LUDWIG CANCER RESEARCH	**Study Protocol**	**LUD2014-012-ALK**	**US-IND# 131960 NCT02898116**
	Amendment 2	**Final**	**14-AUG-2017**

Protocol Title
A Phase 1/2 Study of ALK Inhibitor, ensartinib (X-396), and anti-PD-L1, durvalumab (MEDI4736), in Subjects with ALK-rearranged (ALK-positive) Non-small Cell Lung Cancer (NSCLC)

Objectives and Synopsis

This is an open-label, multicenter, single-arm study to evaluate the safety and preliminary efficacy of a targeted therapy for NSCLC in combination with a checkpoint inhibitor:

- Ensartinib (X-396), an anaplastic lymphoma kinase (ALK) Inhibitor and
- Durvalumab (MEDI4736), an anti-programmed cell death ligand 1 (PD-L1) antibody.

Prior to starting the combination drug therapy, there will be a pre-immunotherapy Run-in Period (one 28-day cycle), where ensartinib will be given as monotherapy. The Run-in Period will be followed by the combination drug therapy, starting with Cycle 1.

The ***dose escalation phase*** (see table below) will utilize a standard 3 + 3 design to determine the Recommended Combination Dose (RCD), followed by an ***expansion phase***, in which the dose escalation cohort at the RCD will be expanded to 20 subjects.

Dose Level	**Doses**	
	Ensartinib	***Durvalumab***
-1	150 mg	1500 mg
Starting	***200 mg***	***1500 mg***
+1	225 mg	1500 mg

NOTE: if a subject's body weight drops to ≤ 30 kg while on the study, the durvalumab dose will be weight based as long as the body weight remains ≤ 30 kg (see Section 6.1.3).

Primary Objective [Endpoints]	**Phase 1 Dose Escalation Phase:** *Recommended Combination Dose (RCD)* *Safety and Tolerability* [CTCAE 4.03, including DLTs and RCD] **Expansion Phase:** *Safety and Tolerability* [CTCAE 4.03]
Secondary Objectives [Endpoints]	**Dose Escalation and Expansion Phases (all subjects):** *Clinical Efficacy by irRECIST and RECIST 1.1* [PFS rate and ORR at 8 and 24 weeks, overall best response, DCR, DoR, OS]
Exploratory Objectives [Endpoints]	**Dose Escalation and Expansion Phases (all subjects):** *Biologic Activity* [Effects on Tumor Microenvironment, Immune Response]

DLT=Dose-limiting Toxicity; RCD=Recommended Combination Dose; ORR=Objective Response Rate; DCR=Disease Control Rate; DoR=Duration of Response; PFS=Progression-free Survival; OS=Overall Survival; CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST = Response Evaluation Criteria in Solid Tumors; irRECIST=immune-related RECIST.

Sponsor: Ludwig Institute for Cancer Research Sponsor Representative Signature and Date	[redacted] Study Chair Signature and Date

Confidentiality Statement

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1 Background

1.1 Checkpoint Inhibitors and ALK Inhibitors in the Treatment of Non-Small Cell Lung Cancer

Lung cancer is responsible for nearly 1 in 5 cancer-related deaths, or an estimated 1.6 million people, worldwide. In the U.S., lung cancer is the leading cause of cancer-related death among both men and women.(1) For patients who are diagnosed with advanced disease, conventional treatment options including surgery, chemotherapy, and radiation are unlikely to result in cure.

Lung cancer has also emerged as an exciting target of immune-based therapies, specifically checkpoint inhibitors.(2) In non-small cell lung cancer (NSCLC), marked single-agent activity has been observed with inhibition of programmed death receptor 1 (PD-1) on immune cells or inhibition of programmed death receptor ligand 1 (PD-L1).(3-5) Notably, PD-L1 appears to be expressed in 25% to 50% of NSCLC tumors, with expression both on tumor cells and within the tumor microenvironment (TME) on tumor-associated macrophages.(6) While the relationship of expression to therapeutic response is still being defined, early studies indicate there may be some activity of such inhibitors in NSCLC.(7-9)

PD-1/PD-L1 inhibitors in NSCLC

Checkpoint inhibitors, particularly PD-1/PD-L1 antibodies, have been shown to be effective in the treatment of NSCLC (10-12), and in 2015, nivolumab and pembrolizumab were approved by FDA for the treatment of lung cancer after progression on or after platinum-based chemotherapy.

In March 2015, FDA approved the PD-1 checkpoint inhibitor nivolumab for the treatment of advanced squamous NSCLC that has stopped responding to chemotherapy. This approval was based on results of a Phase 3 trial in which subjects receiving nivolumab had median overall survival was 9.2 months versus 6.0 months with docetaxel.(11) In October 2015, FDA expanded its approval of nivolumab to include non-squamous NSCLC that has stopped responding to chemotherapy. This approval was based on the results of a Phase 3 trial that showed that subjects who received nivolumab had a median overall survival of 12.2 months compared to 9.4 months for those receiving docetaxel. (10)

Also in October 2015, pembrolizumab, a PD-1 checkpoint inhibitor was approved for patients with NSCLC (both squamous and non-squamous) with tumors that test positive for PD-L1. In a Phase 1 clinical trial, PD-L1 expression level of 50% was associated with the likelihood of clinical benefit. Among subjects with a proportion score of at least 50%, the response rate was 45.2%. (12)

For both of these immunotherapies, it is recommended that patients with epidermal growth factor receptor (EGFR) or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy prior to receiving nivolumab or pembrolizumab.

Both nivolumab and pembrolizumab are being studied in multiple indications in randomized Phase 3 trials compared to standard of care chemotherapy as first-line treatment, and several other PD-1/PD-L1 checkpoint inhibitors are also in late stage clinical testing.

ALK Inhibitors

Anaplastic lymphoma kinase (ALK) was first identified as a chromosomal rearrangement in anaplastic large cell lymphoma (ALCL). Genetic studies indicate that abnormal expression of ALK is a key driver of certain types of NSCLC and neuroblastomas. Since ALK is generally not expressed in normal adult tissues, it represents a highly promising target for molecularly targeted cancer therapy.

Crizotinib was the first ALK inhibitor approved in 2011 for the treatment of patients with metastatic ALK positive NSCLC. More recently, ceritinib and alectinib, second generation ALK inhibitors, have also been approved for the treatment of patients with ALK positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Ensartinib (X-396) is also a next generation ALK inhibitor that has shown greater potency than crizotinib *in vitro* and *in vivo*.

Rationale for combination therapy

PD-L1 expression may be modulated by anti-cancer therapies and may be more important in the setting of oncogene-driven cancers. For instance, oncogenic EGFR signaling induces PD-L1 upregulation in EGFR-mutant NSCLC cell lines, and mouse models of EGFR-driven lung adenocarcinoma show tumor shrinkage and prolonged survival with PD-1 inhibition.(13) Therefore, in oncogene-driven NSCLC in particular, combining targeted therapy with PD-1/PD-L1 checkpoint inhibitor therapy may be particularly important, as the effective tumor shrinkage seen with targeted agents combined with the durable responses seen with PD-1/PD-L1 checkpoint inhibitor agents may result in lasting tumor control.

The EML4-ALK fusion oncogene is molecular target in NSCLC. EML4-ALK positive NSCLC patients also have higher PD-L1 expression levels, compared to those negative for the fusion gene,(14) suggesting that their tumors are not only driven by EML4-ALK activity but also repress T-cell function. Thus, the simultaneous inhibition of EML4-ALK by ensartinib and de-repression of T-cell function by checkpoint inhibitors might be necessary, leading to additive or synergistic outcomes.

Tumor lysis due to ALK inhibition may enhance immune priming and thus also contribute to the synergy. In addition, ensartinib has some Axl (IC50: 24nM) and CSF1R (IC50:13nM) inhibitory activities. Inhibition of Axl activates T-cells,(15) while inhibition of CSF1R modulates the tumor microenvironment including tumor-associated macrophages and myeloid-derived suppressor cells.(16) Both might further potentiate response to T-cell checkpoint immunotherapy.

This study will evaluate a checkpoint inhibitor, durvalumab, which targets PD-L1, in combination with ensartinib.

1.2 Study Drugs

1.2.1 Durvalumab (MEDI4736) - PD-L1 Antibody

[redacted]

[redacted]

1.2.2 Ensartinib (X-396)

[redacted]

[redacted]

[redacted]

2 Study Rationale

As described in Section 1.1, checkpoint inhibitors, particularly PD-1/PD-L1 antibodies, have been shown to be effective in the treatment of NSCLC. Checkpoint inhibitors are also associated with minimal toxicities compared with chemotherapy or targeted therapies and function quite distinctly from other therapies. Therefore, the potential for effective and safe combination with existing therapies is significant.

Effective therapies, such as targeted therapies in oncogene-driven NSCLC, generate visible tumor shrinkage within days to weeks, suggesting rapid tumor lysis that should generate large amounts of tumor antigen for antigen presentation and subsequent priming of tumor-specific T-cells.(21) The addition of checkpoint inhibitor therapy could capitalize on this immunologic priming effect of targeted therapies for a potentially marked synergistic efficacy.(22)

As with EGFR-mutant NSCLC, no subject with an ALK rearrangement is cured with crizotinib, and the median PFS is less than 1 year. Second generation ALK inhibitors, including ensartinib, have substantially increased potency compared with crizotinib and have demonstrated activity in both crizotinib-naïve and crizotinib-resistant subjects.(20, 23) Therefore, this study, which will combine durvalumab with ensartinib, represents an opportunity to test the synergy of immunotherapy with a potentially more effective ALK tyrosine kinase inhibitor (TKI) than crizotinib.

PD-L1 expression may be modulated by anti-cancer therapies and may be more important in the setting of oncogene-driven cancers. Therefore, in oncogene-driven NSCLC in particular, combining targeted therapy with PD-1/PD-L1 checkpoint inhibitor therapy may be particularly important, as the effective tumor shrinkage seen with targeted agents combined with the durable responses seen with PD-1/PD-L1 checkpoint inhibitor agents may result in lasting tumor control.

EML4-ALK positive NSCLC patients have higher PD-L1 expression levels, compared to those negative for the fusion gene, (14), suggesting that their tumors are not only driven by EML4-ALK activity but also repress T-cell function. Thus, the simultaneous inhibition of EML4-ALK by ensartinib and de-repression of T-cell function by checkpoint inhibitors might be necessary, leading to additive or synergistic outcomes.

Tumor lysis due to ALK inhibition may enhance immune priming and thus also contribute to the synergy. In addition, ensartinib has some Axl (IC50: 24nM) and CSF1R (IC50:13nM) inhibitory activities. Inhibition of Axl activates T-cells,(15) while inhibition of CSF1R modulates the tumor microenvironment including tumor-associated macrophages and myeloid-derived suppressor cells.(16) Both might further potentiate response to T-cell checkpoint immunotherapy such as durvalumab.

2.1 Ensartinib Dose

In this study, the starting dose for ensartinib will be 200 mg, which is considered an efficacious dose. Based on the results of the dose escalation phase, this dose may be escalated to the recommended ensartinib single agent dose of 225 mg or de-escalated to the minimum effective dose of 150 mg in the case of overlapping toxicities.

2.2 Durvalumab Dose

A durvalumab dose of 20 mg/kg every 4 weeks (Q4W) is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase 1 trial performed in Japanese patients with advanced solid tumor (D4190C00002). See durvalumab IB for details.

2.2.1 Pharmacokinetics (PK)/Pharmacodynamics (PD) Data

Based on available PK/PD data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. For further information on immunogenicity, please see the current IB.

2.2.2 Clinical Data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy and PK for the 20mg/kg Q4W regimen.

2.2.3 Fixed Dosing for Durvalumab

[redacted]

2.3 Rationale for Amendment 2

[redacted]

3 Experimental Plan

3.1 Study Design

This is an open-label, multicenter, Phase 1/2 study to evaluate the safety and preliminary efficacy of a targeted therapy for NSCLC in combination with a checkpoint inhibitor:

- Ensartinib (X-396), an ALK Inhibitor and
- Durvalumab (MEDI4736), an anti-PD-L1 antibody.

There will be a pre-immunotherapy **Run-in Period** prior to starting the combination drug therapy. During the Run-in Period, ensartinib will be given for one 28-day cycle as monotherapy prior to starting the combination therapy (durvalumab and ensartinib) in Cycle 1.

