Clinical Study Protocol	
Drug Substance	MEDI9447 (Oleclumab)
Study Code	D6070C00006
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A Phase I, Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Activity of MEDI9447 (Oleclumab) in Japanese Patients with Advanced Solid Malignancies

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Regulatory Agency Identifying Number(s): Not applicable

VERSION HISTORY

Version 3.0, 08 April 2019		
Section, Heading	**Revision Summary**	**Reason for Revision**
1.1 Schedule of Activities (SoA)	In table 2, the texts underlined were corrected in footnote b (English version only): All subjects are required to be hospitalized for the first week after administration on Day 1. Subjects will be monitored carefully throughout the hospitalisation. If any clinically important symptoms or signs are observed, appropriate tests/examinations will be performed. When transition from inpatient to outpatient setting is considered, investigators will conduct sufficient examinations and questioning of patients, and determine whether discharge is appropriate based on the results.	To correct a typo
1.1 Schedule of Activities (SoA)	In table 2, footnote k was added as below and footnote k was changed to l: On Day 1, serum samples for MEDI9447 ADA will be collected pre-dose (within 30 minutes prior to start of MEDI9447 infusion).	To clarify descriptions
6.4 Treatment compliance	The Japanese term of the first paragraph was modified. (Japanese version only)	To modify the Japanese term for revising insufficient descriptions
6.6.2 Definition of dose-limiting toxicity and evaluable subject	The first paragraph was corrected as below: DLT evaluable patients are defined as those who received 2 planned doses of MEDI9447 per protocol during the DLT assessment period and completed the safety follow-up through the DLT assessment period, or those who experienced a DLT. Also, the period for DLT evaluation is defined as the time from receiving the first dose of investigational product until assessments prior the planned administration of the third dose; this corresponds to 28 days after receiving the first dose of the investigational product or 14 days after the second dose, whichever occurs later (defined as Cycle 1). Subjects who do not remain in the study up to this time for reasons other than DLT will be considered non-evaluable for DLT assessment and will be replaced with another subject at the same dose level. In case of discontinuation from or interruption of treatment due to AE during the DLT evaluation period (e.g., ≥ grade 3 IRR), whether the AE should be a DLT will be discussed by the SRC based on the	To delete wrong descriptions

	below mentioned DLT definition 11. Grading of DLTs will be according to the NCI CTCAE v4.03.	
8.5.1 Determination of drug concentration in serum	The text was modified as below: Serum concentration of MEDI9447 will be measured utilizing a validated bioanalytical method. The results of the measurement will be reported either in the CSR itself or as an addendum, or separately in another report or a scientific report or publication. Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will be reported either in the CSR itself or as an addendum, or separately in another report or a scientific report or publication.	To change measurement sites and the way of reporting result
8.5.2 Storage and destruction of pharmacokinetic samples	The text was modified as below: PK samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. After PK analysis, remaining PK samples may be used for biomarker analysis. The results of this research will be reported either in the CSR itself or as an addendum, or separately in another report or a scientific report or publication.	To change storage period and handling of samples including rest samples after measurement
8.10 Immunogenicity	The first paragraph was corrected as below: At each time point a whole blood sample of approximately 3.5 mL will be collected for immunogenicity assessment of MEDI9447 as specified in the SoA, and more than 0.75 mL of serum sample will be obtained from it. Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site. The actual collection date and time (24-hour clock time) of each sample will be recorded.	To correct a typo
9.3 Populations for analyses	The definition of the pharmacokinetic analysis set was changed as below: Subjects who received at least 1 dose of MEDI9447 and provided at least 1 post-treatment sample	To change the study-specific definition of the previous version to the standard definition
9.3 Populations for analyses	The tumor response evaluable analysis set was removed.	To remove the tumor response evaluable analysis set and reduce analysis sets to be used for efficacy analysis to the efficacy analysis set because the

		number of subjects is very small and it is redundant to define multiple analysis sets for efficacy analysis.
9.4.4 Efficacy analyses	The first paragraph was changed as below: The efficacy analyses will be based on the efficacy analysis set. More details will be provided in the statistical analysis plan. The following efficacy endpoints will be analyzed:	To change description according to removing the tumor response evaluable analysis set

Version 2.0, 29 August 2018

Section, Heading	Revision Summary	Reason for Revision
1.1 Schedule of Activities (SoA)	In table 1, 2 and 3, the assessment "Vital signs" was changed into "Vital signs, SpO_2", a footnote "If a finding suggestive of interstitial lung disease (ILD) is observed, additional complete examination will be conducted as clinically indicated." and an abbreviation "SpO_2 = percutaneous arterial oxygen saturation" were added.	To monitor possible drug related adverse events adequately
1.1 Schedule of Activities (SoA)	In table 2, the texts underlined were added in footnote b: All subjects are required to be hospitalized for the first week after administration on Day 1. Subjects will be monitored carefully throughout the hospitalisation. If any clinically important symptoms or sings are observed, appropriate tests/examinations will be performed. When transition from inpatient to outpatient setting is considered, investigators will conduct sufficient examinations and questioning of patients, and determine whether discharge is appropriate based on the results.	To clarify descriptions
2.2.2 MEDI9447 background Appendix GAbbreviations	"Immunoglobulin 1 lambda (IgG1λ)" was corrected to "immunoglobulin G1 lambda (IgG1λ)". (Japanese version only)	To correct a typo
5.2 Exclusion criteria	The Japanese term for "its compounds" was modified in exclusion criterion 5. (Japanese version only)	To modify the Japanese term
5.2 Exclusion criteria	The exclusion criterion 13 "Patients with history of, or current ILD" was added. (Subsequent numbering was shifted by 1.)	To exclude patients who have higher risks of adverse events
5.3.1 Pregnancy	In table 5, methods of contraception that are not approved in Japan was added.	To correct a typo

6.6.2 Definition of dose-limiting toxicity and evaluable subject	The texts underlined were added in the first paragraph: DLT evaluable patients are defined as those who received 2 planned doses of MEDI9447 per protocol during the DLT assessment period and completed the safety follow-up through the DLT assessment period, or those who experienced a DLT. Also, the period for DLT evaluation is defined as the time from receiving the first dose of investigational product until assessments prior the planned administration of the third dose (Day 29); this corresponds to 28 days after receiving the first dose of the investigational product or 14 days after the second dose, whichever occurs later (defined as Cycle 1). Subjects who do not remain in the study up to this time for reasons other than DLT will be considered non-evaluable for DLT assessment and will be replaced with another subject at the same dose level. In case of discontinuation from or interruption of treatment due to AE during the DLT evaluation period (e.g., ≥ grade 3 IRR), whether the AE should be a DLT will be discussed by the SRC based on the below mentioned DLT definition 11. Grading of DLTs will be according to the NCI CTCAE v4.03.	To clarify descriptions
6.6.2 Definition of dose-limiting toxicity and evaluable subject	The text was changed in 5 and 7 as below: 5. Grade 4 anemia or anemia requiring red cell transfusion 7. Grade 3 thrombocytopenia with bleeding or thrombocytopenia requiring platelet transfusion	To evaluate drug related adverse events adequately
6.6.2 Definition of dose-limiting toxicity and evaluable subject	The text ”4 Grade 3 IRR (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.” was deleted out of “A DLT excludes”. (Subsequent numbering in “A DLT excludes the following” was shifted by 1.)	To evaluate drug related adverse events adequately
8.2.4 Vital signs and percutaneous arterial oxygen saturation (SpO_2)	The Title” Vital signs” was changed into “Vital signs and percutaneous arterial oxygen saturation (SpO_2)”. And the text was changed as below: ・ Temperature, pulse rate, respiratory rate, ~~and~~ blood pressure, and percutaneous arterial oxygen saturation (SpO_2) will be assessed after a full rest.	To monitor possible drug related adverse events adequately
8.4.5 Management of investigational product-related toxicities	The paragraph below was added as the third paragraph:	To clarify management procedures of adverse event

	If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Appendix F "Dosing Modification and Toxicity Management Guidelines" will be applied. The results of the full diagnostic workup will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory CT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.	
Appendix G Abbreviations	Percutaneous arterial oxygen saturation (SpO_2) was added.	To add an abbreviation

Version 1.0, 20 July 2018
Initial creation

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Procedures and assessments during study entry, as well as subsequent assessments are provided in the clinical protocol in Table 1 - Table 3.

Details of the various procedures and assessments are provided in the subsequent protocol sections.

Table 1 Schedule of Screening Procedures

Procedure	Screening Visit 1 (Day -28 to Day -1)	For details see Section
Written informed consent /assignment of SID number	X	8
Demographics (age, race, and ethnicity)	X	NA
Medical history, including relevant exposure (smoking, prior therapies) history	X	NA
Full physical examination [a], height, weight	X	8.2.2, 8.2.5
Vital signs, SpO_2 [a]	X	8.2.4
Electrocardiogram	X	8.2.6
ECOG Performance Status	X	8.2.3
Urinalysis	X	8.2.1
Serum chemistry	X	8.2.1
Hematology	X	8.2.1
Pregnancy test (serum hCG) [b]	X	8.2.1
Coagulation parameters	X	8.2.1
Thyroid function test [c]	X	8.2.1
Hepatitis B, C; HIV	X	8.2.1
Biomarker evaluation		
Blood samples	X	8.8
Archival tumor sample [d]	X	8.8
CCI [redacted]	[redacted]	[redacted]
Tumor and tumor markers evaluation [f]	X	8.1.1, Appendix E
Assessment of AEs/SAEs	X	8.3
Concomitant medications	X	6.5
Verify eligibility criteria	X	5.1, 5.2, 8

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; NA = not applicable; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; SAE = serious adverse event; CCI [redacted] SID = subject identification, SpO_2 = percutaneous arterial oxygen saturation.

[a] If a finding suggestive of interstitial lung disease (ILD) is observed, additional complete examination will be conducted as clinically indicated.

[b] Females of childbearing potential only. For women of childbearing potential, defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause): A blood sample to determine serum hCG is required.

[c] Thyroid stimulating hormone (TSH), free triiodothyronine (T_3) and free thyroxine (T_4) will be evaluated. Assessment of adrenocorticotropic hormone (ACTH) and cortisol will be considered when clinically indicated.

