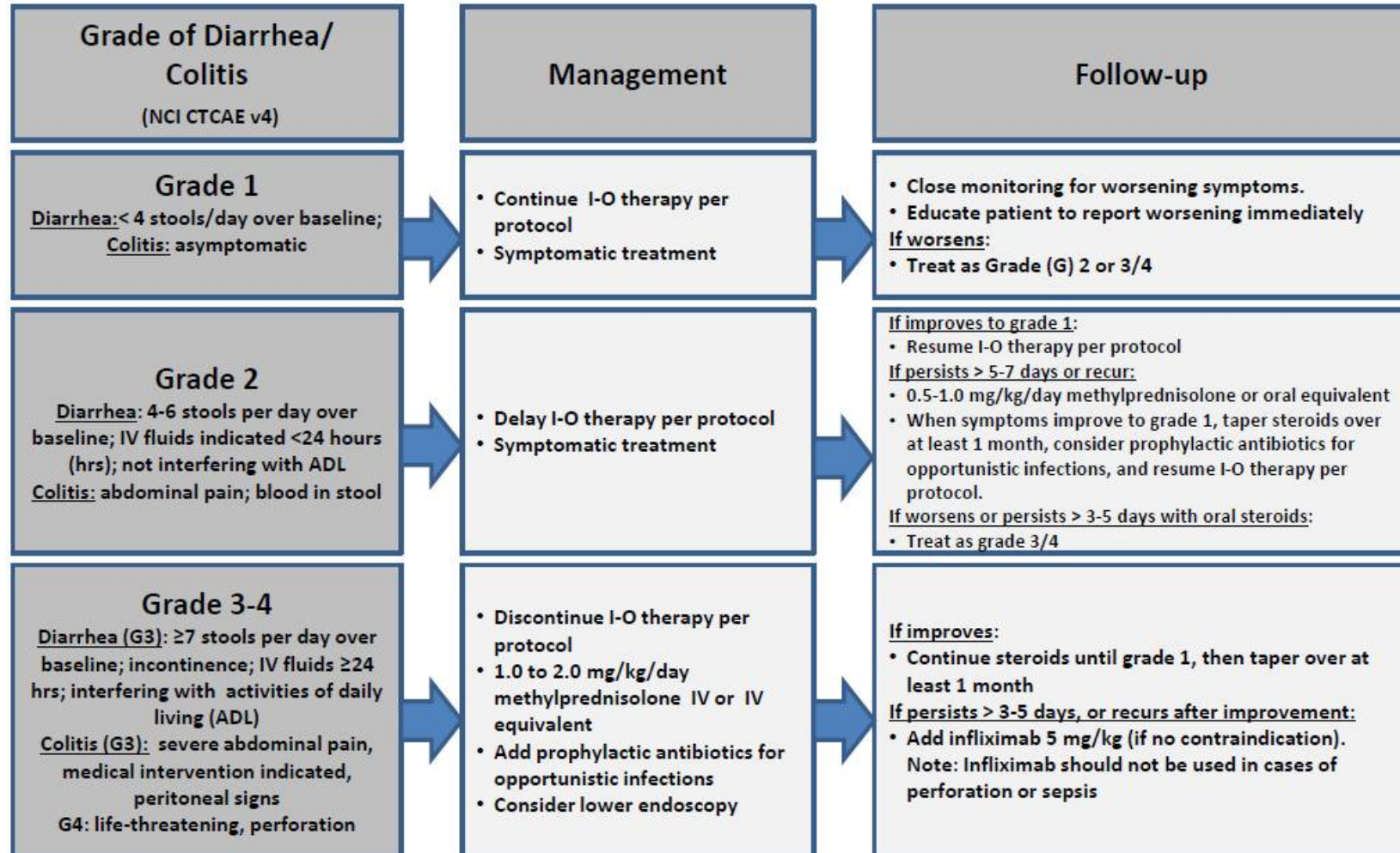
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