The ***dose escalation phase*** will utilize a standard 3 + 3 design to determine the Recommended Combination Dose (RCD), followed by an ***expansion phase***, in which the dose escalation cohort at the RCD will be expanded to 20 subjects (inclusive of the subjects from the dose escalation cohort).

3.1.1 Study Phase

Phase 1/2

3.1.2 Enrollment/Randomization

Enrollment will occur in a sequential fashion. See Section 3.1.7.1 for a description of the Run-in Period. After the RCD is determined, the expansion phase will start (n =20 subjects, inclusive of the subjects from the dose escalation cohort treated at the RCD).

3.1.3 Blinding/Unblinding

This is an open-label study.

3.1.4 Subject Population

Subjects with histologically confirmed metastatic NSCLC. Subjects must have confirmed ALK rearrangement as assessed by immunohistochemistry (IHC). Subjects may have had prior therapy with ALK inhibitors or be ALK inhibitor naïve. ALK inhibitor naïve subjects will be informed of the availability of approved ALK inhibitors. Details on subject eligibility are found in Section 5.

3.1.5 Number of Sites/Subjects

Up to 8 sites in the US, with a total of up to 32 subjects.

3.1.6 Sample Size Considerations

The *dose escalation phase* will utilize a standard 3 + 3 design, which will result in the enrollment of 9 to 18 subjects.

In the *expansion phase*, 20 subjects are thought to provide sufficient data to adequately identify essential safety and preliminary efficacy signals. Therefore, 14 additional subjects will be added to the 6 treated at the RCD of the dose escalation phase. The sample size, n=20, for the expansion phase is deemed to provide sufficient precision for the estimation of incidence of

adverse events. The Clopper Pearson confidence intervals (CI) for incidence of adverse events based on a sample size of 20 subjects are provided below:

Number of Subjects with Event	Incidence	95% Confidence Interval (Clopper Pearson)
1/20	0.05	(0.00127, 0.24873)
2/20	0.10	(0.01235, 0.31698)
3/20	0.15	(0.03207, 0.37893)
4/20	0.20	(0.05733, 0.43661)
5/20	0.25	(0.08657, 0.49105)
6/20	0.30	(0.11893, 0.54279)
7/20	0.35	(0.15391, 0.59219)
8/20	0.40	(0.19119, 0.63946)
9/20	0.45	(0.23058, 0.68472)
10/20	0.50	(0.27196, 0.72804)
11/20	0.55	(0.31528, 0.76942)
12/20	0.60	(0.36054, 0.80881)
13/20	0.65	(0.40781, 0.84609)
14/20	0.70	(0.45721, 0.88107)
15/20	0.75	(0.50895, 0.91343)
16/20	0.80	(0.56339, 0.94267)
17/20	0.85	(0.62107, 0.96793)
18/20	0.90	(0.68302, 0.98765)
19/20	0.95	(0.75127, 0.99873)

3.1.7 Treatment Schema

The study drugs used in this study are administered per cycle as shown below:

Dosing Schedule:			
Period	***Cycle***	**Ensartinib** *(p.o.)*	**Durvalumab** *(i.v.)*
Run-in Period: see Section 3.1.7.1	***Run-in (-1)***	Daily for 28 days	None
Combination Treatment	***1 to 12***	Daily for 28 days each cycle	Q4W on Cycle Day 1 (±3 days)
p.o. = by mouth; i.v. = intravenous; Q4W = every 4 weeks			

Subjects will receive a monthly supply of ensartinib. At each study visit, they will return the unused portion to the study site; the number of pills returned will be counted to determine compliance.

3.1.7.1 Run-in Period

Prior to starting durvalumab in Cycle 1 of the combination therapy, there will be a run-in period where ensartinib will be given as a monotherapy for 1 cycle (28 days, Cycle -1) in order to determine a safety signal that might compromise combination therapy and also to determine the effect of ALK inhibitor therapy on the immune tumor microenvironment.

During the run-in period, subjects will be evaluated for rash, where a Grade ≥2 is a DLT.

Subjects with no DLTs in the run-in period will proceed to Cycle 1 of the combination therapy (See Section 3.2.1, Flowchart for Subjects Who Proceed with Combination Therapy after Run-in).

Subjects who experience a DLT during the run-in period will not go on to receive durvalumab in Cycle 1 of the combination therapy and will be replaced. In addition, subjects who experience any toxicity that requires a dose reduction of ensartinib (see Section 8.4) during the run-in period, will not go on to receive durvalumab in Cycle 1 of the combination therapy and will be replaced.

The subjects who do not proceed with combination treatment, may continue treatment with ensartinib monotherapy after resolution of DLT. See Section 3.2.2, Flowchart for Subjects who Continue Treatment with Ensartinib (X-396) Monotherapy after Run-in, for details on assessments during continued monotherapy treatment.

Dose escalations and de-escalations for the determination of RCD will be performed according to Section 3.1.7.2. For each dose level in the dose escalation phase, enrollment of Subjects 1-3 will be staggered according to the 1-cycle run-in period (i.e., one subject will be enrolled every 1 cycle to monotherapy with ensartinib).

After 3 subjects have proceeded to the combination therapy, enrollment to the dose level cohort may be held if additional time is needed to determine the dose level for the next 3 subjects according to the 3 + 3 design.

3.1.7.2 Dose Escalation Phase

Each subject enrolled in the dose escalation cohorts of the study will be evaluated for DLTs, as defined in Section 3.1.9. Dose escalations and de-escalations for the determination of RCD will be performed based on the available dose levels (see table below) and the respective rules for a standard 3 + 3 dose escalation study design (see Figure 1).

The dose for durvalumab is based on the currently recommended dose of 1500 mg (see Section 2.2.3). If a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of durvalumab as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.

Dose Level Table:		
Dose Level	**Doses**	
	Ensartinib	***Durvalumab***
-1	150 mg	1500 mg
Starting	***200 mg***	***1500 mg***
+1	225 mg	1500 mg

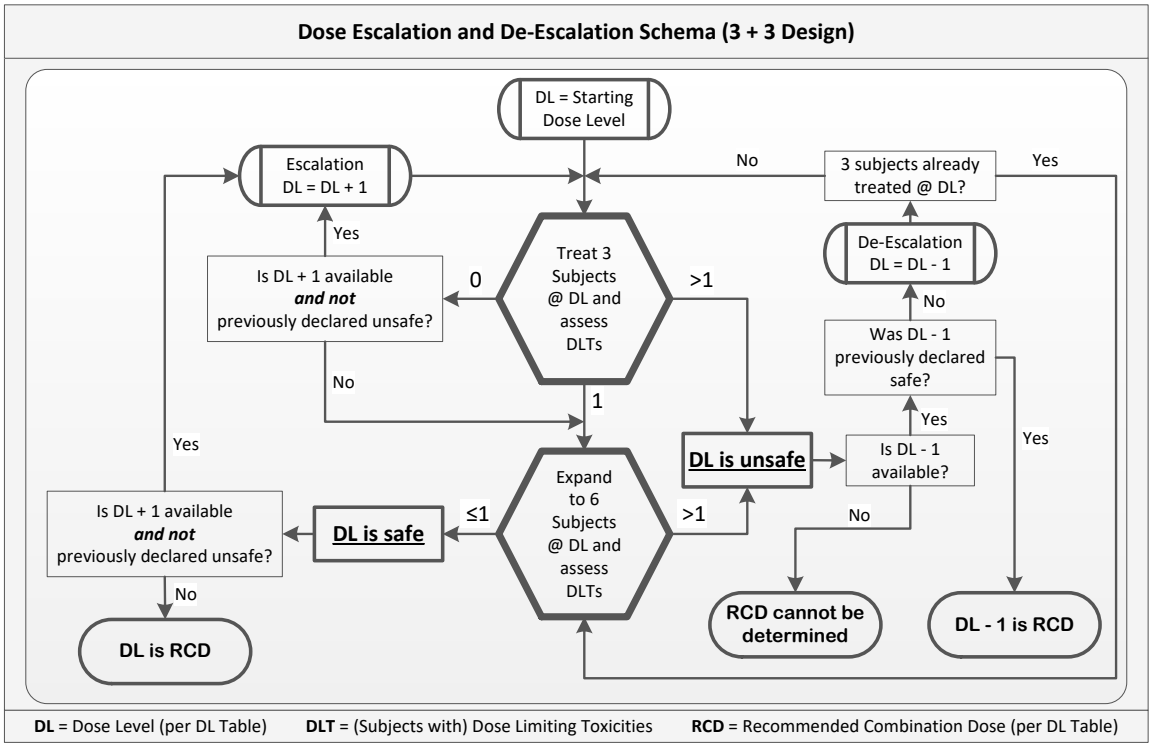


Figure 1. Dose Escalation and De-Escalation Schema

Per Figure 1, the RCD is defined as the highest dose level at which no more than 1 of 6 subjects (i.e., < 33%) experience DLTs. The RCD cannot be determined if none of the predefined dose level cohorts fulfill that criterion.

Upon determination of an RCD, respective intra-subject dose escalation or de-escalation for subjects still on study, and previously treated at dose levels other than the RCD, may be permitted upon agreement by the Sponsor and Investigator.

3.1.7.3 Dose Expansion Phase

The RCD dose level cohort will be expanded to 20 subjects (14 subjects added to the 6 treated at the RCD in the dose escalation phase).

3.1.8 Dosing Adjustments, Delays, and Discontinuations

Individual subject dosing adjustments due to toxicity will be allowed/may be required in accordance with the "Dose Adjustment and Management Guidelines" for toxicity related to durvalumab and ensartinib, outlined in Section 8.3 and Section 8.4, respectively. If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

3.1.8.1 Monitoring for Hepatic Toxicity During Combination Therapy

During the ensartinib/durvalumab combination therapy, all hepatic toxicity events related at least to durvalumab will be considered and treated as immune-related events. In order to monitor the hepatic combination toxicities more closely, in addition to the ongoing measurements that occur every 4 weeks, liver function tests (ALT, AST, alkaline phosphatase, and total bilirubin) will be performed at 2 weeks after the durvalumab dose during Cycle 1 of the combination therapy.

The main difference between monotherapy and combination therapy hepatic toxicities is that ensartinib dosing will not be stopped for Grade 2 hepatic toxicity during ensartinib monotherapy, whereas it will be held during combination therapy.

Please refer to Sections 8.3 and 8.4 for general instructions and for respective monotherapy dose modifications. For hepatic toxicities following ensartinib/durvalumab combination treatment, follow the instructions given below:

Grade 1
No dose modification is required for a Grade 1 hepatic toxicity.

Grade 2
Hold ensartinib and durvalumab until resolution to ≤ Grade 1 (and after the end of any steroid taper), and discontinue drugs permanently if such resolution does not occur within 28 days. Upon resolution to ≤ Grade 1, ensartinib dosing may resume and durvalumb dosing may resume at the next scheduled dose.

Grade 3
In general, **hold both drugs until resolution to ≤ Grade 1** (and after the end of any steroid taper). Upon resolution to ≤ Grade 1, ensartinib dosing may resume at a lower dose as outlined in Section 8.4; and durvalumb dosing may resume at the next scheduled dose.

Discontinue ensartinib permanently for any of the following:

- Grade 3 toxicity lasting longer than 7 days
- Elevated ALT ≥3 x ULN in conjunction with a total bilirubin ≥2 x ULN, and no correctable, non-drug related cause

Discontinue durvalumab permanently for any of the following:

- Transaminases or bilirubin not resolving to ≤ Grade 1 or baseline within 14 days
- Transaminases > 8 × the upper limit of normal (ULN) or bilirubin > 5 × ULN
- Any case meeting Hy's law criteria (as defined in FDA Guidance Document "Drug-Induced Liver Injury")

Grade 4
Discontinue drugs permanently

3.1.9 DLT and MTD/RCD for the Combination Therapy

MTD will not be determined in this study. Instead, the RCD will be determined in the context of the predefined dose levels used during the dose escalation phase as per Section 3.1.7.2.