[d] In the setting where archival material is unavailable or unsuitable for use, subjects must consent to and undergo fresh tumor biopsy.

[e] CCI [redacted]

[f] Chest, abdomen and pelvis will be evaluated. If subjects have central nervous system (CNS) malignancy or sign of CNS malignancy, CNS metastatic disease will be evaluated with contrasted computed tomography (CT) or magnetic resonance imaging (MRI) (preferred) scan. Tumor makers are evaluated if established tumor markers are available.

Table 2 Schedule of Treatment Period Study Procedures

Procedure									For details see Section
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9 - Vn**	
Day [a]	**D1**	**D15 (±1D)**	**D29 (±1D)**	**D43 (±1D)**	**D57 (±3D)**	**D71 (±3D)**	**D85 (±3D)**	**Q2W (±3D) starting on D99 (unless otherwise noted)**	
Hospitalization [b]	X								NA
Verify eligibility criteria	X								5.1, 5.2, 8
Pregnancy test (urine hCG) [c]	X			X			X	Q8W (± 3D) starting on D113	8.2.1
MEDI9447 administration Q2W	X	X	X	X	X	X	X	X	6
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	8.3
Concomitant medications	X	X	X	X	X	X	X	X	6.5
Physical examination [d,e], weight	X		X		X		X	Q4W (± 3D) starting on D113	8.2.2, 8.2.5
ECOG Performance Status	X		X		X		X		8.2.3
Vital signs [f], SpO_2 [e]	X	X	X	X	X	X	X	X	8.2.4
Electrocardiogram [g]	X				X			D113 (± 3D) only	8.2.6
Tumor and tumor markers evaluation [h]					X			Q8W (± 3D) starting on D113	8.1.1, Appendix E
Serum chemistry [i]	X	X	X	X	X	X	X	X	8.2.1
Hematology [i]	X	X	X	X	X	X	X	X	8.2.1

Procedure									**For details see Section**
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9 - Vn**	
Day [a]	**D1**	**D15 (±1D)**	**D29 (±1D)**	**D43 (±1D)**	**D57 (±3D)**	**D71 (±3D)**	**D85 (±3D)**	**Q2W (±3D) starting on D99 (unless otherwise noted)**	
Thyroid function test [i]				X			X	Q12W (± 3D) starting on D113	8.2.1
Urinalysis					X			Q8W (± 3D) starting on D113	8.2.1
PK and immunogenicity									
Serum for MEDI9447 PK [j]	X	X	X		X			Q8W (± 3D) starting on D113	8.5
Serum for MEDI9447 ADA	X[k]		X		X				8.10
Biomarker evaluation									
Blood samples [l]	X	X	X		X			Q8W (± 3D) starting on D113	8.8

ADA = antidrug antibody; AE = adverse event; D = day(s); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; hCG = human chorionic gonadotropin; NA = not applicable, PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event; SpO_2 = percutaneous arterial oxygen saturation, V = visit.

[a] On treatment days, evaluations and sample collections should be conducted prior to infusion of the investigational product unless otherwise indicated. Consecutive investigational product infusions must always be administered at least 10 days apart.

[b] All subjects are required to be hospitalized for the first week after administration on Day 1. Subjects will be monitored carefully throughout the hospitalisation. If any clinically important symptoms or signs are observed, appropriate tests/examinations will be performed. When transition from inpatient to outpatient setting is considered, investigators will conduct sufficient examinations and questioning of patients, and determine whether discharge is appropriate based on the results.

[c] Females of child-bearing potential only; if positive or indeterminate, quantitative test of serum human chorionic gonadotropin (hCG) will be performed for confirmation.

[d] Physical examination should be symptom directed and performed prior to administration of investigational product.

[e] If a finding suggestive of ILD is observed, additional complete examination will be conducted as clinically indicated.

[f] On designated days of investigational product administration, vital signs will be measured:
within 30 minutes prior to start of MEDI9447 infusion, every 30 minutes (± 5 minutes) during infusion, at the end of infusion (± 5 minutes), and 30 minutes (± 5 minutes) post end of MEDI9447 infusion.
On Day 1, additional vital sign measurements will be taken at 60 minutes (± 5 minutes) and 3 hours (± 15 minutes) post end of MEDI9447 infusion.

[g] All ECGs will be obtained as a single read. Electrocardiograms will be recorded within 60 minutes prior to start of MEDI9447 infusion and within 60 minutes post end of MEDI9447 infusion.

[h] Tumor assessments will be performed Q8W (± 3 days) during the treatment period or as indicated by signs/symptoms. Tumor makers are evaluated if established tumor markers are available.

[i] If screening assessments have been performed within the 5 days prior to Day 1 (i.e., Days -5 to -1), then assessment does not need to be performed on Day 1 pre dose. All safety laboratory results must be reviewed by the investigator prior to administration of the scheduled dose of MEDI9447. For thyroid test, TSH will be evaluated. If TSH is abnormal or if there is clinical suspicion of endocrine disorders, free T_3 and free T_4 will be evaluated. Assessment of ACTH and cortisol will be considered when clinically indicated.

[j] On Day 1, serum samples for MEDI9447 PK will be collected pre-dose (within 30 minutes prior to start of MEDI9447 infusion) and 10 minutes (± 5 minutes), and 2 hours (± 10 minutes) post end of MEDI9447 infusion. On Days 15, 29, 57, and Q8W starting on Day 113, serum samples for MEDI9447 PK will be collected pre-dose (within 30 minutes prior to start of infusion) and 10 minutes (± 5 minutes) post end of MEDI9447 infusion.

[k] On Day 1, serum samples for MEDI9447 ADA will be collected pre-dose (within 30 minutes prior to start of MEDI9447 infusion).

[l] On designated days of MEDI9447 administration, blood samples for biomarker evaluation will be collected within 30 minutes prior to start of MEDI9447 infusion.

Table 3 Schedule of Follow-up Period Study Procedures

Procedure	Follow-up after the study treatment discontinuation		For details see Section
	30 days post last dose (± 5 days)	90 days post last dose (± 7 days)	
Pregnancy test (urine hCG) [a]	X		8.2.1
Assessment of AEs/SAEs	X	X	8.3
Concomitant medications including subsequent anticancer treatment after the last dose of investigational product	X	X	6.5
Physical examination [b], weight	X		8.2.2, 8.2.5
ECOG Performance Status	X		8.2.3
Vital signs, SpO_2 [b]	X		8.2.4
Electrocardiogram [c]	X		8.2.6
Tumor and tumor markers evaluation [d]	X	X	8.1.1, Appendix E
Serum chemistry	X		8.2.1
Hematology	X		8.2.1
Thyroid function test [e]	X		8.2.1
PK and immunogenicity			
Serum for MEDI9447 PK	X	X	8.5
Serum for MEDI9447 ADA	X	X	8.10

ADA = antidrug antibody; AE = adverse event; ECOG = Eastern Cooperative Oncology Group; hCG = human chorionic gonadotropin; PK = pharmacokinetics; SAE = serious adverse event, SpO_2 = percutaneous arterial oxygen saturation.

[a] Females of childbearing potential only; if positive or indeterminate, quantitative test of serum hCG will be performed for confirmation.

[b] If a finding suggestive of ILD is observed, additional complete examination will be conducted as clinically indicated.

[c] Electrocardiograms will be obtained as a single read.

[d] If progressive disease (PD) is not yet confirmed, tumor evaluation need to be conducted. Tumor makers are evaluated if established tumor markers are available.

[e] TSH will be evaluated. If TSH is abnormal or if there is clinical suspicion of endocrine disorders, free T_3 and free T_4 will be evaluated. Assessment of ACTH and cortisol will be considered when clinically indicated.

1.2 Synopsis

Principal investigator:

Name and address of principal investigators is shown in protocol addendum. There is no coordinating investigator in this study.

For contact details of AstraZeneca personnel see Clinical Study Protocol Addendum.

Protocol Title:

A Phase I, Open-label Study to Assess the Safety, Tolerability, Pharmacokinetics and Anti-tumor Activity of MEDI9447 (Oleclumab) in Japanese Patients with Advanced Solid Malignancies

Rationale:

MEDI9447 inhibits cluster of differentiation (CD)73, which is considered to enhance antitumor activity by disrupting adenosine-mediated immune suppression effect. MEDI9447 is being developed as a potential treatment for multiple tumor types where nonclinical evidence suggests a role for intratumoral adenosine in the tumor biology responses, especially in tumor types with high levels of expression of CD73, therefore it is considered appropriate to assess tolerability of MEDI9447 for Japanese patients.

Objectives and Endpoints

Objective:	Endpoint:
Primary objective:	
To assess the safety and tolerability, describe any dose-limiting toxicity (DLT) for MEDI9447	Adverse events (AEs), Serious adverse events (SAEs), DLTs, vital signs, electrocardiogram (ECG) results, and laboratory parameters
Secondary objective:	
To determine the pharmacokinetics (PK) characteristics of MEDI9447	Summary PK parameters for MEDI9447
To determine the immunogenicity of MEDI9447	Development of detectable anti-drug antibodies following MEDI9447
To evaluate candidate biomarker of MEDI9447 activity in archival tumor biopsy specimens	Assessment of biomarker expression including CD73 in archival tumor biopsy samples
To describe the preliminary antitumor activity of MEDI9447	Objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and progression free survival (PFS) assessed by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

Objective:	Endpoint:
Exploratory Objective:	
To explore profile of biomarker status, with MEDI9447 treatment	Explore the relationship(s) between biomarker status and PK of MEDI9447, clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate

Overall design:

This is a phase I, open-label study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of MEDI9447 in Japanese patients with advanced solid malignancies.

This study consists of 2 cohorts. Cohort 1, MEDI9447 1500 mg every 2 weeks (Q2W) and Cohort 2, MEDI9447 3000 mg Q2W.

At least 3 or up to 6 evaluable Japanese patients with advanced solid malignancies will be enrolled in each cohort. The total number of subjects will depend upon the available data in each cohort and Safety Review Committee (SRC)'s decision.