## GI Adverse Event Management Algorithm

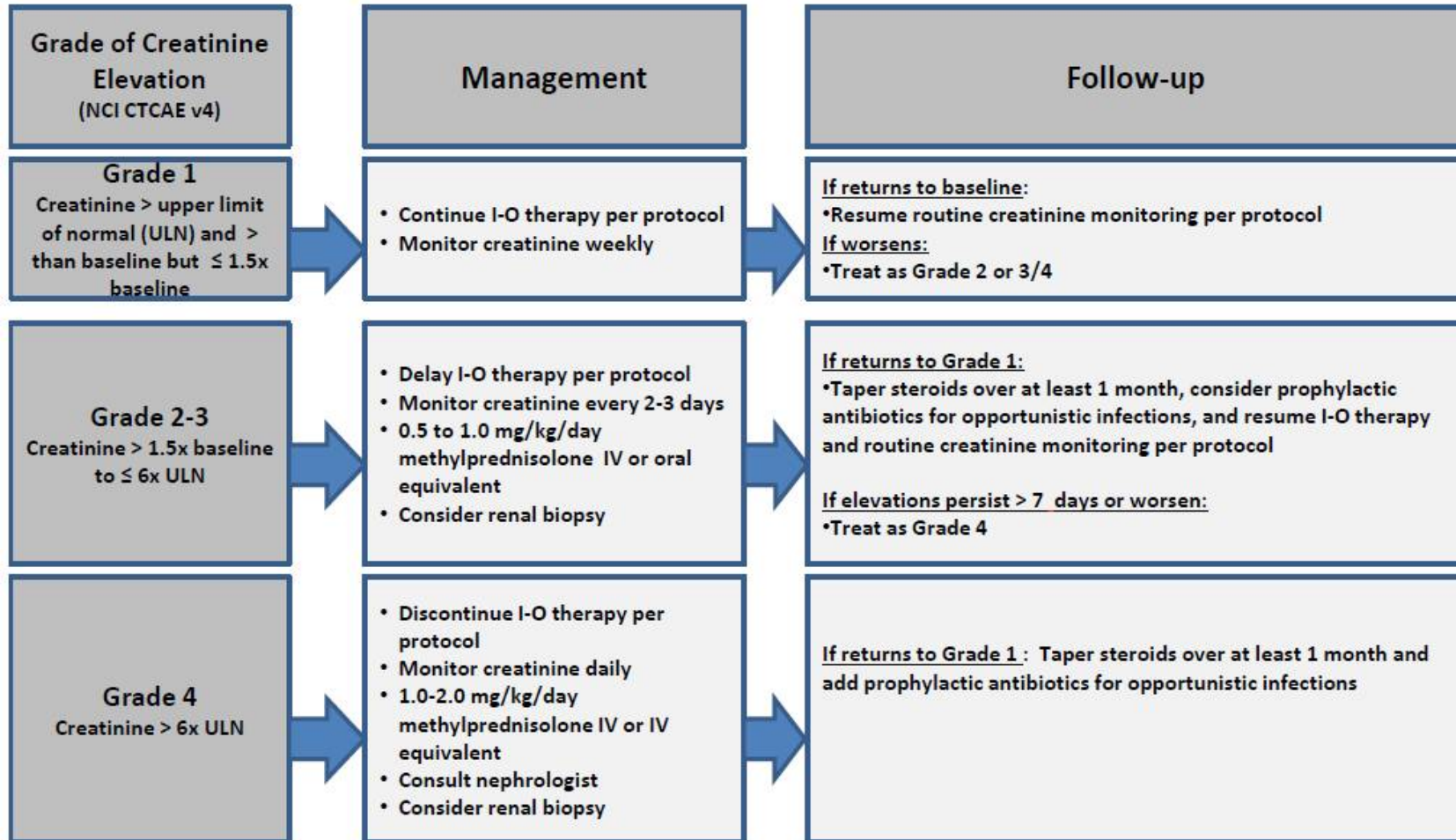
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Renal Adverse Event Management Algorithm