DLTs will be observed over a period of the first 2 Cycles of the combination therapy, including the pre-dose assessment for Cycle 3, defined as the "DLT Evaluation Period." The decisions for dose escalations, de-escalations and RCD, as described in Section 3.1.7.2 will primarily be based on the number of subjects with DLTs occurring during the DLT Evaluation Period. DLTs occurring outside the DLT Evaluation Period will also be evaluated and may impact such decisions.

DLTs are defined as any adverse events that are possibly, probably, or definitely related to the administration of durvalumab or ensartinib and fulfill any of the following criteria:

1. Any Grade ≥ 3 rash, colitis, pneumonitis, neurological event or uveitis.
2. Any Grade 2 pneumonitis, neurological event or uveitis, with the *following exception*:
   - Grade 2 pneumonitis, neurological event or uveitis that downgrade to Grade ≤ 1 within 3 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
3. Any *other* Grade ≥ 3 toxicity, with the *following exceptions*:
   - Grade 3 irAEs that downgrade to Grade ≤ 2 within 3 days, or to Grade ≤ 1 or baseline within 14 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
   - Grade 3 endocrinopathy that becomes asymptomatic when managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
   - Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).
   - Grade 3 fatigue for ≤ 7days.
   - Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
   - Liver transaminase elevation ≤ 8 times ULN that downgrades to Grade ≤ 2 (≤ 5 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
   - Total bilirubin ≤ 5 times ULN that downgrades to Grade ≤ 2 (≤ 3 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
   - Grade ≥ 3 neutropenia that (1) is not associated with fever or systemic infection, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
   - Grade 3 and 4 lymphopenia.
   - Grade 3 thrombocytopenia that (1) is not associated with clinically significant bleeding, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
   - Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.
   - Any pre-existing laboratory abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by both Investigator and Sponsor.

Immune-related AEs are defined as AEs of 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.

While rules for adjudicating DLTs are specified above, an AE that is Grade < 3 or listed as exempt above may also be defined as DLT after consultation with the Sponsor and Investigators, based on the emerging safety profiles of durvalumab and ensartinib. Likewise, subjects who become not evaluable for DLT, because they discontinued or interrupted treatment due to toxicities other than DLTs, may be counted as DLT subjects, if the toxicities cannot be managed in accordance with the dosing modifications described in Section 3.1.8.

Subjects who experience a DLT will be discontinued from study treatment and will enter the On Study and Post Study Follow-up (see Section 3.1.16). However, if it is in the best interest of the subject, the Investigator, subject and Sponsor may agree to continue treatment with ensartinib, possibly at a lower dose level.

3.1.10 Subject Withdrawal from Treatment or from Study

A subject will be **withdrawn from study treatment** for any of the following reasons:

1. Withdrawal of consent for further treatment
2. Pregnancy or intent to become pregnant.
3. DLT at any time (see Section 3.1.9).
4. Progressive disease requiring alternative systemic treatment.
5. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal.
6. Development of intercurrent, non-cancer-related illnesses or complications that prevent either continuation of therapy or regular follow-up.
7. Best medical interest of the subject (at the discretion of the Investigator)

A subject will be **withdrawn from the study** for the following reasons:

1. Best medical interest of the subject at the discretion of the Investigator
2. Initiation of alternative anti-cancer therapy (marketed or investigational).
3. Withdrawal of consent for all follow-up.
4. Lost to follow-up.
5. Death.

Discontinuation from receiving study treatment does not mean that the subject is withdrawn from the study. If applicable, subjects who are withdrawn from study treatment should undergo the planned On Study Follow-up procedures (see Study Flowchart, Section 3.2.1), followed by the Post Study follow-up period (see Section 3.1.16).

Section 7.2.6 provides additional details regarding documentation for early subject withdrawal from study treatment and early withdrawal from study.

See also Sections 8.3, and 8.4 for subject withdrawal from treatment due to necessary dosing interruptions or discontinuations.

3.1.10.1 Treatment beyond Progression

Subjects meeting criteria for progression by RECIST 1.1 (Section 8.5) will be allowed to continue on therapy until confirmation of progression if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and as long as the following criteria are met at the discretion of the Investigator:

a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression;
b. No significant decline in ECOG performance status;
c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

See Section 8.5 for additional information regarding RECIST 1.1 and irRECIST.

3.1.11 Subject Evaluability and Subject Replacements

In the *dose escalation phase*, subjects are fully evaluable for DLT if they fulfill the criteria described for the Per-Protocol Population for DLT Assessment (as defined in Section 4.1.2).

Subjects who are not fully evaluable for DLT per Section 4.1.2 will be replaced.

Subjects are fully evaluable for secondary endpoints of PFS rate and ORR if they fulfill the criteria for the Per-Protocol Population for Clinical Efficacy (as defined in Section 4.2.2).

Subjects who are not fully evaluable for PFS rate and ORR may be replaced.

3.1.12 Optional Study Treatment Extension

Subjects who still benefit from treatment at the end of the 12 cycles (Core Study) may continue treatment with ensartinib and/or durvalumab until progression, if agreed upon by subject, Sponsor and Investigator.

See flowchart in Section 3.2.1 for assessments to be performed during this period.

3.1.13 Interim Analysis

Interim Safety Reviews will be performed to assess DLTs in the dose escalation cohorts (see Section 3.1.7.2). Interim analyses may be performed to analyze the 8- and 24-week ORR endpoints.

3.1.14 Safety Monitoring and Study Stopping Rules

In accordance with the Administrative, Legal, and Ethical Requirements section of the protocol (see Section 7), Safety Monitoring will be performed by an internal data safety monitoring panel, consisting of the Principal Investigators (and co-investigators as needed), the Sponsor's Medical Monitor, and drug safety personnel from MedImmune/AstraZeneca, and Xcovery, providers of the study drugs. Additional Investigators and staff, or additional Sponsor personnel and consultants, shall participate in reviews, if indicated. The safety monitoring panel will communicate by phone and/or email on a regular basis, and in particular, to review the safety of individual cohorts for the purpose of dose escalation or de-escalation as per Section 3.1.7.2.

An Independent Data Safety Monitoring Board will not be utilized for this open-label study.

The study will be suspended or possibly stopped prematurely for any of the following reasons:

1. A death that is unexpected and at least probably related to study drug.
2. Severe anaphylactic reaction (i.e., with respiratory and cardiovascular failure) to any of the study drugs.

3. Any events that, in the judgment of the medical monitor, are deemed serious enough to warrant immediate review by the internal data safety monitoring panel. This may include any symptomatic and/or irreversible treatment-related Grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related Grade ≥ 3 neurological toxicity or uveitis.
4. Any other safety finding assessed as related to study drug that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.
5. Any interim findings that, in the opinion of the Investigators and the Sponsor, suggest that the study treatment has no clinical benefit for the subjects.

General criteria for premature trial termination are outlined in the Administrative Sections.

3.1.15 Duration of Study

Length of Study per subject:	Up to 16 months: 1 month for Run-in, 12 months for treatment and 3 months for On Study Follow-up (See Section 3.1.12 for optional treatment extension)
Enrollment Period:	24 months
Length of Study:	41 months
Length of Survival Post Study Follow-up	Up to 5 years from initiation of treatment

3.1.16 On Study and Post-Study Follow-up

All subjects, whether they complete the study as planned, discontinue treatment, or prematurely withdraw from the study as per Section 3.1.10, will be followed as per institutional guidelines in accordance with the usual standard of care principles.

Subjects who complete study treatment or discontinue treatment prematurely will enter an On Study Follow-up, which will be conducted for 90 days after the last administration of study drug according to the flowchart in Section 3.2.1. Refer to Section 7.1.5 for information on recording AEs during the On Study Follow-up.

See Section 3.2.2 for Ensartinib On Study Follow-up for subjects who continue treatment with ensartinib monotherapy after run-in according to Section 3.1.7.1.

If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On-Study Follow-up Period, any assessments required in the first On Study Follow-up visit that are not covered as part of the last on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the last on-treatment visit and the first On Study Follow-up visit should not be repeated.

In addition to the On Study Follow-up, there will be a Post Study Follow-up, during which clinical outcomes data (dates of progression/relapse and survival) will be collected at least every 6 months for up to 5 years from initiation of treatment. If after 5 years there are a significant number of subjects who are still alive, there will be an option to extend this period.

The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 days since the last administration of study drug.

See Section 3.2.2 for Ensartinib Post Study Follow-up for subjects who continue treatment with ensartinib monotherapy after run-in according to Section 3.1.7.1.

For subjects who do not continue Post Study Follow-up at one of the study sites after the end of study, the Principal Investigators or the clinical team, under the supervision of the Principal Investigator, will obtain this data through review of outside records or communication with the subject or his/her physician.

3.1.16.1 End of Study Visit

If a subject is **withdrawn from study** according to the criteria defined in Section 3.1.10, an End of Study visit must be conducted at the time of withdrawal. For subjects not yet in On Study Follow-up, this End of Study visit will be the first planned visit of the On Study Follow-up. For subjects already in On Study Follow-up, this End of Study visit will be the next planned visit of the On Study Follow-up. However, any procedures/assessments that were done within 7 days of the End of Study visit need not be repeated. All subjects of childbearing potential who withdraw from study must have a serum pregnancy test done at the End of Study visit, unless it was done within 7 days prior to End of Study visit.

After the End of Study Visit, the subject will proceed into Post Study Follow-up as described above, unless otherwise unable to do so (e.g., subject withdraws consent for all follow-up).

3.2 Study Flowcharts

3.2.1 Flowchart for Subjects Who Proceed with Combination Therapy after Run-in

3.2.1 - Flowchart for Subjects who Proceed with Combination Therapy after Run-in	Screening / Baseline	Ensartinib Run-In (Cycle -1)		Treatment (4 weeks/cycle)						
				Cycle 1		Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Study Week		-4	-2	1	3	5	9	13	17	21
Cycle Day	Up to 28 days before Tx start			1 (±3)	15 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)
Cumulative Study Day		-28	-14	1	15	29	57	85	113	141
Treatment										
Durvalumab (1500 mg)				X		X	X	X	X	X
Ensartinib (X-396) (oral; see Sections 3.1.7.1 and 3.1.7.2)		daily	daily	daily	daily	daily	daily	daily	daily	daily
Tumor & Disease Assessments										
Disease Staging (date/stage at 1st diagnosis and at study entry)	X									
Disease Assessment by irRECIST/RECIST[a]	X			X			X		X	
Study Procedures & Examinations										
Eligibility Assessment and Informed Consent (IC)[e]	X									
Demographics (incl. DoB; sex; height; race; ethnicity)	X									
Medical history	X									
Physical Exam (incl. weight and ECOG Perf Status)[b]	X	X	X	X		X	X	X	X	X
12-Lead ECG[a]	X	X		X		X		X		X
Vital Signs (T, HR, BP, RR)[g]	X	X	X	X		X	X	X	X	X
Concomitant Medications / Procedures	X	X	X	X		X	X	X	X	X
Adverse Events (starting or worsening after IC)[f]	X	X	X	X		X	X	X	X	X
Specimens for Routine Laboratory Procedures										
Blood Hematology (CBC, differential, platelets)[a]	X	X	X	X		X	X	X	X	X
Chemistry (glucose, BUN, creat., Na, K, Cl, CO_2, Ca, Mg, total protein, albumin, Tbili., AST, ALT, ALP, LDH)[a]	X	X	X	X		X	X	X	X	X
AST, ALT, ALP, and Tbili[a,J]					X					
Chemistry cont. (Free T3, Free T4, TSH)[a]	X	X		X		X	X	X	X	X
Chemistry cont. (Amylase and lipase)[a]	X	X		X		X	X	X	X	X
Testosterone (males only)	X									
Urinalysis[a,c]	X	X		X		X	X	X	X	X
Coagulation parameters (PT, aPTT, INR)[a,d]	X									
Serum pregnancy test (Urine test only pre-dose on first day of ensartinib and first day of combination drug)[a]	Up to 1 week before Tx start	X		X			X		X	
Specimens for Other Peripheral Blood Assays										
Whole blood for (PBMC and plasma) for flow cytometry and biological assays)[a]	X			X			X		X	
Blood for Biomarker analyses[a]	X			X			X		X	
Tumor Biopsy										
Biopsy (or FFPE slides) for tumor microenvironment[h]	X[h]		X[h]							
Long Term Follow-up										
Overall Survival										
Progression Free Survival										