Study Period:

The study is expected to start in October 2018 and end in July 2019.

The end of the study is defined as the last visit of the last subject undergoing the study.

Number of Subjects:

Maximum 12 evaluable patients will be enrolled in this study.

Treatments and treatment duration:

Subjects will receive MEDI9447 on Day 1 and Day 15 in a 4-week cycle.

Subjects participating in the study may continue to receive study treatment(s) as long as they are continuing to show clinical benefit, as judged by the Investigator, unless the subject has progressive disease (PD) with either clinical deterioration and/or no further benefit from treatment, experiences unacceptable toxicity, or should discontinue for any other reason. In such cases, the Investigator needs to consult with the sponsor and they agree to continue study treatment in advance.

Statistical methods:

The primary objective of this study is to assess the safety and tolerability profile of MEDI9447.

All safety data will be summarized using the safety analysis set. Evaluations of safety and tolerability will include, but not be limited to, AEs, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), and electrocardiograms using summary statistics.

For secondary and exploratory efficacy endpoints, all analyses will be descriptive, and no formal statistical testing will be performed. Data will be summarized and plotted appropriately according to data type.

PK concentration data for MEDI9447 will be listed for each subject and each dosing day, and summary statistics will be tabulated. Immunogenicity results will be listed by subject, and summaries of the number and percentage of subjects who develop detectable antidrug antibodies (ADAs) against MEDI9447 will be provided. The immunogenicity titre will be listed for samples confirmed positive for the presence of ADAs. Neutralizing ADAs may be reported for samples confirmed positive for the presence of ADAs.

All analyses and reporting will be conducted for each cohort.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design

Dose escalation in solid tumor patients (3+3 desin)

Cohort	MEDI9447 Q2W	Subjects
1	1500 mg	3-6[a]
2	3000 mg	3-6[a]

[a] If no DLT is observed in the first 3 subjects in a cohort, safety assessment will be done with 3 evaluable subjects.

2 INTRODUCTION

2.1 Study rationale

It is predicted that paracrine signalling mediated by adenosine produced from CD73 expressing cells in the tumor microenvironment will suppress the effector T cells that might otherwise mount a productive immune response and facilitate the proliferation of both immune suppressive regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) (Antonioli et al, 2013).

MEDI9447 inhibits CD73, which is considered to enhance antitumor activity by disrupting adenosine-mediated immune suppression effect. MEDI9447 is being developed as a potential treatment for multiple tumor types where nonclinical evidence suggests a role for intratumoral adenosine in the tumor biology responses, especially in tumor types with high levels of expression of CD73, therefore it is considered appropriate to assess tolerability of MEDI9447 for Japanese patients.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of MEDI9447 is provided in the Investigator's Brochure (IB).

2.2.1 CD73

Adenosine is a regulatory autocrine and paracrine factor that accumulates in the tumor microenvironment, influencing immune activity, angiogenesis, and metastasis. Upon apoptotic or necrotic cell death, tumor cells release adenosine triphosphate (ATP) into the extracellular space. ATP has been shown to lead to a pro-inflammatory response. To prevent an immune reaction stimulated by cell death, tissues express CD39 and CD73 to enzymatically convert ATP to adenosine monophosphate (AMP) and AMP to adenosine, respectively.

CD73 is considered as one mechanism by which tumors may have evolved to evade the immune system. Overexpression of CD73 has been associated with poor prognosis in multiple cancer types (Inoue et al, 2017; Lu et al, 2013; Turcotte et al, 2015; Wang et al, 2012; Yang et al, 2013; Yu et al, 2015). It is considered that immunotherapy to target CD73 and inhibit its activity will reduce adenosine production, thus augmenting host and/or immunotherapy response to tumor.

2.2.2 MEDI9447 background

MEDI9447 is a human immunoglobulin (Ig) G1 lambda (IgG1λ) monoclonal antibody (mAb) that selectively binds to CD73 and inhibits adenosine production from CD73-associated ectonucleotidase activity and leads to a reduction in CD73 expression due to both

internalization of the receptor and shedding of the extracellular domain. It contains a triple mutation in the heavy chain constant region for reduced effector function.

2.2.3 MEDI9447 nonclinical experience

No MEDI9447-related adverse effects were noted in CD-1 mice (5-week, repeat intravenous [IV] bolus dose, once every 4 days, total 9 doses) at doses up to 200 mg/kg or in cynomolgus monkeys (5-week, repeat IV 30-minute infusion dose, once weekly, total 5 doses) at doses up to 300.7 mg/kg in Good Laboratory Practice (GLP) toxicity studies. There were also no MEDI9447-related effects on ECG, blood pressure, or behavioral examinations evaluated in the 5-week cynomolgus monkey study. The no-observed-adverse-effect-level (NOAEL) was 200 mg/kg/dose in CD-1 mice and 300.7 mg/kg/dose in cynomolgus monkeys.

2.2.4 MEDI9447 clinical experience

2.2.4.1 Safety

Study CCI [redacted] is ongoing in overseas countries and is a first-time-in-human, Phase 1, multicenter, open-label, dose escalation, and dose expansion study of MEDI9447 to be administered as a single agent or in combination with durvalumab in adult subjects with selected advanced solid tumors. CCI [redacted]

CCI

[redacted]

2.2.4.2 Clinical activity

CCI

[redacted]

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of MEDI9447 may be found in the IB.

The overall benefit risk profile of the proposed treatment combinations is expected to be favorable, therefore supporting the current study design.

2.3.1 Potential risks

Important potential risks for MEDI9447 include arterial calcifications, arterial ischemic disorder, thrombosis and increased microvascular permeability, and potential risks for MEDI9447 include joint calcifications. These events were determined as potential risks for MEDI9447 based on clinical findings in individuals with CD73 deficiency and findings in CD73-deficient mice. Additional important potential risks include infusion-related reactions (IRRs), hypersensitivity (anaphylaxis and serious allergic reactions), and immune complex disease. Additional potential risks associated with any IV administration are localized infection, redness, swelling, pain, and induration at the administration site. Refer to the IB for additional information.

The design of the current study aims to minimize potential risks to subjects based on the protocol inclusion and exclusion criteria, restrictions on concomitant medication during the study, safety monitoring (including review of all safety, PK, and other relevant data by the SRC), toxicity management guidelines, starting dose selection, dose escalation scheme, and stopping criteria.

2.3.2 Potential benefits

MEDI9447 inhibits the catalysis of AMP to adenosine and organic phosphate by CD73. The enzymatic blockade of CD73 caused by binding of MEDI9447 to CD73 may lead to increased antitumor immunity. Since MEDI9447 may be applicable to multiple types of advanced solid tumor which few treatments are available, subjects with advanced solid malignancies who are targeted for this study and do not have effective treatments are able to get an opportunity to receive treatment by taking part into this study. Refer to Section 2.2.4.2 and IB for clinical efficacy.

3 OBJECTIVES AND ENDPOINTS

Table 4 Study objectives

Objective:	Endpoint:
Primary objective:	
To assess the safety and tolerability, describe any dose-limiting toxicity (DLT) for MEDI9447	Adverse events (AEs), Serious adverse events (SAEs), DLTs, vital signs, electrocardiogram (ECG) results, and laboratory parameters
Secondary objective:	
To determine the pharmacokinetics (PK) characteristics of MEDI9447	Summary PK parameters for MEDI9447
To determine the immunogenicity of MEDI9447	Development of detectable anti-drug antibodies following MEDI9447
To evaluate candidate biomarker of MEDI9447 activity in archival tumor biopsy specimens	Assessment of biomarker expression including CD73 in archival tumor biopsy samples
To describe the preliminary antitumor activity of MEDI9447	ORR, DCR, DoR and PFS assessed by RECIST v1.1
Exploratory Objective:	
To explore profile of biomarker status, with MEDI9447 treatment	Explore the relationship(s) between biomarker status and PK of MEDI9447, clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate

4 STUDY DESIGN

4.1 Overall design

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1.

For details on what is included in the efficacy and safety endpoints, see Section 1.2 and 3.

Subject will receive MEDI9447 via IV infusion at a starting dose of 1500 mg.

At least 3 subjects will be enrolled in each cohort by 3 + 3 design. Cohorts of 3 to 6 subjects will each receive MEDI9447 (1500, or 3000 mg) via IV infusion. Treatment will continue until unacceptable toxicity, documentation of disease progression, or other reason for subject withdrawal develops.

The study treatment may be continued in the setting of PD as long as the subject does not meet any of the investigational product discontinuation criteria and all of the following criteria are met:

1 Absence of clinical symptoms or signs indicating clinically significant PD
2 No decline in Eastern Cooperative Oncology Group (ECOG) Performance Status
3 Absence of threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention

Subjects with PD who are eligible to continue receiving the investigational product will be explained on the potential benefits and risks of continuing the investigational product in the setting of PD and must provide a separate written informed consent prior to initiating treatment beyond PD.

4.2 Scientific rationale for study design

This is a phase 1 open-label study primarily design to demonstrate the safety of MEDI9447 in Japanese patients with advanced solid malignancies who had no responding to standard treatments or for which no standard of care regimen currently exists. Since MEDI9447 may have broad applicability in multiple tumors, this study targets patients with advanced solid malignancies which few treatments are available. Other data to be evaluated include the PK, ADA, and antitumor activity of MEDI9447. The results from this study will form the basis for decisions for future studies.

4.3 Justification for dose

Doses of MEDI9447 in the study (1500 mg Q2W for cohort 1 and 3000 mg Q2W for cohort 2) are supported by target efficacious concentrations, clinical safety, tolerability, efficacy and PK data.

CCI

[redacted]

Considering there is no experience in treating Japanese patients with MEDI9447, the starting dose of MEDI9447 will be 1500 mg Q2W, which is -1 dose level of 3000 mg Q2W, which is the current dose used in the global study.

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed his/her last scheduled procedure shown in the SoA.

See Appendix A 6 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Investigators should keep a record (i.e., patient screening log) of patients who entered pre-study screening.