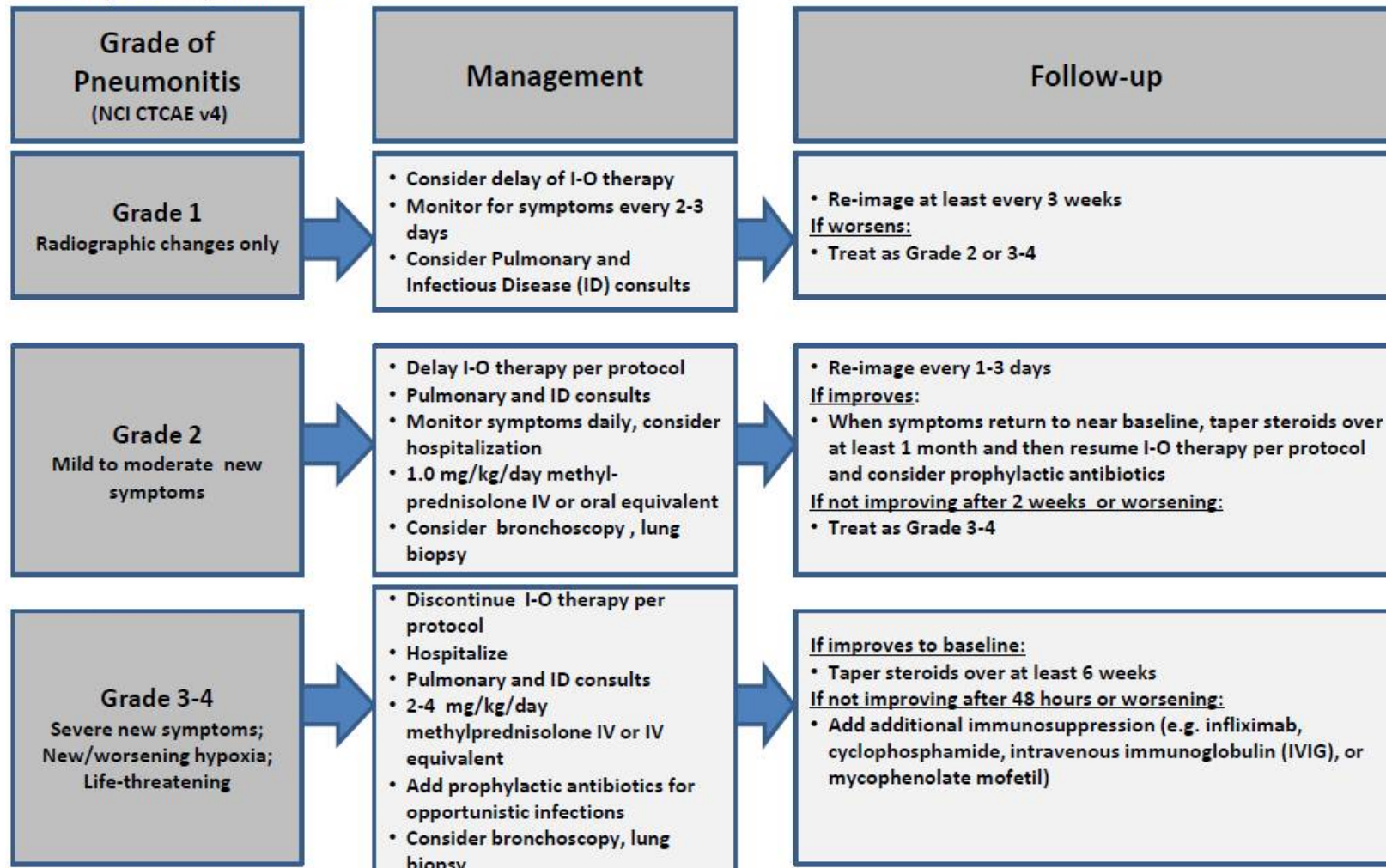
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Pulmonary Adverse Event Management Algorithm