3.2.1 - Flowchart for Subjects who Proceed with Combination Therapy after Run-in (cont.)	Treatment (4 weeks/cycle)							On Study Follow-up[f]			Post Study Follow-up
	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Optional Study Treatment Extension[i]				
Study Week	25	29	33	37	41	45		Last Study Drug Dose +28 (±4) days	Last Study Drug Dose +56 (±4) days	Last Study Drug Dose + 91 (±7) days End of Study	Every 6 months up to 5 years post initiation of treatment
Cycle Day	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)	1 (±3)				
Cumulative Study Day	169	197	225	253	281	309					
Treatment											
Durvalumab (1500 mg)	X	X	X	X	X	X	X[i]				
Ensartinib (X-396) (oral; see Sections 3.1.7.1 and 3.1.7.2)	daily	daily	daily	daily	daily	daily	daily				
Tumor & Disease Assessments											
Disease Staging (date/stage at 1st diagnosis and at study entry)											
Disease Assessment by irRECIST/RECIST[a]	X		X		X		Q8W starting on Week 49 or SOC	Q8W starting 8 weeks after last disease assessment			
Study Procedures & Examinations											
Eligibility Assessment and Informed Consent (IC)[e]											
Demographics (incl. DoB; sex; height; race; ethnicity)											
Medical history											
Physical Exam (incl. weight and ECOG Perf Status)[b]	X	X	X	X	X	X	X[i]	X	X	X	
12-Lead ECG[a]		X		X		X	Q8W starting on Week 53	X			
Vital Signs (T, HR, BP, RR)[g]	X	X	X	X	X	X	X[i]	X	X	X	
Concomitant Medications / Procedures	X	X	X	X	X	X	X[i]	X	X	X	
Adverse Events (starting or worsening after IC)[f]	X	X	X	X	X	X	X[i]	X	X	X	
Specimens for Routine Laboratory Procedures											
Blood Hematology (CBC, differential, platelets)[a]	X	X	X	X	X	X	X[i]	X	X	X	
Chemistry (glucose, BUN, creat., Na, K, Cl, CO_2, Ca, Mg, total protein, albumin, Tbili., AST, ALT, ALP, LDH)[a]	X	X	X	X	X	X	X[i]	X	X	X	
AST, ALT, ALP, and Tbili[a,J]											
Chemistry cont. (Free T3, Free T4, TSH)[a]	X	X	X	X	X	X	X[i]	X	X	X	
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X[i]	X	X	X	
Testosterone (males only)											
Urinalysis[a,c]	X	X	X	X	X	X	X[i]	X			
Coagulation parameters (PT, aPTT, INR)[a,d]								X			
Serum pregnancy test (Urine test only pre-dose on first day of ensartinib and first day of combination drug)[a]	X		X		X		Q8W starting on Week 49	X		X	
Specimens for Other Peripheral Blood Assays											
Whole blood for (PBMC and plasma) for flow cytometry and biological assays)[a]	X		X		X	X	Week 49	X			
Blood for Biomarker analyses[a]	X		X		X	X	Week 49	X			
Tumor Biopsy											
Biopsy (or FFPE slides) for tumor microenvironment[h]								optional			
Long Term Follow-up											
Overall Survival											X
Progression Free Survival											X

Footnotes for Flowchart 3.2.1

a: pre durvalumab dose, when applicable. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results	
are reviewed before dosing.	
b: Full physical examination at baseline; targeted physical examination at other timepoints	
c: Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.	
d: Coagulation tests: prothrombin time, aPTT and INR – only performed at Screening and as clinically indicated.	
e: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart	
f: See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration	
g: See Section 6.4 for assessment of vital signs before/during/after durvalumab	
h: A fresh tissue biopsy will be required prior to treatment with ensartinib and following the run-in period but before initiation of durvalumab (up to	
14 days prior to initiation of durvalumab). These biopsies should include a minimum of 3 cores from lung tissue and minimum 4 cores from any other site.	
If subjects are ALK inhibitor naïve, either archival tissue or pre-treatment biopsy will be acceptable. See Section 4.3.1.1 for details	
-Optional core biopsies will be obtained at the time of tumor progression or at the completion of treatment from subjects who consent to this procedure.	
-If possible, a minimum of 8 subjects will have fresh tissue sampling from which fine needle aspiration (FNA) can be also obtained for immune profiling	
i: Dosing/assessments for subjects who continue treatment after completion of 12 cycles (Core Study). Durvalumab dose and assessments for both drugs	
will continue every 4 weeks starting on Week 49 (unless otherwise indicated) until PD or until treatment is discontinued by the Investigator.	
J: In addition to the pre-durvalumab testing Q4W, AST, ALT, ALP, and Tbili will be performed at 2 weeks after the durvalumab dose for Cycle 1 of the comb.therapy. See Section 3.1.8.1.	

3.2.2 Flowchart for Subjects who Continue Treatment with Ensartinib (X-396) Monotherapy after Run-in

3.2.2 - Flowchart for Subjects who Continue Treatment with Ensartinib (X-396) Monotherapy after Run-in (and <u>do not</u> proceed with Combination Therapy)[a]	**Post Run-in Monotherapy[a]**	**Ensartinib On Study Follow-up**	**Post Study Follow-up**
		Last dose of Ensartinib + 30 days	Every 6 months up to 5 years post initiation of treatment
Treatment			
Ensartinib (X-396) – oral	**daily**		
Tumor & Disease Assessments			
Disease Assessment by RECIST	**Q8W**	**X**	
Study Procedures & Examinations			
Physical Exam (incl. weight and ECOG Perf Status)	**Q4W**	**X**	
12-Lead ECG	**Q8W**	**X**	
Vital Signs (T, HR, BP, RR)	**Q4W**	**X**	
Concomitant Medication / Procedure	**Q4W**	**X**	
Adverse Events (starting or worsening after IC)	**Q4W**	**X**	
Specimens for Routine Laboratory Procedures			
Blood Hematology (CBC, differential, platelets)	**Q4W**	**X**	
Chemistry (glucose, BUN, creat., Na, K, Cl, CO_2, Ca, Mg, total protein, albumin, Tbili., AST, ALT, ALP, LDH)	**Q4W**	**X**	
Urinalysis	**Q8W**	**X**	
Serum pregnancy test	**Q8W**	**X**	
Long Term Follow-up			
Overall Survival			X
Progression Free Survival			X
a: Drug administration/assessments for subjects who continue treatment with ensartinib (daily) after run-in period, according to Section 3.1.7.1;			
- safety assessments will continue every 4 weeks (unless otherwise indicated) until PD or until treatment is discontinued by the Investigator.			
- final safety assessments should be completed within 30 days of study completion; adverse events should continue to be collected			
for 30 days after last dose of study drug.			
Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed at every assessment point			
Q4W = every 4 weeks; Q8W = every 8 weeks			

4 Study Objectives and Endpoints

Primary Objective [Endpoints]	**Phase 1 Dose Escalation Phase:** *Recommended Combination Dose (RCD)* *Safety and Tolerability* [CTCAE 4.03, including DLTs and RCD] **Expansion Phase:** *Safety and Tolerability* [CTCAE 4.03]
Secondary Objectives [Endpoints]	**Dose Escalation and Expansion Phases (all subjects):** *Clinical Efficacy by irRECIST and RECIST 1.1* [PFS rate and ORR at 8 and 24 weeks, overall best response, DCR, DoR, OS]
Exploratory Objectives [Endpoints]	**Dose Escalation and Expansion Phases (all subjects):** *Biologic Activity* [Effects on Tumor Microenvironment, Immune Response]
DLT=Dose-limiting Toxicity; RCD=Recommended Combination Dose; ORR=Objective Response Rate; DCR=Disease Control Rate; DoR=Duration of Response; PFS=Progression-free Survival; OS=Overall Survival; CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST = Response Evaluation Criteria in Solid Tumors; irRECIST=immune-related RECIST	

4.1 Safety and Tolerability

Assessment of safety and tolerability will be performed by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the Investigators.

4.1.1 Endpoints and Assessment Methods

Clinical laboratory tests, vital signs and weight measurements, physical exams, ECG, ECOG performance status evaluation, imaging scans and any other medically indicated assessments, including subject interviews, will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. The Investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as adverse events. All treatment-emergent clinically significant abnormalities and deteriorations from time of signing the informed consent to the end of study visit will be recorded in the Case Report Forms (CRFs) as adverse events and graded according to the CTCAE Version 4.03. See further adverse event documentation and reporting requirements in Section 7.1.

For the dose escalation phase, DLTs and RCDs will be assessed as per Sections 3.1.9 and 3.1.7.2, respectively.

4.1.2 Subject Evaluation and Statistics

The **Per-Protocol (PP) Population for DLT assessment** includes:

- All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9
- All subjects with no DLT who received at least 75% of the scheduled doses of durvalumab and ensartinib drugs as well as respective safety assessments, without major protocol violations, over the entire DLT Evaluation Period (as defined in Section 3.1.9).

Refer to Section 3.1.11 for subject replacements.

The **Safety Population** is defined as all subjects who receive at least one dose of either of the study drugs.

In the Dose Escalation Phase, for the primary endpoint of determining DLTs and the RCD, the analysis of safety and tolerability will be based on the **PP Population for DLT Assessment.**

In both phases (escalation and expansion), the overall analysis of safety and tolerability will be based on the **Safety Population.**

Appropriate summaries of AEs, SAEs, laboratory data and vital signs data will be presented for the Safety Population overall and by cohort. Adverse events will be coded using the MedDRA dictionary. Incidences of treatment-emergent adverse events (TEAE, those events that started after dosing or worsened in severity after dosing) will be presented overall and by maximum severity and relationship to study drugs.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. Additionally, for each continuous hematology and chemistry parameter, descriptive statistics will be presented for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented for the changes in vital signs from baseline to each post-treatment assessment time point.

4.2 Clinical Efficacy

4.2.1 Endpoints and Assessment Methods

Clinical efficacy will be assessed by irRECIST and RECIST 1.1 (see Section 8.5), measuring progression free survival (PFS) rate and objective response rate (ORR) at 8 and 24 weeks based on disease assessments at the scheduled Weeks 9 and 25 visits, as well as overall best response, disease control rate (DCR), duration of response (DoR), and overall survival (OS). Tumor disease assessments will be made at a minimum of every 8 weeks on study. See the sections below for additional details.

For the primary analysis, all efficacy endpoints will be assessed at the completion of the On Study Follow-up or completion of 12 cycles of therapy.

PFS and OS will be updated at yearly intervals during the Post Study Follow-up and can be provided as addenda to the final report.

4.2.1.1 Objective Response Rate (ORR)

ORR is defined as the percentage of subjects meeting criteria of Complete Response (CR) or Partial Response (PR) with confirmation over a period of at least 4 weeks.

4.2.1.2 Disease Control Rate (DCR)

DCR is defined as the percentage of subjects meeting criteria of Stable Disease (SD), PR, or CR with confirmation over a period of at least 4 weeks.

4.2.1.3 Duration of Response (DoR)

DoR is defined as the interval between the date of earliest determination of CR or PR to the date of earliest determination of PD, or to the date of death, if PD does not occur.

4.2.1.4 Progression-free Survival (PFS)

PFS is defined as the interval between the date of first dose to the date of earliest determination of Progressive Disease (PD), or to the date of death, if PD does not occur. Subjects without documentation of progression at the time of the analysis will be censored at the date of last response assessment. Subjects with no tumor response assessment will be censored at the start date of the treatment. Subjects who discontinued treatment or withdrew from the study for reasons other than documented PD or death will be censored at the date of last response assessment prior to discontinuation or withdrawal.

4.2.1.5 Overall Survival (OS)

OS is defined as the interval between the date of first dose until the date of death or the date of last follow-up. Subjects who are still alive will be censored on the date of last follow-up. Every effort will be made to follow subjects for OS after they discontinue the study.

4.2.2 Subject Evaluation and Statistics

The Intent-To-Treat (ITT) Population is defined as all subjects who receive at least one dose of any of the study drugs. The Per-Protocol (PP) Population for clinical efficacy is defined as all subjects who received at least 75% of the scheduled doses of the study drug over the first 2 cycles of combination therapy, as well as, respective disease assessments, without major protocol violations.