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study at the time of allocation in each cohort of the study. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

1 Adult subjects; age ≥ 20 years at the time of study entry

2 Written and signed informed consent obtained from the subject or, where permissible, legal representative prior to performing any protocol-related procedures, including screening evaluations

3 Has a histologically confirmed solid malignancy that is refractory to standard therapy or for which no standard of care regimen currently exists.

4 Subjects must have at least 1 lesion that is measureable using RECIST v1.1 (Eisenhauer et al, 2009): A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable per RECIST v1.1, and has clearly progressed.

5 All subjects must consent to provide archived tumor specimens (block or 10 unstained slides, preferably obtained within 3 years) for biomarker studies. Tumor tissue must be identified and availability confirmed prior to initiation of study therapy. In the setting where an archived tumor specimen is unavailable or unsuitable for use, subjects must consent to and undergo tumor biopsy obtained from a low-risk anatomical site. Sites are encouraged to confirm adequacy of tumor biopsy material at the time of the procedure.

6 ECOG Performance Status of 0 or 1

7 Life expectancy ≥12 weeks in the opinion of the investigators

8 Adequate organ function as determined by:

- Albumin > 3 g/dL

- Hematological (without growth factor or transfusion support within 14 days prior to screening) and coagulation test:
  - Absolute neutrophil count ≥ 1.5 × 10^9/L (1,500/mm^3)
  - Platelet count ≥ 75 × 10^9/L (75,000/mm^3)
  - Hemoglobin ≥ 9.0 g/dL
  - Prothrombin time-international normalized ratio and activated partial thromboplastin time ≤ 1.5 × upper limit of normal (ULN)
- Renal:
  - Calculated creatinine clearance* (CrCl) or 24 hour urine CrCl > 40 mL/minute
    *Cockcroft-Gault formula will be used to calculate CrCl
- Hepatic:
  - Total bilirubin ≤ 1.5 × ULN; for subjects with documented/suspected Gilbert's disease, total bilirubin ≤ 3 × ULN
  - AST and alanine aminotransferase (ALT) ≤ 2.5 × ULN
- Serum electrolytes:
  Potassium, sodium, magnesium, and calcium (corrected for serum albumin) ≤ NCI CTCAE v4.03 Grade 1 or within the institutional ranges of normal. If clinically appropriate, electrolytes may be corrected and values re-assessed prior to enrollment (Electrolytes correction should not be within 14 days prior to screening).

9 Body weight ≥ 35 kg

5.2 Exclusion criteria

Any of the following would exclude the subject from participation in the study:

1 Patients must have completed any previous cancer-related treatments before enrollment. Concurrent use of hormones for noncancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. The following intervals between the end of the prior treatment and first dose of study drug must be observed:
- Minor surgical procedures (as defined by the Investigator): ≥24 postoperative hours
- Major surgery (as defined by the Investigator): ≥4 weeks
- Receipt of any anticancer therapy: within 5 half-lives or 28 days (whichever is longer)
- Current or prior use of immunosuppressive medication: within 14 days with the exceptions of intranasal, inhaled, topical or local steroid injections (e.g., intra-articular injection), systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone (or prednisolone, which is available in Japan in place of

prednisone) or equivalent, and steroids as premedication for hypersensitivity reactions (e.g., contrast CT premedication).

- Receipt of live, attenuated vaccine: within 28 days. Vaccination with a killed vaccine is permitted at any time with consultation with the Study Physician.

2 Prior treatment with CD73 antagonist, tumor necrosis factor receptor superfamily agonists including OX40, CD27, CD137 (4-1BB), CD357 (glucocorticoid-induced tumor necrosis factor receptor family-related protein). Prior treatment with a monotherapy tumor vaccine will be allowed.

3 All cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), or programmed cell death ligand 1 (PD-L1) antagonists related-AEs must have resolved to ≤ NCI CTCAE v4.03 Grade 1 or baseline prior to screening and not worsened before the first dose of study drug. Must not have experienced a related ≥ Grade 3 AE or neurologic or ocular AE of any grade which was deemed to be related to the prior immunotherapy. Subjects with an endocrine AE of any grade are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

4 Must not have required the use of additional immunosuppression other than corticosteroids for the management of an CTLA-4, PD-1, or PD-L1 related AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone (or prednisolone, which is available in Japan in place of prednisone) or equivalent per day

5 Known allergy or hypersensitivity to the study drug, its compounds, or agents similar biologic composition (e.g., antibody therapeutics)

6 History of more than one event of IRR requiring permanent discontinuation of IV drug treatment

7 History of severe drug allergies or anaphylaxis to 2 or more food products or medicine (including known sensitivity to acetaminophen/paracetamol, diphenhydramine or equivalent antihistamine, and methylprednisolone or equivalent glucocorticoid)

8 Cardiac or peripheral vascular disease meeting any of the following criteria:

- Past history of myocardial infarction within 3 months prior to the first dose of study drug
- Past history of stroke or transient ischemic attack within 3 months prior to the first dose of study drug
- Congestive heart failure ≥ Class 3 based on New York Heart Association (NYHA) Functional Classification

9 NCI CTCAE v4.03 Grade 3 or greater edema (e.g., peripheral, pulmonary)

10 Uncontrolled massive ascites or pleural effusion

11 History of NCI CTCAE v4.03 Grade 3 or greater thromboembolic events within 3 months prior to the first dose of study drug or thromboembolic event of any grade with ongoing symptoms

12 Active tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice). Patients who is positive in tuberculosis testing with no radiographic findings are eligible.

13 Patients with history of, or current ILD

14 Active or prior documented autoimmune (including inflammatory bowel disease [e.g., colitis, Crohn's disease], celiac disease, or other serious gastrointestinal chronic conditions associated with diarrhea; autoimmune vasculitis, systemic lupus erythematosus; Wegener syndrome [granulomatosis with polyangitis]; myasthenia gravis; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:

- Vitiligo or alopecia.
- Hypothyroidism (e.g., following Hashimoto syndrome) which is stable on hormone replacement or psoriasis not requiring systemic treatment.

15 Untreated or unstable central nervous system (CNS) metastatic disease, leptomeningeal disease, or cord compression. Note: Subjects previously treated for CNS metastases that are radiographically and neurologically stable for at least 4 weeks prior to the first dose of study drug and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to the first dose of study drug are not excluded.

16 Concurrent enrollment in another clinical study, unless it is an observational (non interventional) clinical study or the follow-up period of an interventional study

17 Any concurrent chemotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. In addition, local treatment (e.g., with a local surgery or radiotherapy) of isolated lesions for palliative intent is acceptable beyond the DLT-evaluation period with prior consultation and in agreement with the Study Physician.

18 Toxicities from prior anticancer therapy that have not resolved to ≤ NCI CTCAE v4.03 Grade 1 or baseline prior to the first dose of study drug, with the exception of alopecia and laboratory values per inclusion criteria. The eligibility of patients who are still experiencing irreversible toxicity that is not reasonably expected to be exacerbated by the study drugs in this study (e.g., hearing loss) must be reviewed and approved by both the Principal Investigator and the Study Physician.

19 History of primary immunodeficiency or solid organ transplantation

20 Active hepatitis B (known positive hepatitis B virus [HBV] surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (HIV) (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] IgG and absence of HBsAg and HBV deoxyribonucleic acid [DNA]) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).

21 Females who are pregnant, lactating, or intend to become pregnant during their participation in the study. Females who suspended breast-feeding before the first dose of study drug can participate in this study, but those patients must not resume breast-feeding from the first dose of study drug to 90 days after the last dose of study drug.

22 Other invasive malignancy within 2 years prior to the first dose of study drug except for noninvasive malignancies such as cervical carcinoma in situ, in situ prostate cancer, non-melanomatous carcinoma of the skin, ductal carcinoma in situ of the breast that has been surgically cured, and gastrointestinal malignancies that have been cured with endoscopic resection

23 Uncontrolled concomitant illness including, but not limited to, ongoing or active infection, active peptic ulcer disease or gastritis, uncontrolled hypertension, uncontrolled diabetes, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from the study drug, or compromise the ability of the subject to give written informed consent

24 Judgment by the Investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions, and requirements.

25 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

5.3 Lifestyle restrictions

5.3.1 Pregnancy

1 Female subjects of childbearing potential who are sexually active with a non sterilized male partner must use at least one highly effective method of contraception from the time of screening and must agree to continue using such precautions for 90 days after the last dose of investigation product. Male partners of a female subject must use a male condom plus spermicide throughout this period. Cessation of birth control contraception after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial study and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female subjects should refrain from breastfeeding throughout this period.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., have not undergone bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or who are not post-menopausal (defined as 12 months with no menses without an alternative medical cause).
- Highly effective methods of contraception are described in Table 5. A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette® (desogestrel) which is considered highly effective]; and triphasic combined oral contraceptive pills).

2 Nonsterilized males who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from the initial dose of investigational product through 90 days after receipt of the last dose of investigational product. It is strongly recommended for the female partner of childbearing potential of a male subject to also must use a highly effective method of contraception throughout this period, as described in Table 5. In addition, male subjects must refrain from fathering a child or donating sperm while on study and for 90 days after the final last dose of investigational product.

Table 5 Effective Methods of Contraception

Barrier/Intrauterine methods	Hormonal methods
• Male or female condom with spermicide [a,b,c,e] • Cap [f], diaphragm, or sponge [f] with spermicide [a,b,c,e] • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®) [d]	• Implants [f] • Hormone shot or injection [f] • Combined pill • Minipill[b] [f] • Patch [f]

[a] Female partners of male subjects must use an effective method of birth control.
[b] Only highly effective (<1% pregnancy rate per year) when used with additional methods of birth control.
[c] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.
[d] This is also considered a hormonal method.
[e] A single agent of spermicide has been approved in Japan. However, it is not in production now.
[f] Not approved in Japan.

5.3.2 Blood donation

Donating blood and or blood components should be avoided during the study through 90 days after the last dose of the study drug.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form (ICF) to participate in the clinical study but are not subsequently administered the study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects should be assigned the same subject number as for the initial screening. However, rescreening should be documented so that its effect on study results, if any, can be assessed.

These subjects should have the reason for study withdrawal recorded in the electronic Case Report Form (eCRF).

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to MEDI9447.