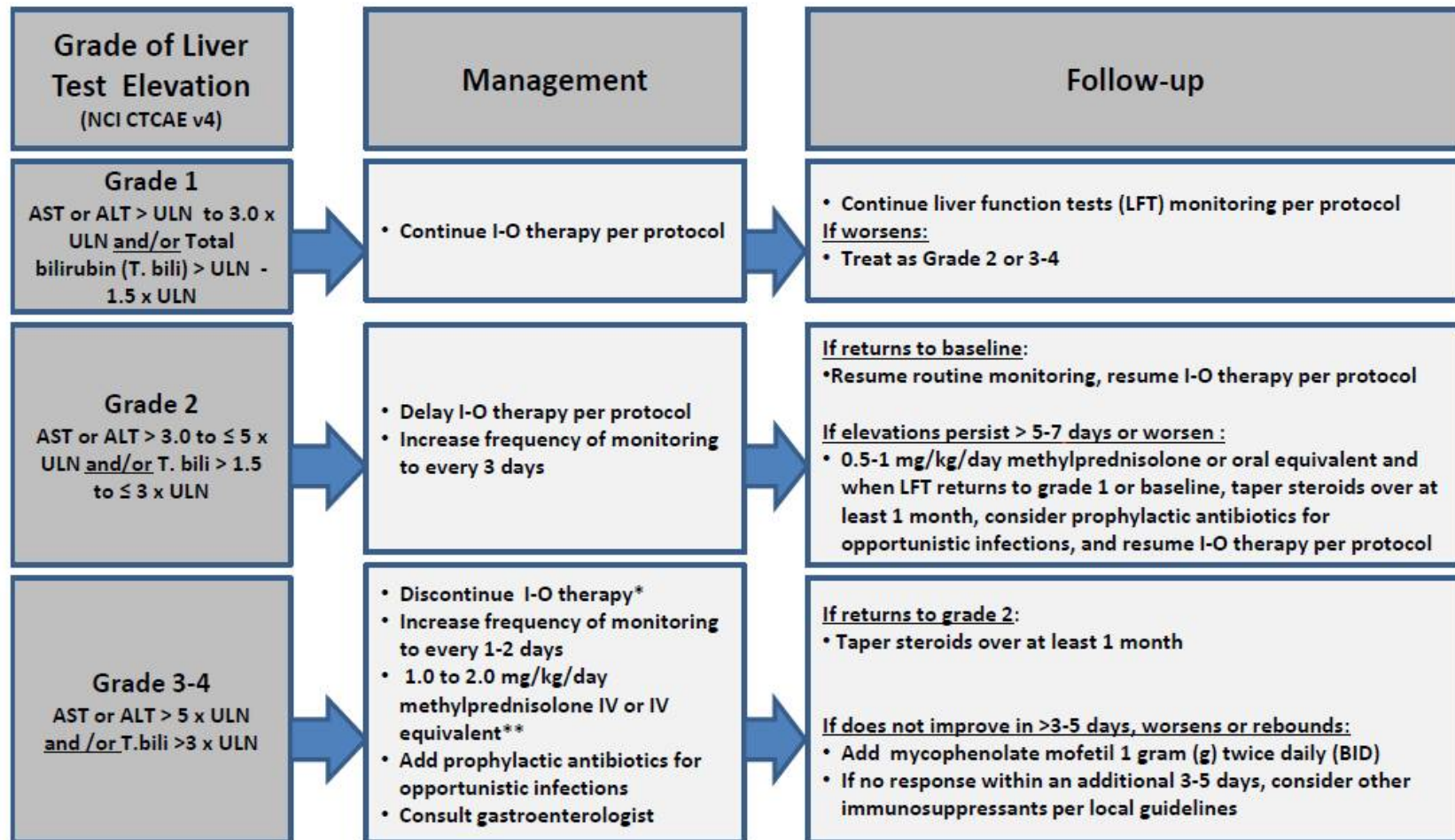
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