All efficacy analyses will be performed for both ITT and PP populations for all cohorts and for the expansion cohort separately. Tumor Response will be summarized and analyzed descriptively. A 95% CI based on binomial distribution will be constructed for the estimated DCR and ORR at 8 and 24 weeks.

The number and percentage of subjects who died or had a confirmed progression, who survived without a confirmed progression, and who were lost to follow-up (unknown survival and/or progression status) will be summarized. PFS rate at 8 and 24 weeks and the corresponding 95% CIs will be calculated based on Kaplan-Meier product limit estimates and will be displayed along with the corresponding number of subjects at risk.

PFS and OS will be summarized using the 25^{th} percentile, Median, and 75^{th} percentile as well as the minimum and maximum survival time, calculated by Kaplan-Meier method, and will be displayed graphically.

4.3 Biological Activity

4.3.1 Endpoints and Assessment Methods

Samples for exploratory assessment of correlative immunologic response will be collected according to the Study Flowchart in Section 3.2.1. Correlative data will be obtained to assess the effects of the regimen on the tumor microenvironment and biological activity in blood. The exploratory assessments will help to determine whether protein expression, mutational burden, gene expression, soluble PD-L1 or immune cell profiling can be associated with clinical benefit or resistance to combination therapy.

4.3.1.1 Tumor Microenvironment

This study will examine biopsies taken prior to ensartinib initiation, after ensartinib exposure (following the run-in period) and optionally at the time of progression or end of combination therapy (end of study, if clinically feasible) to evaluate PD-L1 expression as assessed by immunohistochemistry, neoantigen signature and immune biomarker expression in tissue, and to assess the correlation of these evaluations with clinical response as well as changes in profiling associated with resistance. Analyses may include the following:

- Mutational burden, gene expression profiling, and immune profiling from before therapy
- Immune markers of response and resistance in pre-treatment and post-treatment tumor biopsies.

A minimum of 25 slides (5-µm, formalin-fixed, paraffin embedded (FFPE)) will be required.

A fresh tissue biopsy will be required prior to treatment with ensartinib and following the run-in period with ensartinib but before initiation of durvalumab (up to 14 days prior to initiation of durvalumab). These biopsies should include a minimum of 3 cores from lung tissue and minimum 4 cores from any other site. If subjects are ALK inhibitor naïve, either archival tissue or pre-treatment biopsy will be acceptable. Optional core biopsies will be obtained at the time of tumor progression or at the completion of treatment from subjects who consent to this procedure. A minimum of 3 cores will be required.

If possible and as determined by the Investigator, a minimum of 8 subjects will have fresh tissue sampling from which fine needle aspiration (FNA) will also be obtained for immune profiling.

Remaining core biopsies will be formalin-fixed and paraffin-embedded as per institutional standards for further evaluation with IHC or tumor DNA/RNA extraction for sequencing or nanostring.

4.3.1.1.1 Immunohistochemistry

Quantitative immunofluorescence will be used to evaluate multiple immune biomarkers simultaneously in FFPE archival tissue or in pre- and post- treatment biopsy samples as available.

PD-L1 has been examined in studies of PD-1/PD-L1 inhibitors with mixed results in terms of prevalence and impact on clinical benefit from anti-PD1/PD-L1 therapy, although this has been

attributed to variability in different assays and in different definitions of positivity. It is unknown how the introduction of ALK inhibition may alter PD-L1 expression and the immune microenvironment and whether that may influence outcomes to combination therapy.

In this study, a pre-treatment biopsy will allow the evaluation of PD-L1 and other immune biomarkers to determine correlation with response to combination therapy. A post run-in biopsy will also be performed in order to assess changes in PD-L1 that may have occurred as a result of ALK inhibition. In addition to PD-L1 immunohistochemistry, CD3 immunostaining will be performed to evaluate the degree of immune infiltrate in tumor specimens pre- and post-therapy. Finally, other markers of immune suppression (FoxP3 to stain T regulatory cells, TIM-3, Lag-3 and others) may be evaluated.

4.3.1.1.2 DNA sequencing

Whole-exome sequencing (WES) and targeted next-gen sequencing will be performed, as feasible, on pre-treatment, post run-in, and post combination treatment biopsies (as available). The targeted sequencing (Oncopanel) is a cancer genomic assay performed at Dana Farber Cancer Institute to detect somatic mutations, copy number variations, and structural variants in tumor DNA that surveys exonic DNA sequences of 275 cancer genes and 91 introns across 30 genes for rearrangement detection.

4.3.1.1.3 Gene expression

Inflammatory or immune-related gene expression signatures may serve as predictors of clinical benefit beyond PD-L1 expression and may be evaluated in a subset of biopsies.

4.3.1.1.4 Immune profiling

Immune profiling in tumor biopsies collected pre and post durvalumab treatment (as clinically feasible) will be performed to evaluate correlates of response and resistance. FNA samples will be used, if available.

4.3.1.2 Biological Activity in Blood Samples

Blood samples (PBMCs and plasma) will be collected according to Section 3.2 for evaluation of PBMC profile by flow cytometry, cytokine profile, soluble PD-L1 analysis, and next-gen sequencing of circulating tumor DNA (to evaluate ALK, KRAS, EGFR fusions or mutations). Blood may also be used for the evaluation of cytokine profiles and exosomal profiling.

4.3.2 Subject Evaluation and Statistics

Only subjects who receive at least 1 dose of each drug and who provide the baseline and at least 1 on-treatment sample (if applicable) will be evaluated. As these analyses represent exploratory evaluations of potential biomarkers of response or resistance to therapy, descriptive statistics will be used to describe findings and potential relationships to outcomes to therapy.

The exploratory pharmacodynamic assessment of the immunologic changes in the tumor microenvironment will include the correlation between clinical activity and the expression level of PD-L1 and tumor-infiltrating lymphocyte (TILs) changes in biopsies pre and post treatment. The association between response and PD-L1 expression overall and within each cohort will be assessed descriptively. Confidence intervals for the overall odds ratio and the odds ratio within

each cohort will be presented. The association between response and TILs changes (increase, decrease, or no change) will be evaluated similarly.

All other exploratory results will be summarized descriptively.

5 Subject Eligibility

NOTE: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.

5.1 Inclusion Criteria

*Eligible subjects **must fulfill** all of the following criteria:*

<table>
<tr><td>1.</td><td>Histologic confirmation of metastatic NSCLC. Subjects must have confirmed ALK rearrangement as assessed by IHC. Subjects may have had prior therapy with ALK inhibitors (other than ensartinib) or be ALK inhibitor naïve. ALK inhibitor naïve subjects will be informed of the availability of approved ALK inhibitors.</td></tr>
<tr><td>2.</td><td>Measurable disease according to RECIST 1.1, defined as ≥ 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded for non-lymph node lesions, shortest diameter to be recorded for lymph node lesions). Each lesion must be ≥ 10 mm when measured by CT, MRI, or caliper measurement by clinical examination or ≥ 20 mm when measured by chest x-ray.</td></tr>
<tr><td>3.</td><td>Willing to provide a fresh pre-treatment biopsy; however, if subject is ALK inhibitor naïve, either archival or pre-treatment biopsy will be acceptable.</td></tr>
<tr><td>4.</td><td>Asymptomatic subjects with surgically treated brain metastases must be ≥ 14 days post surgery at the time of first dosing, while clinically stable with no requirement for steroids.
Asymptomatic subjects with radiation-treated brain metastases may enter the study immediately after completion of the radiation (and be off steroids, if applicable).
Symptomatic subjects (those experiencing headache, seizure etc.), must have been relieved from all symptoms of their CNS disease, and must have completed radiation and be off steroids prior to first dosing (anti seizure medicine permitted).</td></tr>
<tr><td>5.</td><td>Laboratory parameters for vital functions should be in the normal range. Laboratory abnormalities that are not clinically significant are generally permitted, except for the following laboratory parameters, which must be within the ranges specified, regardless of clinical significance:
<table>
<tr><td>Hemoglobin</td><td>≥ 9 g/dL</td></tr>
<tr><td>Neutrophil count</td><td>≥ 1.5 x 10^9/L</td></tr>
<tr><td>Platelet count</td><td>≥ 100,000/mm^3</td></tr>
<tr><td>Serum creatinine, or Creatinine Clearance</td><td>≤ 1.5x Institutional Upper Limit of Normal (ULN), or ≥ 50 mL/min (by Cockcroft-Gault formula)</td></tr>
<tr><td>Serum total bilirubin</td><td>≤ 1.5 × ULN (except for subjects with Gilbert's syndrome who will be allowed after consultation with their physician)</td></tr>
<tr><td>AST/ALT</td><td>≤ 2.5 x ULN</td></tr>
<tr><td>Alkaline phosphatase</td><td>≤ 2.5 x ULN</td></tr>
</table></td></tr>
<tr><td>6.</td><td>ECOG Performance Status ≤ 2.</td></tr>
<tr><td>7.</td><td>Age ≥ 18 years.</td></tr>
<tr><td>8.</td><td>Able and willing to provide valid written informed consent.</td></tr>
</table>

9.	Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up
10.	Body weight > 30 kg

5.2 Exclusion Criteria

*Subjects **<u>may not</u>** enter the study if they fulfill any of the following criteria:*

1.	Treatment with an investigational agent within 4 weeks of starting treatment, and any prior drug-related toxicity (except alopecia) should have recovered to Grade 1 or less.
2.	Prior treatment with anti-PD-1, PD-L1 (including durvalumab), or CTLA4, or ensartinib (X-396).
3.	Active, suspected or prior documented autoimmune disease (including but not restricted to inflammatory bowel disease, celiac disease, Wegner's granulomatosis, Hashimoto's thyroiditis, rheumatoid arthritis, systemic lupus, scleroderma and its variants, multiple sclerosis, myasthenia gravis). Vitiligo, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted.
4.	Subjects with clinically significant cardiovascular disease, including: a. New York Heart Association (NYHA) Class II or higher congestive heart failure. b. Myocardial infarction, unstable angina, cerebrovascular accident or transient ischemic attack within 6 months of start of study drug (Day -28). c. Clinically significant supraventricular or ventricular arrhythmia. d. QTcF ≥ 450 ms (male) or QTcF ≥ 470 ms (female). e. Clinically uncontrolled hypertension.
5.	History of pneumonitis or interstitial lung disease, or any unresolved immune-related adverse events following prior therapy.
6.	Major surgery within 4 weeks of starting treatment (or scheduled for surgery during the projected course of the study).
7.	Women of child bearing potential who are pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) or nursing.
8.	**Female subjects of childbearing potential** who are sexually active with a non-sterilized male partner must use at least one <u>highly effective</u> method of contraception (see table below) from the time of screening and must agree to continue using such precautions for 90 days after the final dose of investigational products. Non-sterilized male partners of a female subject must use male condoms plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug

	washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female subjects should refrain from breastfeeding throughout the period described above. Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Females will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply: • Females <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy). • Females ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy. **Non-sterilized male subjects who are sexually active with a female partner of childbearing potential** must use male condoms plus spermicide from screening through 90 days after receipt of the final dose of investigational products. Male subjects should refrain from sperm donation throughout this period. Female partners (of childbearing potential) of a male subject must use a highly effective method of contraception (see table below) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Highly effective methods of contraception are described in the table below. 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). Acceptable highly effective methods of contraception are described in the following table:

	Highly Effective[a] Methods of Contraception
	Barrier/Intrauterine Methods / **Hormonal Methods**
	• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (e.g., Mirena®)[b] • "Implants":Etonogestrel-releasing implants: e.g. Implanon® or Norplan® • "Intravaginal devices": Ethinylestradiol and etonogestrel-releasing intravagibal devices: e.g. NuvaRing® • "Injection": Medroxyprogesterone injection: e.g. Depo-Provera® • "Combined Pill": Normal and low dose combined oral contraceptive pill • "Patch": Norelgestromin /ethinylestradiol releasing transdermal system: e.g. Ortho Evra® • "Minipill[c]": Progesterone based oral contraceptive pill using desogestrel: e.g. Cerazette®
	a - Highly effective (i.e. failure rate of <1% per year) b - This is also considered a hormonal method c - Cerazette® is currently the only highly effective progesterone based pill.
9.	Subjects who are immunosuppressed, including those with known immunodeficiency.
10.	Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
11.	History of severe allergic reactions to any unknown allergens or components of the study drugs.
12.	Other serious illnesses (e.g., serious infections requiring antibiotics, bleeding disorders).
13.	Mental impairment that may compromise compliance with the requirements of the study.
14.	Lack of availability for immunological and clinical follow-up assessment.
15.	Inability to swallow or retain oral medication, presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of ensartinib.
16.	Any condition that, in the clinical judgment of the treating physician, is likely to prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.
17.	History of allogeneic organ transplant
18.	Subjects must not donate blood while on study and for at least 90 days following the last durvalumab treatment.