6.1 Treatments administered

6.1.1 Investigational products

Table 6 Investigational Product

Investigational Product	Concentration and Formulation as Supplied
MEDI9447	Supplied as a solution for infusion containing 500 mg of MEDI9447 50 mg/mL per vial

The sponsor will provide study drugs as shown in Table 6.

The sponsor will provide MEDI9447 as concentrate for solution for infusion containing 500 mg of MEDI9447 per vial. The solution contains 50 mg/mL MEDI9447 in 25 mM histidine/histidine hydrochloride, 240 mM sucrose, 0.03% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL.

Vials should be stored at 2°C to 8°C and not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

See Figure 1 as for dosing for each cohort.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) Ordinance. Details are specified in the document explaining the reconstitution procedures and other handling procedures for the investigational products.

6.2 Preparation/ handling/ storage/ accountability

Each vial selected for dose preparation should be inspected. If any defects (if the solution is turbid or if any discoloration etc.) are noted with the investigational product(s), the sponsor should be notified immediately and the vial(s) should be stored in QUARANTINE at 2°C to 8°C.

After removing the required number of vials for dose preparation (3 vials for the 1500 mg dose; 6 vials for the 3000 mg dose) from the carton container, the carton should be immediately returned to storage at 2°C to 8°C.

MEDI9447 doses must be prepared by the investigator's or site's designated investigational product manager using aseptic technique. Total time from needle puncture of the MEDI9447 vial to the start of administration should not exceed: 24 hours at 2°C to 8°C, 4 hours at room temperature. If preparation time exceeds the time limits a new dose must be prepared from new vials. MEDI9447 does not contain preservatives, and any unused portion must be discarded.

Doses of MEDI9447 1500 mg and 3000 mg will be administered using an IV bag containing 0.9% (w/v) saline, with a final MEDI9447 concentration ranging from 1.5 to 30 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. An IV bag made of polyolefin or polyvinylchloride should be used. Add 30 mL (i.e., 1500 mg dose) or 60 mL (i.e., 3000 mg dose) of MEDI9447 to the IV bag. The IV bag size should be selected such that the final concentration is within 1.5 to 30 mg/mL. Mix the bag gently to ensure homogeneity of the bag. MEDI9447 will be administered at room temperature by controlled infusion into a peripheral or central vein. Standard infusion time for MEDI9447 is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 4 hours at room temperature. If this duration is met, then the remainder of the dose should be abandoned and should not be completed with a second prepared dose. Do not co-administer other drugs through the same infusion line. Flush the IV line with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the study drug handling instructions.

6.3 Measures to minimise bias: randomisation and blinding

This is an open-label, non-randomised study.

6.4 Treatment compliance

Any change from the dosing schedule, does interruptions, dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the investigational product from receipt by the study site until the destruction or return of all unused investigational products.

6.5 Concomitant therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject receives from signing of the ICF to 90 days after the last dose of study treatment must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.5.1 Permitted concomitant therapies

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in Section 6.5.2.

6.5.2 Prohibited concomitant therapies

Subjects must be instructed not to take any medications, including over-the-counter products, without consulting with the investigator.

The use of following medications are prohibited during the study. The sponsor must be notified if a subject receives any of these during the study.

1 Other investigational products
2 Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Bisphosphonates or denosumab for bone metastases can be used on a fixed dosing during the study only if the subjects have been on the medication prior to signing the ICF. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable
3 Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone (or prednisolone, which is available in Japan in place of prednisone) or equivalent, methotrexate, azathioprine, and tumor necrosis factor-alpha blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical and intranasal corticosteroids is permitted. Temporary use of corticosteroids for treatment of underlying or concurrent illness or in the setting of palliative radiotherapy may be permitted upon discussion with the Study Physician.
4 Prophylactic antiemetic premedication for nausea or granulocyte colony stimulating factors is not permitted during the DLT Evaluation period (therapeutic use of anti-emetics and granulocyte colony stimulating factor is allowed.)
5 Live attenuated vaccines during the study through 30 days after the last dose of study drug. Vaccination with a killed vaccine is permitted at any time with consultation with the Study Physician.
6 Herbal and natural remedies including Chinese medicine should be avoided

6.6 Dose modification

6.6.1 Starting dose, dose escalation scheme and stopping criteria

Subject will receive MEDI9447 via IV infusion at a starting dose of 1500 mg.

Rules for Dose Escalation

1 Subjects who do not meet the criteria for the DLT-evaluable subject will be replaced. Subjects will be followed for safety throughout the study. If late emerging imAEs (imAEs occurring after the DLT-evaluation period) are observed, these events will be considered by the SRC during data reviews.
2 Intra-subject dose escalation will not be allowed.
3 A minimum of 3 evaluable subjects will be enrolled in each dose-level cohort. If no DLTs are observed in the first 3 subjects during the DLT evaluation period and all available

safety data have been reviewed by the SRC, dose escalation will continue to the next dose cohort at Cohort 1 or stop and be decided as a tolerated dose at Cohort 2.

4 If 1 of 3 evaluable subjects in a dose-level cohort experiences a DLT, that dose-level cohort will be expanded to a total of 6 evaluable subjects. If no more than 1 of 6 evaluable subjects in the dose-level cohort experiences a DLT, dose escalation will continue to the next dose-level cohort at Cohort 1 or stop and be decided as a tolerated dose at Cohort 2.

5 If unacceptable toxicity is encountered or ≥ 2 subjects experience a DLT at dose-level cohort then the dose-escalation should be terminated and no more subjects will be entered in that cohort.

6 Intermediate or lower dose levels of MEDI9447 may be evaluated at the discretion of the sponsor based on available data.

6.6.2 Definition of dose-limiting toxicity and evaluable subject

DLT evaluable patients are defined as those who received 2 planned doses of MEDI9447 per protocol during the DLT assessment period and completed the safety follow-up through the DLT assessment period, or those who experienced a DLT. Also, the period for DLT evaluation is defined as the time from receiving the first dose of investigational product until assessments prior the planned administration of the third dose; this corresponds to 28 days after receiving the first dose of the investigational product or 14 days after the second dose, whichever occurs later (defined as Cycle 1). Subjects who do not remain in the study up to this time for reasons other than DLT will be considered non-evaluable for DLT assessment and will be replaced with another subject at the same dose level. In case of discontinuation from or interruption of treatment due to AE during the DLT evaluation period (e.g., ≥ grade 3 IRR), whether the AE should be a DLT will be discussed by the SRC based on the below mentioned DLT definition 11. Grading of DLTs will be according to the NCI CTCAE v4.03.

A DLT will be defined as any of the events listed below that occurs during the DLT-evaluation period (defined above). Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

1 Grade 4 immune-mediated adverse event (imAE)

2 ≥ Grade 3 colitis

3 ≥ Grade 3 nausea, vomiting, or diarrhea that does not resolve to Grade 2 or less within 3 days of the initiation of maximal supportive care

4 ≥ Grade 3 pneumonitis or ILD

5 Grade 4 anemia or anemia requiring red cell transfusion

6 Grade 4 thrombocytopenia or neutropenia that is present for more than 4 days

7 Grade 3 thrombocytopenia with bleeding or thrombocytopenia requiring platelet transfusion

8 Febrile neutropenia

9 Isolated liver transaminase elevation ≥ 5 × but ≤ 8 ×ULN or isolated total bilirubin ≥ 3 × but ≤ 5 × ULN that does not downgrade to Grade 2 or less within 14 days after onset with optimal medical management, including systemic corticosteroids. Isolated liver transaminase elevation > 8 × ULN or isolated total bilirubin > 5 × ULN regardless of duration.

10 Increase in AST or ALT > 3 × ULN and concurrent increase in total bilirubin > 2 × ULN (Hy's Law) without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver)

11 Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, and is judged to be a DLT by the SRC

A DLT excludes the following:

1 Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is manageable with or without systemic corticosteroid therapy and/or hormone replacement therapy

2 Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc) that resolved to ≤ Grade 1 within 30 days

3 Vitiligo or alopecia of any AE grade

4 ≥ Grade 3 lymphopenia

5 Grade 3 fever

6 Isolated laboratory changes of any grade without clinical sequelae or clinical significance that are not defined as a DLT above.

ImAEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Late-emerging imAEs (imAEs occurring after the DLT-evaluation period) will be considered by the SRC during data reviews.

6.6.3 Safety Review Committee

This study's SRC will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data. This committee may also meet to review data at other time points (e.g., in response to AEs assessed as medically relevant by the Study Physician). This committee will be responsible for dose-escalation decisions and making recommendations regarding further conduct of the study. All decisions by this committee will be documented and shared with all participating sites in writing.

The SRC will consist of:

- Study Physician, who will chair the committee, or delegate
- Principal Investigator or delegate from all investigational sites who have recruited patients in the cohort

In addition, one other physician from the following may be invited:

  - Global Safety Physician or delegate
  - Medical Science Director or delegate
  - Senior physician from another project

The Study Pharmacokineticist, Study Statistician, Patient Safety Scientist and Study Leader may also be invited as appropriate. The SRC Remit document for this study will define the exact membership and who should be present for decisions to be made.

Further internal or external experts may be consulted by the SRC as necessary. The Global Safety Physician or delegate should always be present at the SRC if there are safety issues for discussion.

Once there are at least 3 evaluable subjects in each cohort, the SRC will review and assess all available safety and PK data from the cohort to make a decision on the cohort.

The decision may include to:

1 Proceed to next cohort
2 Expand the cohort to a maximum of 6 evaluable subjects
3 Stop the enrollment of the study

Any subject started on treatment in error, as he/she failed to comply with all of the selection criteria, will be reviewed on a case by case basis by the SRC to determine if the subject should be included or excluded in the decision for moving to next cohort.

The decisions and decision-making of the SRC will be documented and provided to the investigators prior to dosing any new subjects.