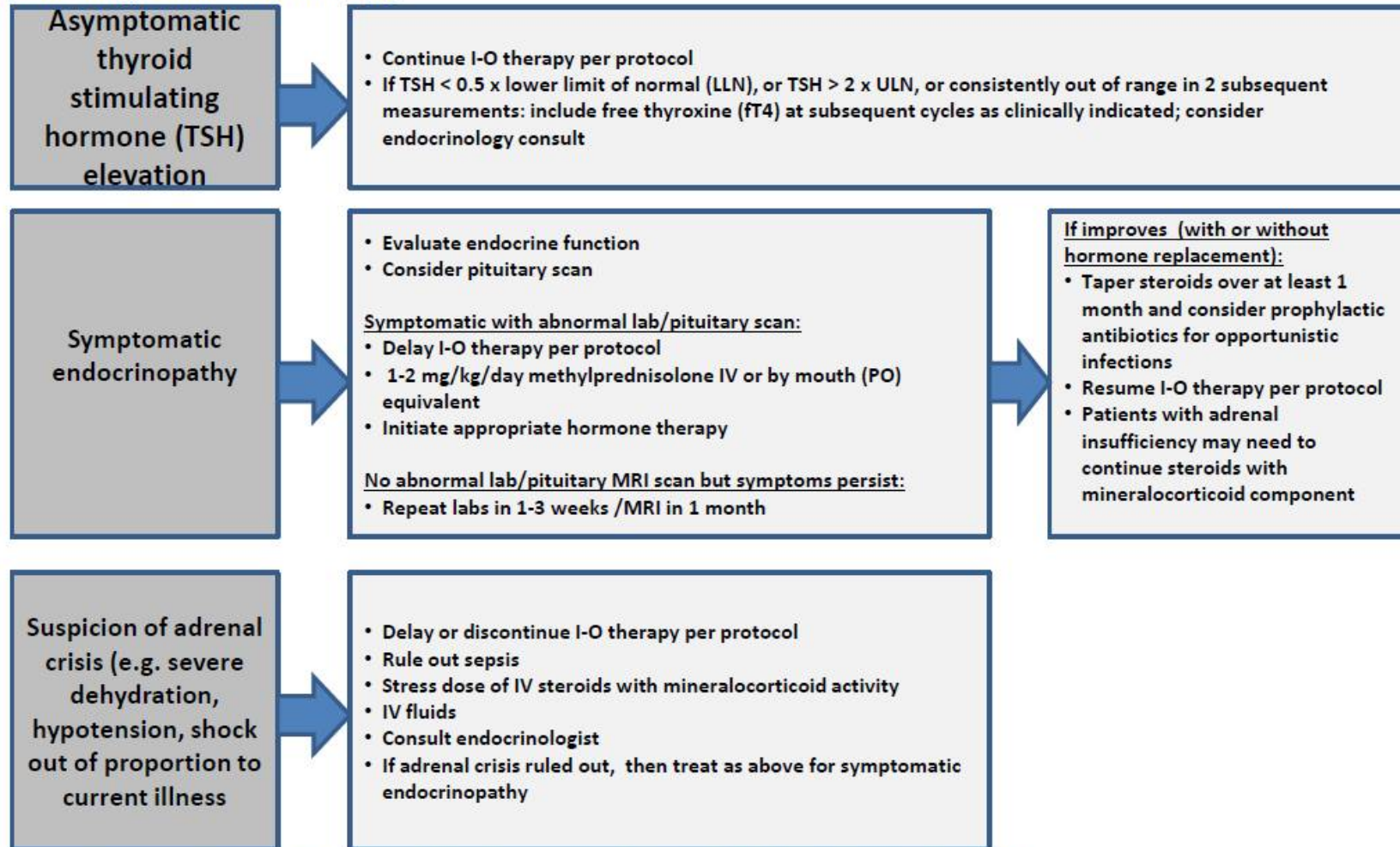
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

\*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.