5.3 Restrictions on Concomitant Therapies

5.3.1 Non-Permitted Concomitant Therapies

*Subject **may not** receive the following concomitant therapies during the study:*

1.	Systemic treatment with high-dose corticosteroids (greater than Prednisone 10 mg daily or equivalent) or other immunosuppressive treatments (e.g., methotrexate, chloroquine, azathioprine). See Section 5.3.2 for exceptions. [Wash-out period: 2 weeks prior to Day -28 (start of study drug).]
2.	Other cancer therapy (e.g., drug, non-palliative radiation, or immunotherapy). [Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day -28 (start of study drug); 6 weeks for nitrosoureas, 7 days for ALK TKIs].
3.	Live/attenuated vaccines 1 month prior to Day -28 (start of study drug) and for at least 6 months after the last dose of treatment.
The wash-out period prior to Day -28 (start of study drug) of the study for all non-permitted drugs should be at least 1 week, unless stated otherwise above.	

NOTE for ensartinib: Although only minimal QTc prolongation has been observed with ensartinib therapy to date, subjects will be monitored with electrocardiograms and electrolytes, and caution should be exercised if concomitant medications with known risk of Torsades de Pointes (see Section 8.7) are to be administered.

5.3.2 Permitted Concomitant Therapies

*Subject **may** receive the following concomitant therapies during the study:*

1.	Inhaled or oral steroids for treating mild to moderate asthma or allergies, or topical steroids for localized (< 5% of body surface area) dermatitis, not to exceed 10mg/day prednisone or bioequivalent corticosteroid.
2.	Oral steroids for the treatment of ensartinib-associated rash is permitted during ensartinib monotherapy only.
3.	Physiologic replacement of glucocorticoids as maintenance therapy for adrenal insufficiency. Standard doses of hydrocortisone for maintenance therapy are up to 10–20 mg/m2/day divided 2–4 times per day. For a subject with a body surface area (BSA) of 1.73 m^2, this translates to a total dose of up to 34.6 mg of hydrocortisone per day. The equivalent dose of dexamethasone is up to 1.2 mg per day. Some subjects may additionally receive mineralocorticoid-replacement maintenance therapy with fludrocortisone. The maintenance dose of fludrocortisone for this indication is 0.05–0.1 mg/day.
4.	NSAIDs, acetylsalicylic acid, and specific COX-2 inhibitors.
5.	Antihistamines and other non-steroidal anti-allergy medication.
6.	Hormone or hormone-related anti-cancer therapy.
7.	At the discretion of the Investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high-dose corticosteroids to treat immune-mediated adverse reactions. Subjects should receive full supportive care, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheal, and analgesics, and other care as deemed appropriate, and

	in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted; however, caution should be exercised and additional international normalized ratio (INR) monitoring is recommended.
All prescription and nonprescription drugs must be recorded in the concomitant medications section of the case report form (CRF), listing generic (preferably) or brand name, indication, dose, route, and dates of administration. All non-drug therapies must be recorded in the respective sections of the CRF.	

6 Study Drug Preparation and Administration

All study drugs are supplied by the Sponsor (see Section 7.2.8). Commercially available water for injection (WFI) and 0.9% (w/v) saline or 5% (w/v) dextrose will be supplied by each site. See Section 6.4 for monitoring of subjects after durvalumab doses.

6.1 Durvalumab (MEDI4736)

6.1.1 Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	*Expiration/retest dates are documented in the QA Disposition of Investigational Medicinal Product (IMP) Report.*		
Container Description	*Type:* Single use vial	*Material:* Glass	*Size:* 10 mL
Formulation	[redacted]		
Active Ingredient Content	*Mass/Weight:* 500 mg	*Volume:* 10mL	*Concentration:* 50 mg/mL
Storage Conditions	2°C–8°C (36°F–46°F) Do not freeze		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.1.2 Durvalumab Investigational Product Inspection

Each vial of durvalumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately. Please see Section 7.2.8 for additional details.

6.1.3 Durvalumab Preparation

Preparation of durvalumab and preparation of the intravenous bag dose are to be performed by the IP manager or designated personnel using aseptic technique. No incompatibilities between durvalumab and polyvinylchloride or polyolefin copolymers have been observed.

Dose Calculation:
Subjects will receive a fixed dose of durvalumab: 1500 mg Q4W for subjects > 30 kg.

NOTE: If a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of durvalumab as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.

The volume of durvalumab (in mL) to add to the IV bag is calculated as follows:

Volume of Durvalumab (mL)	=	Dose level (mg)	÷	Durvalumab Concentration (nominal 50 mg/mL)

Dose Preparation:
Durvalumab will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, and delivered through an IV administration set with a 0.2 or 0.22 µm in-line filter. A volume of diluent equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab. The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Example: For a 1500 mg dose (for subjects > 30 kg in weight), 30 mL of durvalumab is to be diluted in a 250 mL IV bag. First, 30.0 mL of diluent is removed from the IV bag, and then 30 mL of durvalumab is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Durvalumab does not contain preservatives; any unused portion must be discarded.

6.1.4 Durvalumab Administration

Following preparation of the dose, durvalumab will be administered according to the following guidelines:

- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational products. Fully functional resuscitation facilities should be available.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- Durvalumab must not be administered via IV push or bolus but as an IV infusion.
- Durvalumab solution should not be infused with other solutions or medications.
- Durvalumab must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- The entire contents of the IV bag should be administered as an IV infusion over approximately 60 (± 5) minutes, using a 0.2- or 0.22-µm in-line filter. [redacted]
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.
- The total time between needle puncture of the durvalumab vial to start of administration should not exceed 4 hours at room temperature, or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. [redacted]

[redacted]

- [redacted]

6.2 Ensartinib (X-396)

6.2.1 Study Drug Information

Manufacturer	Xcovery		
Expiration/Retest Date	Expiration/retest dates are documented on the Certificate of Analysis and/or stability certification.		
Container Description	Type: Bottle	Material: HDPE	Size: 60cc (30 capsules)
Formulation	Dry blend in capsule		
Active Ingredient Content	*Mass/Weight:* 25 or 100 mg	*Volume:* Not applicable	*Concentration:* Not applicable
Storage Conditions	Room temperature, 15°C to 30°C (59°F to 86°F)		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.2.2 Preparation

Not applicable

6.2.3 Administration

Subjects will receive a 4-week supply of ensartinib. At each study visit, they will return the unused portion to the study site; the number of pills returned will be counted to determine compliance.

Ensartinib is taken orally, once per day. It may be taken with or without food; however, subjects may tolerate the drug better (i.e., have fewer gastrointestinal side effects), if it is taken with food. It is recommended that the subjects take the medication at approximately the same time each day. The time of day for administration of study medication should be consistent.

6.3 Estimated Study Requirements

Drug	Requirements
Ensartinib (25 mg capsules)	1,000 bottles (30 capsules/bottle)
Ensartinib (100 mg capsules)	1,000 bottles (30 capsules/bottle)
Durvalumab	350 kits (4 vials/kit)

6.4 Monitoring of Durvalumab Dose Administration

Subjects will be monitored before, during and after durvalumab infusion with assessment of vital signs according to the table below:

Vital Signs Assessment on Study Drug Administration Days					
Drug	**Pre Dose**	**During Infusion**	**End of Infusion (± 5 minutes)**	**30 (± 5) Minutes Post Infusion**	**60 (± 5) Minutes Post Infusion**
Durvalumab	X	Every 15 (± 5) minutes	X	X	x

If a subject tolerates treatment well for the first 4 doses of durvalumab (i.e., no infusion reactions), subsequent infusions in that subject can be monitored according to the table below. A longer duration of observation after the end of infusion can be used if the Investigator deems it clinically necessary.

Vital Signs Assessment on study drug administration days (after first 4 doses)	**Pre Dose**	**During Infusion**	**End of Infusion (± 5 minutes)**	**15 (± 5) Minutes Post Infusion**
Durvalumab	X	Every 30 (± 5) minutes	X	X

6.5 Drug Overdose Management

There are no known antidotes available for durvalumab or ensartinib. Any overdoses with these drugs should be managed symptomatically. An overdose is defined as a subject receiving any dose in excess of that specified in this protocol by > 10%. All such overdoses must be reported, with or without associated AEs/SAEs, according to Section 7.1.2.2.

7 Administrative, Legal and Ethical Requirements

7.1 Documentation and Reporting of Adverse Events

7.1.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

N.B.: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of LICR studies to include any events, intercurrent diseases and accidents observed while the patient/subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods, under placebo or in a reference group receiving drug or non-drug therapy or no treatment.

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

1. Results in death,
2. Is life-threatening[A],
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly / birth defect or
6. Is another medically important condition[B].

A The term "life-threatening" in the definition of "serious" refers to an event in which the patient/subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

B Medically important conditions that may not result in death, be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient/subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

N.B.: The term "severe" is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient's life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.2 Additional Expedited Reporting Requirements for this Study

For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (see Section 7.1.6 for Sponsor contact information) and may result in submission of an SAE based on certain criteria outlined below:

- Pregnancy
- Overdose (as defined in Section 6.5)
- Hepatic Function Abnormality (as defined in Section 7.1.8)

7.1.2.1 Pregnancy

7.1.2.1.1 Maternal Exposure

Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the final dose of investigational product (see Section 5.2, #8).

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the drug under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs (see section 7.1.6). 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, the Investigator or other site personnel should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The Sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.1.2.1.2 Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the final dose of investigational product (see Section 5.2, #8).

Pregnancy of the subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

7.1.2.2 Overdose

Any overdose (as defined in Section 6.5) of a study subject, with or without associated AEs/SAEs, is required to be reported **within 24 hours of knowledge of the event to the Sponsor**. If the overdose results in an AE, the AE must also be recorded as an AE according to Section 7.1.5. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE according to Section 7.1.6. There is currently no specific treatment in the event of an overdose of the study drugs. The Investigator will use clinical judgment to treat any overdose. See Section 6.5 for additional details.

7.1.2.3 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 7.1.8) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" **within 24 hours of knowledge of the event** to the Sponsor, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed (see Section 7.1.6 for Sponsor contact information).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the Investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the Investigator and evaluated by the Sponsor and MedImmune/AstraZeneca.

7.1.3 Severity of an Adverse Event

The severity of all serious and non-serious adverse events should be assessed according to the National Cancer Institute CTCAE Scale (Version 4.03).

7.1.4 Relationship of Adverse Events to Study Drug

The relationship of all serious and non-serious adverse events to the investigational agent(s) will be determined by the Investigator on the basis of their clinical judgment, using one of the following terms (in accordance with NCI Guideline "Expedited Adverse Event Reporting Requirements for NCI Investigational Agents", NCI Cancer Therapy Evaluation Program, January 2001):

Definitely related (The AE is *clearly related* to the investigational agent)
Probably related (The AE is *likely related* to the investigational agent)
Possibly related (The AE *may be related* to the investigational agent)
Unlikely related (The AE is *doubtfully related* to the investigational agent)
Unrelated (The AE is *clearly not related* to the investigational agent)

N.B.: When making the assessment on causality, it should be taken into consideration that immune-therapeutic agents have the potential to cause very late and/or permanent effects on

the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal relationship. Information provided in the IB and/or in "Background" of this protocol may support these evaluations.

7.1.5 General Reporting Requirements

All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur:

a. from the date of signing the informed consent, and
b. until the off-study date or 90 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment).

Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 90 days after the last dose of the last study treatment (regardless of initiation of another therapy).