6.7 Treatment after the end of the study

Not Applicable

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from investigational product in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- DLT or adverse event which the investigator judges that the study treatment discontinuation is clinically reasonable
- Severe non-compliance with the Clinical Study Protocol
- Clinical deterioration and/or no further benefit from treatment regardless unconfirmed or confirmed PD according to RECIST v1.1.
- Confirmed PD and/or subject are not receiving any further benefit compared to the risks of continuing as judged by the investigator
- Subjects incorrectly initiated on investigational product (see Section 7.3)
- If a female subject becomes pregnant during the course of the study
- Investigator discretion
- Sponsor decision

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

A subject that decides to discontinue Study treatment will always be asked about the reason(s) and the presence of any AEs at the time of study treatment discontinuation. The date of last administration of Study treatment should be documented in the eCRF. Subjects permanently discontinuing Study treatment should be given clinically available care therapy, at the discretion of the Investigator.

Discontinuation of Study treatment, for any reason, does not impact on the subject´s participation in the study. The subject should continue attending subsequent study visits and data collection should continue according to the study protocol. If the subject does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the subject, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A subject that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or next of kin by e.g. repeat telephone calls, certified letter to the subject´s last known mailing address, or local equivalent methods. These contact attempts should be documented in the subject's medical record.
- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study the subject should be considered to be lost to follow up.

7.3 Withdrawal from the study

A subject may withdraw from the study (e.g., withdraw consent), at any time (investigational product **and** assessments) at his/her own request, without prejudice to further treatment.

A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or information from medical records).

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up subjects as medically indicated.

See Table 3, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

At enrollment, obtain signed informed consent from the potential subject before any study specific procedures are performed. (Please see Appendix A for ethical and regulatory requirements.)

The study site staff will assign a unique enrollment number to subjects in sequence and register it into Electronic Data Capture (EDC) system. If a subject withdraws from participation in the study, then his/her enrollment number cannot be reused.

In order to confirm eligibility (see Section 5.1 and 5.2), screening tests will be conducted on each subject within 28 days prior to the first dose of investigational products (see Table 1).

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The study site staff will enter the necessary information into appropriate pages of EDC system immediately after screening assessment completion. The investigator confirms that all screened subjects fulfil the eligibility criteria for the study, and register and keep the screening assessment details including screen failure reasons as applicable.

The sponsor will inform the investigator of suspension and restarting of enrollment by email etc.

The investigator will ensure that data are recorded on the eCRFs. The EDC system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Principal investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Please refer to Table 7 for the amount of blood collected from subject. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 Tumor assessments

Tumor assessments and tumor marker evaluation will be performed according to the study plan in SoA.

Baseline tumor assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual subjects. Baseline assessments should be performed no more than 28 days before the start of study treatment and ideally should be performed as close as possible to the start of study treatment. Tumor assessments obtained as standard of care before consent may be used for the study provided the assessments fall within the protocol-specified period before the first dose of study treatment.

Sites will be required to store electronic copies of all scans, and the study Sponsor may arrange for possible centralised storage of all imaging data. The centralised storage of imaging data would be for possible independent centralised review of tumor assessments.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

See Table 7 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.8.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, haematology, thyroid function test, coagulation test and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Please see the blood volume of each sampling to Table 7.

The timing of blood samples may be altered depending on the emerging PK and safety profile. Additional sampling times may be added if indicated by the emerging data.

Table 7 Laboratory safety variables

Haematology	Clinical Chemistry	Thyroid function tests	Coagulation test	Urinalysis (dipstick)
4 mL / sample	**9 mL / sample**		**2.5 mL / sample**	**-**
White blood cells count White blood cells count with differential Absolute neutrophil count Absolute lymphocyte count Hemoglobin Hematocrit Platelet count	Calcium Magnesium Creatinine Sodium Blood urea nitrogen Glucose AST Total bilirubin Amylase Lipase Gamma-glutamyl transferase Potassium ALT Alkaline phosphatase (ALP) Albumin Total protein Triglycerides Cholesterol	TSH Free T_3 Free T_4 ACTH (if needed) Cortisol (if needed)	Prothrombin time-international normalized ratio Activated partial thromboplastin time	Specific gravity pH Protein Glucose Ketones Blood Bilirubin If abnormal (urine dipstick), microscopy including white blood cells /high power field (HPF), red blood cells/HPF

Blood samples for HIV, HBV, and HCV serology are required at screening (If those tests are conducted as a part of clinical chemistry, additional samples are not needed.). HIV screening will be based on HIV antibody; HBV screening will include HBsAg and anti-HBc, and HCV screening will be based on anti-HCV. As a result of screening test, if judged to need further tests, additional blood samples will be taken.

For women of childbearing potential a serum blood sample to determine serum hCG is required at screening (If it is conducted as a part of clinical chemistry, an additional sample is not needed.) and urine samples for a urine hCG will be collected at timepoints as specified in Table 2 and at the visit of 30 days after the last dose of investigational product. If positive in a serum hCG blood test is suspected, a pregnancy test for serum beta human chorionic gonadotropin (β-hCG) will be considered.

NB. In case a subject shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix D for further instructions.

8.2.2 Physical examinations

A physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems.

Physical examination will be performed at timelines as specified in the SoA, Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.8 for details.

8.2.3 ECOG Performance Status

ECOG Performance Status will be assessed according to the study plan in the SoA. The ECOG Performance Status will be used to assess how a subject's disease is progressing, assess how the disease affects the subject's daily activities, and help the Investigator determine the appropriate treatment and progress. The ECOG scales and criteria are defined as follows:

0 = Fully active, able to carry out all predisease activities without restrictions

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)

2 = Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care confined to bed or chair more than 50% of waking hours

4 = Completely disabled; cannot carry on self-care; totally confined to bed or chair

5 = Death

8.2.4 Vital signs and percutaneous arterial oxygen saturation (SpO_2)

- Temperature, pulse rate, respiratory rate, blood pressure, and percutaneous arterial oxygen saturation (SpO_2) will be assessed after a full rest.
- The Investigator should assess any abnormal changes (i.e., changes that are out of range) in vital sign measurements for their clinical significance and determine if they require to be recorded as an AE.

8.2.5 Height and weight

- Height (in centimetres) will be obtained at screening.
- Weight (in kilograms) will be obtained according to the study plan in the SoA.

8.2.6 Electrocardiograms

ECG will be obtained according to the SoA.

Ideally, 12-lead ECGs will be obtained after a full rest. All ECGs should be recorded with the subject in the same physical position. A standardised ECG machine should be used and the subject should be examined using the same machine throughout the study, where feasible.

For each time point, ECGs will be obtained as a single read. In case of clinically significant ECG, abnormalities including a QT interval corrected for heart rate using Fridericia's formula (QTcF) value > 500 milliseconds, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm prolongation based on manual over read by a medically qualified person and followed-up as clinically appropriate. These should be considered for evaluation of eligibility and toxicity.

After paper ECGs have been recorded, the Investigator will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the subject's medical records. If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the Investigator, it should be reported as a concurrent condition. For all ECGs, details of rhythm, PR, RR, QRS, and corrected QT interval (QTc) intervals and an overall evaluation will be recorded.

8.3 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section

The definitions of an AE or SAE can be found in Appendix B.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs see Section 8.3.4.

8.3.1 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid

communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of these investigational products.

- Infusion-related reactions
- Anaphylaxis and serious allergic reactions
- Immune complex disease
- Arterial calcifications
- Arterial ischemic disorder
- Increased microvascular permeability
- Thrombosis
- An immune mediated adverse event

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from obtaining a signature on the ICF, throughout the treatment period and including the 90-day follow-up period after the last dose of investigational product.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after the time period for collecting AE and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.4 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAE/non-serious AEs/AEs of special interest (as defined in Section 8.3.1), will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the case report form (CRF). AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.5 Adverse event data collection

Findings from medical history (obtained at screening) shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

'The following variables will be collected for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)
- AE caused subject's withdrawal from study (yes or no)
- Treatment for AE
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication'

8.3.6 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.7 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.8 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs, and other safety assessments will be summarised in the clinical study report (CSR). Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for an AE, SAE, a DLT, or are the reason for discontinuation of treatment with the investigational product unless clearly due to PD under study (see Section 8.3.10).

If deterioration in a laboratory value, vital sign, ECG, or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information. Wherever possible, the reporting Investigator will use the clinical, rather than the laboratory, term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs and symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Sections 8.3.10.

8.3.9 Hy's law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3xULN together with total bilirubin $\geq$ 2xULN may need to

be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

8.3.10 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing lesions to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone, etc.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study subject has received any study drug

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy page in the CRF is used to report the pregnancy.

8.4.2.2 Paternal exposure

Pregnancy of the subject's partner is not considered to be an adverse event. However, any conception occurring from the first dosing until 90 days after the last doing, the investigator should ask the subject's partner to sign "ADULT STUDY INFORMATION AND CONSENT FORM FOR PREGNANT PARTNERS OF STUDY SUBJECTS", report to Sponsor and followed up for its outcome.

8.4.3 Overdose

For this study, any dose of the study drug greater than the protocol-defined dose amount at each infusion or infusion speed greater than the protocol-defined speed at each infusion will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.3. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.3) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.4.5 Management of investigational product-related toxicities

If a subject experiences imAEs, IRRs, or non-immune-mediated reactions refer to Appendix F "Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-related, and Nonimmune mediated Reactions".

In cases where the infusion of MEDI9447 is paused and resumed at a lower infusion rate, the maximum infusion time of 4 hours may not be exceeded. If this duration is met, then the

remainder of the dose should be abandoned and should not be completed with a second prepared dose.

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Appendix F "Dosing Modification and Toxicity Management Guidelines" will be applied. The results of the full diagnostic workup will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory CT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Subjects with an increase in ALT or AST $\geq 3 \times$ ULN and concurrent increase in total bilirubin $\geq 2 \times$ ULN (Hy's Law) will permanently discontinue MEDI9447. Dosing will not be interrupted or discontinued for a Grade 2 laboratory toxicity that does not represent deterioration since study entry.

In addition to the above, it is recommended that management of imAEs follow the guidelines outlined for ipilimumab (Weber et al, 2012). These guidelines recommend the following:

1 Subjects should be evaluated to identify any alternative etiology
2 In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related
3 Symptomatic and topical therapy should be considered for low-grade events
4 Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event
5 More potent immunosuppressives (e.g., infliximab, mycophenolate mofetil, etc) should be considered for events not responding to systemic steroids.