\*\*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

## Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

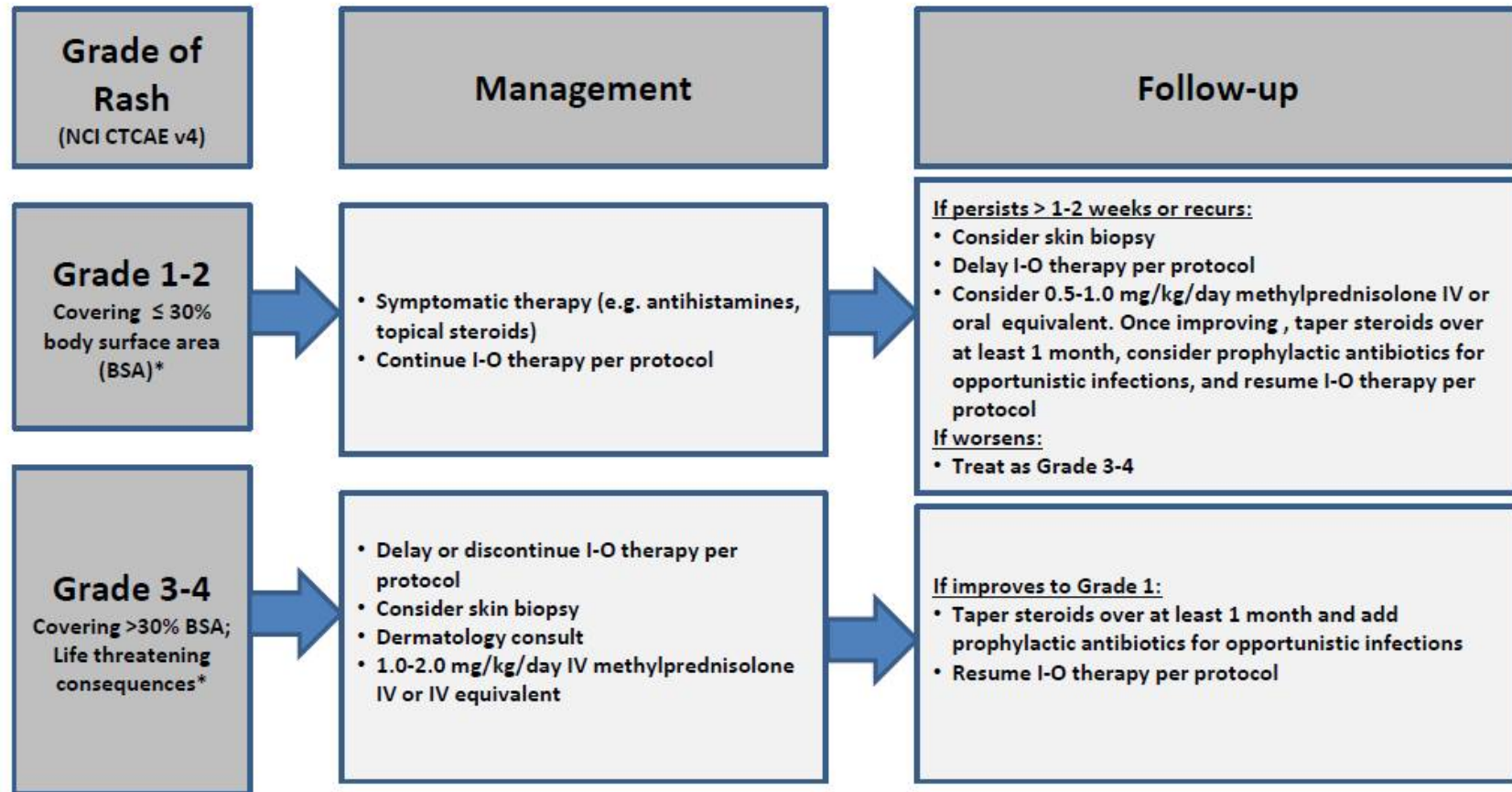


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.



## Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

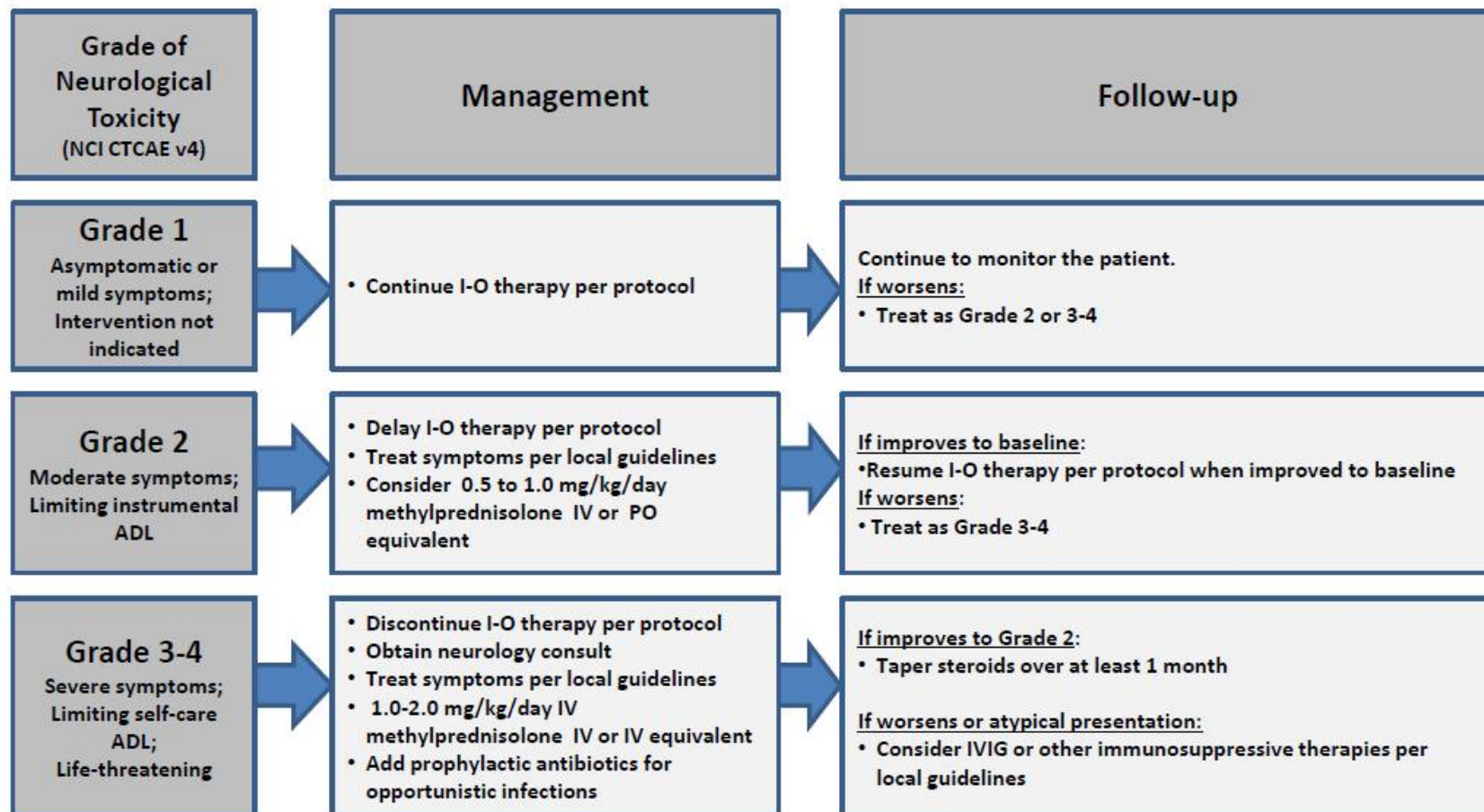


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

\*Refer to NCI CTCAE v4 for term-specific grading criteria.

# Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

## **APPENDIX 3 EFFICACY ASSESSMENTS OF OVERALL TUMOR BURDEN**

### **1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE**

To serially evaluate tumor response to therapy, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT or MRI scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows

#### **1.1 Measurable Lesions**

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT/MRI scan - (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow up, only the short axis will be measured and followed

#### **1.2 Non-Measurable Lesions**

- All other lesions, including small lesions (longest diameter  $< 10$  mm or pathological lymph nodes with  $\geq 10$  to  $< 15$  mm short axis), as well as truly non-measurable lesions
- Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques

#### **1.3 Special Consideration Regarding Lesion Measurability**

##### **1.3.1 Bone Lesions**

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

### **1.3.2 Cystic Lesions**

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are by definition, simple cysts. Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

### **1.3.3 Lesions with Prior Local treatment**

Tumor lesions situated in a previously irradiated area, or in an area subjected to loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

## **1.4 Specifications by Method of Measurement**

### **1.4.1 Measurement of Lesions**

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of treatment.