7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements

In addition to the General Reporting Requirements specified in Section 7.1.5, all events meeting the criteria for an SAE per Section 7.1.1, irrespective of suspected causation, must be reported by the Investigator to the Sponsor's Drug Safety Contact (primarily) or, alternatively, to the Primary Sponsor Contact, within 24 hours of becoming aware of the event (see contact information below). SAEs should be reported via the Medidata RAVE data capture system (which utilizes "Safety Gateway"), using the respective Adverse Event and Safety Case Summary electronic CRFs (eCRFs). This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration. In the event that the SAE cannot be reported via Medidata RAVE, the SAE should be reported using the "Initial Serious Adverse Event Report Form," provided by the Sponsor.

Note: If an SAE cannot be reported via Medidata RAVE or the "Initial Serious Adverse Event Report Form" within 24 hours of becoming aware of the event, the Sponsor's Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact, must be contacted by phone or email within 24 hours of becoming aware of the event. In this case, the phone or email notification can then be followed up through Medidata RAVE or an "Initial Serious Adverse Event Report Form" within one working day of the event.

If the "Initial Serious Adverse Event Report Form" is being used, the expedited reports should be directed by fax or e-mail to the Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact. Studies utilizing Medidata RAVE (and the "Safety Gateway") built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to Medidata RAVE and "Safety Gateway" procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact (see table below for contact information).

In urgent cases, pre-notification via phone or informal e-mail should be considered.

Drug Safety Contact:	*Primary Sponsor Contact:*
[redacted] Senior Manager, Drug Safety Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave, 28th Floor New York, New York 10017 [redacted]	[redacted] Director Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave, 28th Floor New York, New York 10017 [redacted]

Serious adverse events must also be reported by the Principal Investigator to the respective Institutional Review Board after being assigned a serious adverse event tracking number by the Sponsor. Institutional Review Boards may have specific rules on which Adverse Events need to be reported expeditiously, as well as, the time frames for such reporting.

SAE Reports will be evaluated by the Sponsor's Medical Monitor. Regulatory authorities and other Investigators, as well as institutional and corporate partners, will be informed by the Sponsor as required by ICH guidelines, laws and regulations in the countries where the investigational agent is being administered. In particular, SAEs that are unexpected and for which a causal relationship with the study drug cannot be ruled out, will be reported by the Sponsor within 15 calendar days; if they are life-threatening or fatal, they will be reported within 7 Calendar days.

Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement.

7.1.7 Serious Adverse Event (SAE) Follow-up Requirements

Subjects experiencing SAEs should be followed closely until the condition resolves or stabilizes, and every effort should be made to clarify the underlying cause. Follow-up information related to SAEs must be submitted to the Sponsor as soon as relevant data are available.

7.1.8 Adverse Events of Special Interest (AESIs)

[redacted]

[redacted]

7.2 Administrative Sponsor Requirements

7.2.1 Study Master Files

The Investigator must retain a Sponsor-specified comprehensive and centralized filing system ("Study Master File") of all trial-related documentation that is suitable for inspection by the Sponsor and regulatory authorities. Upon completion of the trial, the Investigator is required to submit a summary report to the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time determined by the Sponsor. No part of the Study Master File shall be destroyed or relocated without prior written agreement between the Sponsor and the Investigator.

7.2.2 Case Report Form Data Collection

Electronic Case Report Forms (eCRF) will be completed in accordance with respective guidance and after training provided by the Sponsor. The use of eCRFs encompasses electronic data entry, query management and sign-off. Systems used for electronic data capture will be compliant with FDA regulations 21 CFR Part 11 and within the constraints of the applicable local regulatory agency guidelines (whichever provides the greatest protection to the integrity of the data).

All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.

The Investigator will sign and date the completed eCRF sections. This signature will indicate a thorough inspection of the data in the eCRF and will certify its content.

7.2.3 Language

The protocol is written in English. All correspondence between the study site and the Sponsor should be maintained in English. Case Report Forms must be completed in English. All written material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood, and be in the language appropriate for the trial site.

7.2.4 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site qualification, site initiation, routine monitoring and site close-out. Clinical Monitors and/or other sponsor staff will meet with the Investigator staff and require direct access to source data/documents. Such access may also be required for Institutional Review Board review, and regulatory inspection/audits. Direct access is defined as permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information will be exercised.

It is the Clinical Monitor's responsibility to inspect the CRFs at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to Good Clinical Practice guidelines. The Clinical Monitor will have access

to patient charts, laboratory reports and other subject records needed to verify the entries on the CRFs ("source data verification").

7.2.5 Protocol Amendments

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, Institutional Review Board and, if required, the regulatory authorities. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to such approvals. However, in this case, approval must be obtained as soon as possible after implementation. Implementation of administrative amendments that do not affect the safety of the subjects do usually not require prior Institutional Review Board approval, just notification.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documentation.

7.2.6 Premature Subject Withdrawal from Treatment or from Study

A subject may withdraw from study treatment or from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator and/or Sponsor have the right to withdraw subjects from treatment or from the study. Specific subject withdrawal criteria are listed in Section 3.1.10. Should a subject (or a subject's legally authorized representative) decide to withdraw from study treatment or from the study, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

For all subject withdrawals, a complete final evaluation should be made at the time of withdrawal. The appropriate form in the CRF should be completed with an explanation of why the subject is withdrawing, and an attempt should be made to perform a follow-up evaluation.

7.2.7 Early Trial Termination

Sponsor and Investigator have the right to terminate the study early. Specific study stopping rules are listed in Section 3.1.14. In such case, one party must notify the other in advance in writing about the intent of and the reasons for the termination. The Investigator must also notify the appropriate Institutional Review Board accordingly.

7.2.8 Study Drug Shipments and Accountability

Study drug shipments will be addressed to the Principal Investigator's authorized designee, preferably, the site's pharmacy. The recipient will verify the amount and condition of the drug and will return a signed Acknowledgment of Receipt to the shipper.

A drug dispensing log (inventory) will be kept by the study site, containing at least the following:

- the subject's identification (subject number and code)
- date and quantity of drug dispensed
- date and quantity of drug returned to the Investigator/pharmacy (if applicable)
- date and quantity of accidental loss of drug (if any)

These inventories must be made available for inspection by the Clinical Monitor. The Investigator is responsible for seeing to it that all used and unused trial supplies are accounted for. At the end of the study, the Clinical Monitor will also collect the original study drug dispensing records.

At the end of the study or as directed by the Sponsor, all used and unused supplies, including partially used or empty containers, will be disposed of or transferred as instructed by the Sponsor, and in accordance with local written procedures, if applicable. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log and signed-off by a second person. At the end of the study, the Clinical Monitor will collect the original drug disposition logs.

7.3 Regulatory, Legal and Ethical Requirements

7.3.1 Good Clinical Practice (GCP), Laws and Regulations

The Investigator must ensure that he/she and all authorized personnel for the study are familiar with the principles of Good Clinical Practice (GCP) and that the study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH Guidelines and applicable local laws and regulations, with the understanding that local laws and regulations take precedence over respective sections in the Declaration of Helsinki and/or the ICH Guidelines.

7.3.2 Informed Consent

The Investigator must obtain witnessed (if applicable) written informed consent from the subject or the subject's legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study procedures are performed. The subject should be given a copy of the informed consent documentation. The original signed and dated informed consent form must be retained in the study records at the study site, and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

7.3.3 Institutional Review Board

The Investigator must obtain written approval from the appropriate Institutional Review Board for the protocol and informed consent, and all amendments thereof, prior to recruitment of subjects and prior to shipment of investigational agents.

The Investigator must report Serious Adverse Events (SAEs) to the appropriate Institutional Review Board in accordance with the Institutional Review Board's rules and guidelines (see also Section 7.1).

The Investigator must assure that continuing review (at least once per year) of the study is performed by the Institutional Review Board throughout the duration of the study. If so required by the Institutional Review Board, the Investigator must provide study reports on an annual basis and upon completion of the study.

All correspondence with, and reports to, the Institutional Review Board must be maintained in the study files at the study site and copies must be sent to the Sponsor.