If the investigator has any question in regards to an AE being an imAE, the Investigator should immediately contact the Study Physician. Treatment modifications will not be required for AEs that are clearly not attributed to the study drug (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Dose reduction of the study drug is not allowed.

8.5 Pharmacokinetics

At each time point, a whole blood sample of approximately 3.5 mL will be collected for measurement of MEDI9447 concentrations in serum as specified in the SoA, and more than 0.5 mL of serum sample will be obtained from it. Samples may be collected at additional time

points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site. The actual collection date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of MEDI9447 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The institutional review board (IRB) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5.1 Determination of drug concentration in serum

Serum concentration of MEDI9447 will be measured utilizing a validated bioanalytical method. The results of the measurement will be reported either in the CSR itself or as an addendum, or separately in another report or a scientific report or publication.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will be reported either in the CSR itself or as an addendum, or separately in another report or a scientific report or publication.

8.5.2 Storage and destruction of pharmacokinetic samples

PK samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed.

After PK analysis, remaining PK samples may be used for biomarker analysis. The results of this research will be reported either in the CSR itself or as an addendum, or separately in another report or a scientific report or publication.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

By participating in this study, the subject consents to the collection and use of donated biological samples as described here.

The below samples for biomarker research are required and will be collected from all subjects in this study as specified in the SoA.

To explore the relationship(s) between biomarker status and PK of MEDI9447, clinical outcomes, efficacy, AEs, and/or safety parameters, an archival tumor tissue, whole and plasma blood samples and/or serum samples (for biomarkers including but not limited to sCD73) are tested.

Adequate tumor tissue is defined as a formalin-fixed and paraffin-embedded (FFPE) tumor block or approximately 10 unstained slides, each 4 to 5 microns thick. An archival FFPE sample taken within 3 years prior to screening is preferred.

Blood samples will be taken as specified in the SoA. An approximately 3.5 mL whole blood sample will be collected at each time point, and more than 0.5 mL of serum sample will be obtained from it.

Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site.

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8.8.1 Storage, re-use and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

8.9 Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.10 Immunogenicity

At each time point a whole blood sample of approximately 3.5 mL will be collected for immunogenicity assessment of MEDI9447 as specified in the SoA, and more than 0.75 mL of

serum sample will be obtained from it. Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site. The actual collection date and time (24-hour clock time) of each sample will be recorded.

Samples will be measured for the presence of ADAs for MEDI9447 using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components; positive negative cut points previously statistically determined from drug-naïve validation samples will be employed. Neutralizing ADAs against MEDI9447 may be analyzed and reported for samples confirmed positive for the presence of ADAs.

Samples will be stored for a maximum of 15 years from the date of the Last Subject's Last Visit, after which they will be destroyed. The results of this research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

Statistical hypotheses will not be set in this study.

9.2 Sample size determination

The primary objective of this study is to investigate the safety and tolerability of MEDI9447. Hence the number of subjects has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic data while exposing as few subjects as possible to the investigational product and procedures.

In each cohort, evaluable 3-6 subjects will be enrolled. The total number of subjects relies on the result of DLT assessment.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Safety analysis set	All subjects who received at least 1 dose of MEDI9447
Pharmacokinetics analysis set	Subjects who received at least 1 dose of MEDI9447 and provided at least 1 post-treatment sample
Immunogenicity analysis set	All subjects who have nonmissing baseline ADA and at least 1 nonmissing postbaseline ADA result
Efficacy analysis set	Subjects who had tumor assessment data at baseline and received at least 1 dose of MEDI9447

Population	Description
Biomarker analysis set	All subjects who take part into the biomarker research

9.4 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalised before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

9.4.1 Safety analyses

Safety data will not be formally analysed. All subjects who receive at least one dose of MEDI9447 will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs will be listed individually by subject and cohort. The number of subjects experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of subjects with adverse events in different categories (e.g., causally related, CTCAE grade ≥3 etc) will be summarised by cohort, and events in each category will be further summarised by MedDRA system organ class and preferred term, by cohort. SAEs will be summarised separately if a sufficient number occur.

Any AE occurring before the first dose of the investigational product will be included in the data listings but will not be included in the summary tables of adverse events.

Any AE occurring within the defined 90-day follow-up period after discontinuation of the investigational product will be included in the AE summaries. Any AEs in this period that occur after a subject has received further therapy for cancer will be flagged in the data listings. AEs occurring after the 90-day follow-up period after discontinuation of the investigational product will be listed separately, but not included in the summaries.

Haematology, clinical chemistry, vital signs, ECG data, demographic data, medical histories and concomitant medications will be listed individually by subject and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used.

Details of any deaths will be listed for all subjects.

Any qualitative assessments will be summarised for all subjects using the number of subjects with results of negative, trace or positive.

Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

9.4.2 Pharmacokinetics analyses

Serum concentrations of MEDI9447 will be summarised by nominal sample time. Serum concentrations and derived PK parameters will be summarised by dose level. Parameters following single and multiple dosing will be summarised separately. Derived PK parameters may be changed based on the obtained serum concentrations.

Serum concentrations at each time point will be summarised according to dose by the following summary statistics:

- The geometric mean (Gmean, calculated as exp [μ], where μ is the mean of the data on a logarithmic scale)
- Geometric coefficient of variation (GCV, calculated as 100 $\sqrt{}$ [exp(s^2)-1], where s is the standard deviation of the data on a log scale)
- Gmean ± geometric standard deviation (GSD, calculated as exp[$\mu \pm s$])
- Arithmetic mean calculated using untransformed data
- Standard deviation calculated using untransformed data
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for area under the curve (AUC), $AUC_{0\text{-}14\ day}$, $AUC_{0\text{-}t}$, maximum serum concentration (C_{max}), maximum serum concentration at steady state ($C_{max,\ ss}$), trough serum concentration (C_{trough}) and trough serum concentration at steady state ($C_{trough\ ss}$):

- Gmean
- GCV
- Arithmetic mean
- Standard Deviation
- Minimum
- Maximum
- Number of observations

The following summary statistics will be presented for systemic clearance (CL), clearance at steady state (CL_{ss}), volume of distribution, terminal phase half-life ($t_{½\lambda z}$) and accumulation ratio (R_{AC}):

- Arithmetic mean
- Standard deviation
- Minimum
- Maximum
- Number of observation

The following summary statistics will be presented for time to maximum serum concentration (t_{max}) and time to maximum serum concentration at steady state ($t_{max\ ss}$):

- Median
- Minimum
- Maximum
- Number of observations

The pharmacokinetic data for MEDI9447 after a single-dose and at steady state will also be displayed graphically. Displays will include serum concentration subject profiles (on the linear and log-scale) versus time and Gmean concentration (+/-standard deviation) versus time, stratified by dose.

Scatter plots of exposure to MEDI9447 and dose-normalised exposure to MEDI9447 versus dose will also be considered following both single and multiple dose administration of MEDI9447 to assess dose proportionality.

9.4.3 Immunogenicity analyses

Immunogenicity results will be listed by subject, and analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-MEDI9447 antibody. The immunogenicity titer will be listed for samples confirmed positive for the presence of anti-MEDI9447 antibody. Neutralizing ADAs, if measured, will be listed for samples confirmed positive for the presence of anti-MEDI9447 antibody.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety of MEDI9447 may be evaluated, if the data allow.

9.4.4 Efficacy analyses

The efficacy analyses will be based on the efficacy analysis set. More details will be provided in the statistical analysis plan. The following efficacy endpoints will be analyzed:

- Objective response (OR) is defined as confirmed complete response (CR) or confirmed partial response (PR) based on RECIST v1.1 guidelines (Eisenhauer et al, 2009). The ORR will be estimated by the proportion of OR.
- Disease control (DC) is defined as CR, PR, or stable disease (SD; subjects achieving SD will be included in the DC if they maintain SD for ≥ 8 weeks [± 3 days] from start of treatment). The DCR will be estimated by the proportion of DC.
- DoR is defined as the duration from the first documentation of OR to the first documented disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cut-off for analysis, DoR will be censored at the last tumor assessment date. The DoR will only be evaluated for the subgroup of subjects with an OR.
- Progression-free survival (PFS) will be measured from the start of treatment with the investigational product until the first documentation of disease progression or death due to any cause, whichever occurs first. Progression must be confirmed using RECIST v1.1. For subjects who are alive and progression-free at the time of data cut-off for analysis, PFS will be censored at the last tumor assessment date. The PFS of each subject will be listed.
- The percentage change in target lesion tumor size from baseline will be calculated for each RECIST assessment. Spider plots will be created for visual assessment of change in tumor size over time.

9.4.5 Other analyses

Biomarker exploratory analyses will be described in the statistical analysis plan finalised before database lock. Data obtained from this study may be presented with the population PK analysis. In that case the analysis result will be reported separately from the main CSR.

9.4.6 Methods for multiplicity control

No multiplicity adjustment will be applied.

9.5 Interim analyses

Interim analyses are not planned in this study

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/ independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

If a subjects partner becomes pregnant from starting the investigational product administration until 90 days after the last dose of investigational product, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Subjects" and provide information about the pregnancy accordingly.

Subjects who are rescreened are required to sign a new ICF.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

Data monitoring committee will not be set.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical trial and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in Clinical Study Agreement and/or other documents.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

B 6 Intensity rating scale:

The grading scales found in the revised NCI CTCAE latest version will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred

- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding interactive voice response system [IVRS] / interactive web response system [IWRS] errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

C 2 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 8.4.4 of the Clinical Study Protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational product.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law (PHL)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3 × ULN **together with** total bilirubin ≥ 2 ×ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in total bilirubin, but there is no specified time frame within which the elevations in transaminases and total bilirubin must occur.

D 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- total bilirubin ≥ 2 × ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

D 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

D 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the investigational product. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin elevations other than the investigational product:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to subjects who meet PHL criteria on Study treatment having previously met PHL criteria at a study visit prior to starting Study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the subjects' condition[#] compared with the last visit where PHL criteria were met.

- If there is no significant change, no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix B 5.