### **1.4.2 Method of Assessment**

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

#### **1.4.2.1 CT/MRI Scan**

CT/MRI is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT/MRI scan is based on the assumption that CT/MRI slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Imaging-based evaluation is preferred to clinical examination. Helical (spiral) CT scans of the chest and abdomen are preferred. If not available, conventional (non helical, non spiral CT) should be used. If IV contrast is contraindicated, CT without contrast may be used, or MRI should be used at the Screening exam and at all TA time points. Subjects who develop contrast allergy after study enrollment must be followed by CT without contrast or MRI for subsequent tumor measurements.

Response and progression of disease must be documented by CT or MRI similar to the methods used at Screening.

#### **1.4.2.2 Chest X-Ray**

Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

#### **1.4.2.3 Clinical Lesions**

Clinical lesions will only be considered measurable when they are superficial and  $\geq 10$  mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As previously noted, when lesions can be evaluated both by clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

#### **1.4.2.4 Ultrasound**

Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

#### **1.4.2.5 Endoscopy, Laparoscopy**

The utilization of these techniques for objective tumor evaluation is not advised.

## **2 BASELINE DOCUMENTATION OF “TARGET” AND “NON-TARGET LESIONS”**

### **2.1 Target Lesions**

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted below, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST 1.1 determined response.

### **2.1.1 Lymph Nodes**

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of  $\geq 15$  mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum.

Nodes that have a short axis  $< 10$  mm are considered non-pathological and should not be recorded or followed.

### **2.2 Non-Target Lesions**

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

## **3 TUMOR RESPONSE EVALUATION**

### **3.1 Evaluation of Target Lesions**

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to  $< 10$  mm
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

#### **3.1.1 Target Lesions that Become “Too Small to Measure”**

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

#### **3.1.2 Target Lesions that Split or Coalesce on Treatment**

When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. As lesions coalesce, a plane between them maybe maintained that would aid in obtaining maximal diameter measurements of each

individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

### **3.2 Evaluation of Non-Target Lesions**

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) above the normal limits
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression)

#### ***Special Notes on Assessment of Non-target Lesions***

##### **3.2.1 When the Subject Also Has Measurable Disease**

- To achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy
- A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status

##### **3.2.2 When the Subject Has Only Non-measurable Disease**

- To achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy
- A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status
- Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread, or may be described in protocols as ‘sufficient to require a change in therapy’
- If ‘unequivocal progression’ is seen, the subject should be considered to have had overall PD at that point

### 3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of preexisting lesions. This is particularly important when the subject’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan reported as a ‘new’ cystic lesion, which it is not.)

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered which reveals metastases. The subject’s brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

## 4 RESPONSE CRITERIA (RECIST 1.1)

Table 4-1 provides a summary of the Time Point Response overall response status in subjects with Target and non-Target Disease

<b>Table 4-1: Time Point Response - Subjects With Target ( ± Non-target) Disease</b>			
<b>Target Lesions</b>	<b>Non-Target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Not Evaluable

### 4.1 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is **not evaluable (NE)** at that time point. If only a subset of lesion measurements are made at an



assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time point response.

## 4.2 Confirmation Scans

**Verification of Response:** Confirmation of response (CR or PR) is required. Confirmed CR or PR will be claimed only if the criteria for each are met at a subsequent time point (minimum 4 weeks after criteria for an objective response are first met. **After an initial PR or CR is noted, the subsequent protocol-specified tumor assessment may serve as the confirmation.**

**Verification of Progression:** Progression of disease should be verified only in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per RECIST 1.1.