[#] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

D 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (e.g., chronic or progressing malignant disease, severe infection or liver disease), or did the subject meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix D 6

If **No**: Follow the process described in Appendix D 4.1.

If **Yes**: Determine if there has been a significant[#] change in the subject's condition compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Appendix D 4.

[#] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 guidelines (Eisenhauer et al 2009)for the study with regards to investigator assessment of tumor burden including protocol-specific requirements for this study.

Definition of Measurable, Non-measurable, Target and Non-target Lesions

Subjects with at least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by computerised tomography (CT), magnetic resonance imaging (MRI) or plain X-ray should be included in this study.

Measurable lesions

A lesion, not previously irradiated, that can be measured accurately at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have a short axis ≥ 15 mm with CT or MRI and which is suitable for accurate repeated measurements.

Non-measurable lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm short axis at baseline. Nodes with < 10 mm short axis are considered non-pathological and should not be recorded as non-target lesions (NTLs)
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that are not measurable by CT or MRI
- Previously irradiated lesions as localised post-radiation changes, which affect lesion sizes, may occur. Therefore, lesions that have been previously irradiated will not be considered measurable and should be selected as NTLs at baseline and followed up as part of the NTL assessment
- Skin lesions assessed by clinical examination

Special cases

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.
- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same subject, these non-cystic lesions should be selected as the target lesions (TLs).

Target lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline.

Non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline.

Methods of Measurement

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.

The methods to be used for RECIST assessment are summarised in Table 8 and those excluded for tumor assessments in this study are discussed below, with the rationale provided.

Table 8 Summary of Methods of Assessment

Target Lesions	Non target lesions	New Lesions
CT (preferred) MRI	CT (preferred) MRI Plain X-ray (includes chest X-ray) Clinical examination	CT (preferred) MRI Plain X-ray (includes chest X-ray) Clinical examination Ultrasound Bone scan FDG-PET

CT and MRI

CT and MRI are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identification of new lesions.

In this study it is recommended that CT examinations will be used to assess tumor burden at baseline and follow-up visits. CT examination with intravenous contrast media administration is the preferred method. MRI should be used where CT is not feasible or it is medically contra-indicated. For assessment of brain lesions MRI is the preferred method.

Clinical examination

Clinical examination will not be used for assessment of TLs. Clinically detected lesions can be selected as TLs if they are then assessed by CT or MRI scans. Clinical examination can be

used to assess NTLs in subjects that also have other lesions assessable by CT, MRI or plain Xray and to identify the presence of new lesions.

X-rays

Plain X-ray

Plain X-rays may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Chest X-ray

Chest X-rays will not be used for assessment of TLs as they will be assessed by CT or MRI examination. Chest X-rays can, however, be used to assess NTLs and to identify the presence of new lesions.

Ultrasound

Ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed then new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor measurements.

Tumor markers

Tumor markers will not be used for tumor response assessments per RECIST v1.1.

In this study tumor markers are being collected for separate analysis. However the results will not contribute to tumor response based on RECIST v 1.1 assessment.

Cytology and histology

Histology will not be used as part of the tumor response assessment per RECIST v 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary to differentiate between response / stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or the appearance of a clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be progression of NTLs or disease progression due to new lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI or X-ray at baseline should be recorded as NTLs and followed by the same method as per baseline assessment.

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and x-ray is recommended where bone scan findings are equivocal.

FDG-PET scan

FDG-PET (fluorodeoxyglucose positron emission tomography) scans may be used as a method for identifying new lesions, according with the following algorithm: New lesions will be recorded where there is positive FDG uptake (defined as when an uptake greater than twice that of the surrounding tissue is observed) not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to confirm new lesions.

Tumor response evaluation

Schedule of evaluation

Baseline tumor assessments should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual subjects and should be performed no more than 28 days before the start of study treatment. Follow-up assessments should be performed according to the schedule defined in this protocol. Any other sites at which new disease is suspected should also be adequately imaged at follow-up.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved, should be identified as TLs at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions) but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion

does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimetres. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is > 5mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s)
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion
- When a TL has had any intervention e.g., radiotherapy, embolisation, surgery etc, during the study, the size of the TL should still be provided where possible

Evaluation of target lesions

Table 9 provides the definitions of the criteria used to determine objective tumor visit response for TLs.

Table 9 Overall Visit Response for Target Lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of TLs, 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 5mm.

Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

Non-Target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the investigator. Table 10 provides the definitions of the criteria used to determine and record overall response for NTLs at the investigational site at each visit.

Table 10 Overall Visit Response for Non-Target Lesions

Complete Response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of one or more NTLs.
Progressive Disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST clinically significant for the physician to consider changing or stopping therapy
Not Evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment at this visit. Note: For subjects without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

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

New Lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Subjects with 'symptomatic deterioration' requiring discontinuation of study treatment without objective evidence of disease progression at that time will undergo no further tumor assessments in this study. Tumor response data for such subjects will be censored at the date of their last RECIST assessment.

Evaluation of Overall Visit Response and Best Overall Response

The overall visit response will be derived using the algorithm shown in Table 11

Table 11 Overall Visit Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/non PD)
NE	Non-PD or NE	No	NE
NA	NE	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, NA = not applicable (relevant when no TLs/NTLs at baseline)

Specifications for Radiological Imaging

These notes are recommendations for use in clinical studies. The use of standardised protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

CT Scan

CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomical regions of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST v 1.1 are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

Anatomic coverage

Optimal anatomic coverage for most solid tumors is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual subjects. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

Intravenous contrast administration

Optimal visualisation and measurement of metastases in solid tumors requires consistent administration (dose and rate) of intravenous contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given subject. It is very important that the same technique be used at baseline and on follow- up examinations for a given subject. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the subject should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to

have a different size using a new modality. Oral contrast is recommended to help visualise and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic examination without contrast and abdominal and pelvic MRI with contrast. If MRI cannot be performed then CT without intravenous contrast is an option for the thorax, abdomen and pelvic examinations.

Slice thickness and reconstruction material

It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for the measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TLs should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium-enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimised for the specific body part being imaged as well as the scanner utilised. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

FDG-PET scans

FDG-PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. If FDG-PET scans are included in a protocol, an FDG uptake period of 60 min

prior to imaging has been decided as the most appropriate for imaging of subjects with malignancy. Whole-body acquisition is important since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid-thigh should be obtained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same subject. Whole-body acquisitions can be performed in either 2- or 3-dimensional mode with attenuation correction, but the method chosen should be consistent across all subjects and serial scans in the clinical trial.

PET/CT scans

At present, low dose or attenuation correction CT portions of a combined 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 tumor measurements by RECIST v 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET–CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET–CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

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Appendix F Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-related, and Nonimmune mediated Reactions

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions 1 November 2017 Version

General Considerations	
Dose Modifications	**Toxicity Management**
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1 The event stabilizes and is controlled. 2 The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3 Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).

General Considerations	
Dose Modifications	**Toxicity Management**
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	– More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Pediatric Considerations	
Dose Modifications	**Toxicity Management**
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** after last dose of study drug/study regimen	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. – The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease consult.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. − Hospitalize the patient. − Supportive care (e.g., oxygen). − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks [a]. **Caution**: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Hepatitis (elevated LFTs) **Infliximab should not be used for management of immune-related hepatitis.** **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1**: – Continue LFT monitoring per protocol.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4**: Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Hepatitis (elevated LFTs) **Infliximab should not be used for management of immune-related hepatitis.** **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** **See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used**. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above** **(except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): − **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** − **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** − **Grade 3-4: Permanently discontinue study drug/study regimen**			

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. – If creatinine returns to baseline, resume its regular monitoring per study protocol. – If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1 The event stabilizes and is controlled. 2 The patient is clinically stable as per investigator or treating physician's clinical judgement. 3 Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1 The event stabilizes and is controlled. 2 The patient is clinically stable as per investigator or treating physician's clinical judgement. 3 Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* ° Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. ° Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. ° If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ° It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ° Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* ° Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ° Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ° If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ° It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ° Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. − Consider, as necessary, discussing with the study physician. − Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. – Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back,

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 1 (mild pain)	No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	**For Any Grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2**: The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4**: − Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Appendix G Abbreviations

Abbreviation or special term	Explanation
ACTH	adrenocorticotropic hormone
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{x-y}	Area under the serum concentration-time curve from X to Y
β-hCG	beta human chorionic gonadotropin
CD	cluster of differentiation
CI	confidence interval
CL	systemic clearance
CL_{ss}	clearance at steady state
C_{max}	maximum serum concentration
$C_{max, ss}$	maximum serum concentration at steady state
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CrCl	calculated creatinine clearance
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
C_{trough}	trough serum concentration
$C_{trough\ ss}$	trough serum concentration at steady state
DC	disease control
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

Abbreviation or special term	Explanation
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
FDG-PET	fluorodeoxyglucose positron emission tomography
FFPE	formalin-fixed and paraffin-embedded
GCP	Good Clinical Practice
GCV	geometric coefficient of variation
GLP	Good Laboratory Practice
Gmean	geometric mean
GMP	Good Manufacturing Practice
HBc	hepatitis B core
HBsAg	HBV surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPF	high power field
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
Ig	immunoglobulin
IgG1λ	immunoglobulin G1 lambda
imAE	immune-mediated adverse event
ILD	interstitial lung disease
IRB	institutional review board
IRR	infusion-related reaction
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
mAb	monoclonal antibody

Abbreviation or special term	Explanation
MDSC	myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
NOAEL	no-observed-adverse-effect level
NTL	non-target lesion
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
Q12W	every 12 weeks
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
R_{AC}	accumulation ratio
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse event
CCI	[redacted]
SD	stable disease
SoA	Schedule of Activities
SpO_2	percutaneous arterial oxygen saturation
SRC	Safety Review Committee
$t_{½\lambda z}$	terminal phase half-life
T_3	triiodothyronine
T_4	thyroxine

Abbreviation or special term	Explanation
TL	target lesion
t_{max}	time to maximum serum concentration
$t_{max\ ss}$	time to maximum serum concentration at steady state
Treg	regulatory T cell
TSH	thyroid stimulating hormone
ULN	upper limit of normal
w/v	weight/volume

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