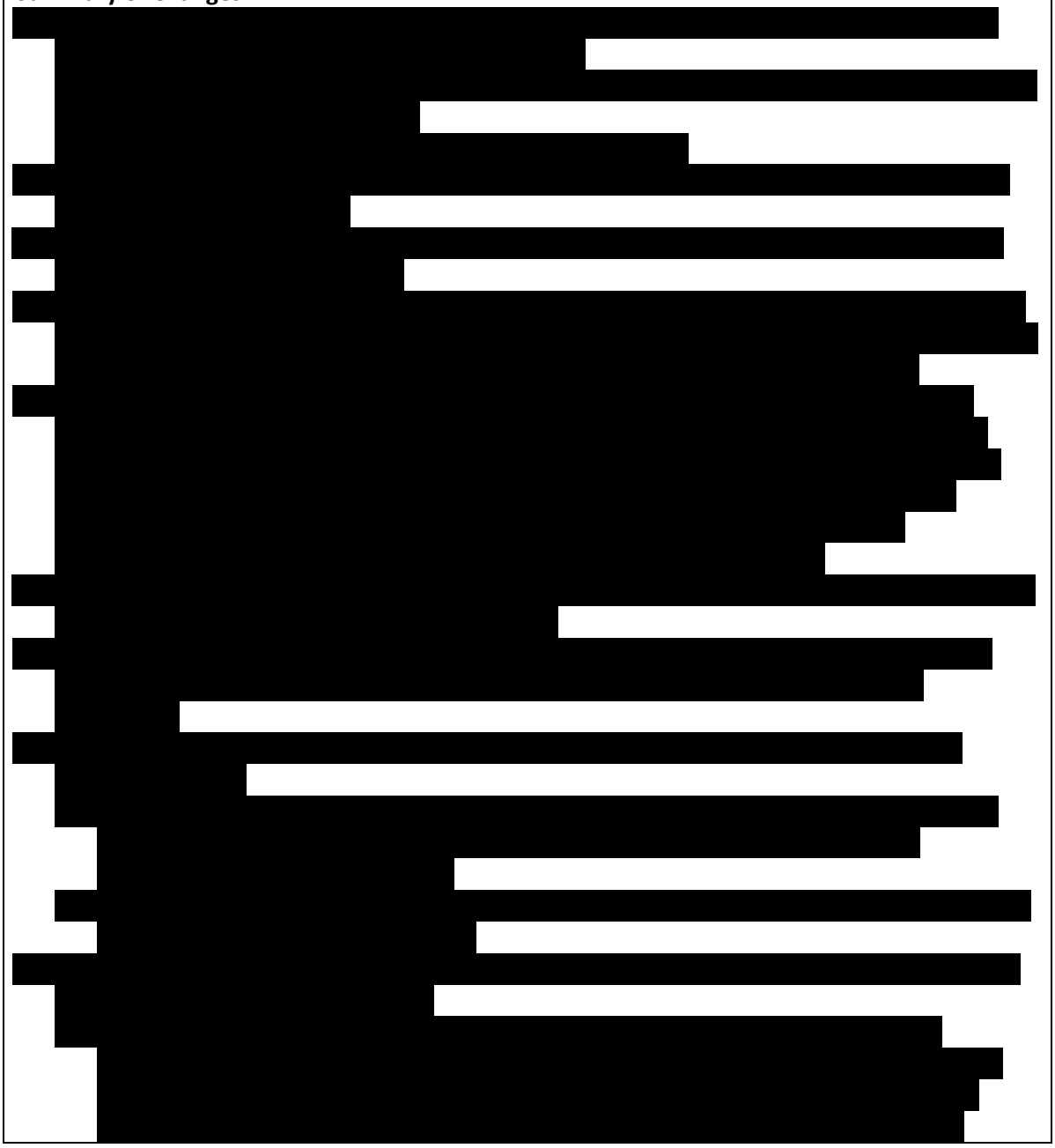
7.3.4 Subject Confidentiality

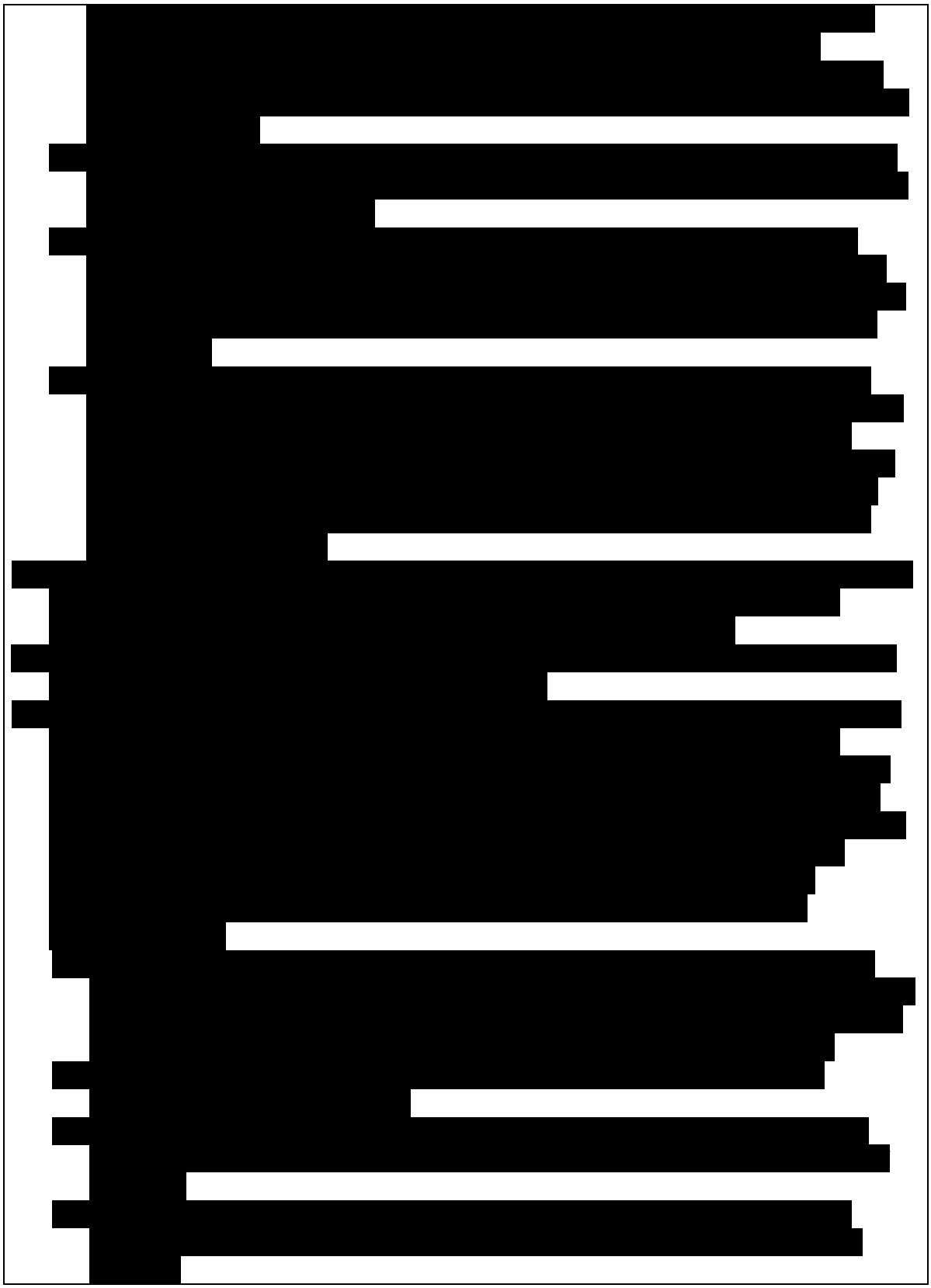
The Investigator must ensure that the subject's privacy is maintained. A subject should only be identified by their initials, date of birth and subject number on the CRFs or other documents submitted to the Sponsor. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential section of the study file by the Investigator.

The Investigator shall permit the Sponsor and authorized representatives of regulatory agencies to review the portion of the subject's medical record that is directly related to the study. As part of the informed consent process, the subject must have given written consent that his/her records will be reviewed in this manner.

8 Appendices

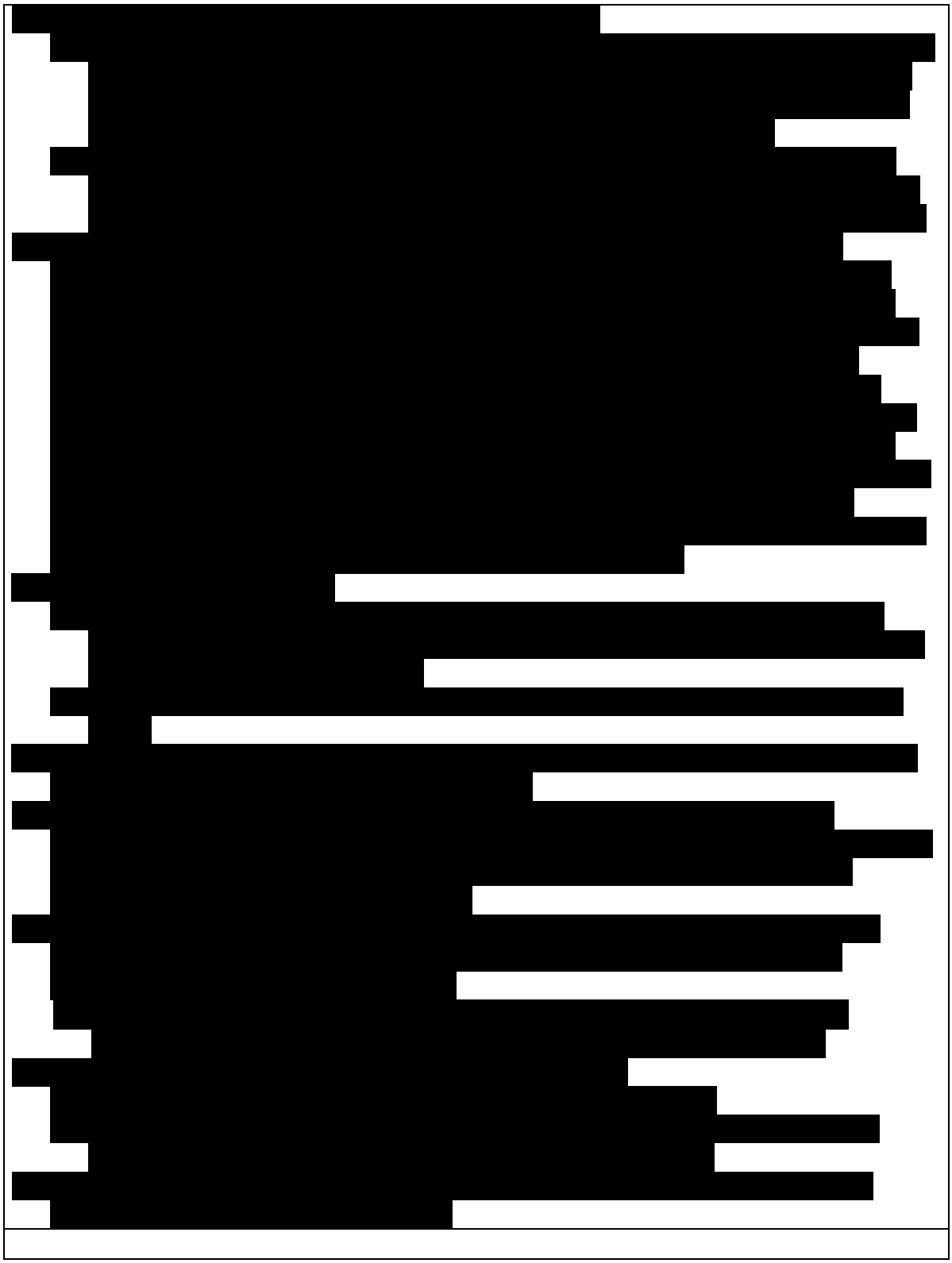
8.1 Protocol Version History

Original Issue **Issue date: 21-JUL-2016** **Summary of Changes:** not applicable
Amendment 1 **Issue date: 11-NOV-2016** **Summary of Changes:** 



Amendment 2
Issue date: 14-AUG-2017
Summary of Changes:

[redacted]



8.2 Participating Study Sites, Investigators and Staff, Laboratories, and Sponsor Information

This information is provided in the Clinical Study File.

8.3 Dose Adjustments and Delays for Durvalumab

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

8.3.1 Durvalumab Dose Modification Due to Toxicity

Durvalumab (MEDI4736) administration may be modified or discontinued as a result of toxicities as described in the table below.

Additional information and guidance regarding dose modification due to toxicity are provided from MedImmune in the following guidelines:

[redacted]

Dose modifications will not be required for AEs that are clearly not attributed to durvalumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Durvalumab (D) Dose Modification Due to Toxicity
Note: If D dosing is held temporarily until resolution of the event as per instructions below, treatment should resume at the next <u>scheduled</u> treatment date.
<u>Immune-related Adverse Events (irAEs)</u> Immune-related adverse events are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Maximum supportive care, including immunosuppressive medications, such as high dose steroids, is allowed to induce resolution of the event**. However, infliximab should not be used for management of immune-related hepatitis.** In addition to the criteria for permanent discontinuation of D depicted below, **<u>permanently discontinue D</u>** also for: • Any Grade rash with bullous skin formations. • 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/regimen. • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing. **Grade 1** • In general, no dose modification required. • For *pneumonitis/interstitial lung disease and myocarditis*, consider holding D dosing as clinically appropriate and during diagnostic work-up for other etiologies.

Durvalumab (D) Dose Modification Due to Toxicity
Grade 2 • In general, hold D until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue D permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of D may differ by event as detailed below. • For *pneumonitis/interstitial lung disease and myocarditis*, the decision to reinitiate D upon resolution shall be based upon treating physician's clinical judgment (as long as the event does not meet DLT criteria). • For *peripheral neuromotor syndromes*, such as *Guillain-Barre* and *Myasthenia Gravis*, follow general instructions above, but always discontinue D permanently if there are signs of respiratory insufficiency or autonomic instability. • For *endocrinopathies, other than isolated hypothyroidism*, follow general instructions above, but subjects may be retreated if the endocrinopathy is controlled and the subject is clinically stable while requiring steroid doses of ≤ 10 mg/day prednisone equivalent. • For *isolated hypothyroidism* managed with hormone replacement therapy, and for *sensory neuropathy/neuropathic pain*, holding D is at the discretion of the Investigator. • For *elevated creatinine* or *rash*, D should be held until resolution to ≤ Grade 1 or baseline. • For *vitiligo*, no dose modification required. **Grade 3** • In general, hold D until resolution to ≤ Grade 1, and after the end of any steroid taper, and discontinue D permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of D may differ by event as detailed below. • For *peripheral neuromotor syndromes (*such as *Guillain-Barre* and *Myasthenia Gravis),* apply respective Grade 2 rules. • For *endocrinopathies*, follow Grade 2 instructions above. • For *pneumonitis/interstitial lung disease, myocarditis, diarrhea/enterocolitis and elevated serum creatinine (e.g., nephritis or renal dysfunction)*, always discontinue D permanently. • For *asymptomatic increases of amylase or lipase* levels, hold D, and if complete work up shows no evidence of pancreatitis, D may be continued. • For *hepatitis*, discontinue D permanently for (1) transaminases or bilirubin not resolving to ≤ Grade 1 or baseline within 14 days, (2) transaminases > 8 × the upper limit of normal (ULN) or bilirubin > 5 × ULN, or (3) any case meeting Hy's law criteria (as defined in FDA Guidance Document "Drug-Induced Liver Injury"). • For *rash*, D should be held until resolution to ≤ Grade 1 or baseline. **Grade 4** • In general, discontinue D permanently. • For *endocrinopathies,* follow Grade 2 instructions above. • For *asymptomatic increases of amylase or lipase* levels, hold D, and if complete work up shows no evidence of pancreatitis, D may be continued.

Durvalumab (D) Dose Modification Due to Toxicity
Infusion-related Reactions **Grade 1** • The infusion rate of D may be decreased 50% or temporarily interrupted until resolution of the event. • Acetaminophen and/or antihistamines may be administered per institutional standards at the discretion of the Investigator. • Premedication for subsequent doses should be considered. • Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions. **Grade 2:** • **Same as Grade 1**, but consider giving subsequent infusions at 50% of the initial infusion rate. **Grade 3 and 4:** • **The infusion must be stopped i**mmediately and treatment permanently discontinued. • Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).
All other Adverse Events **Grade 1** • No dose modification required. **Grade 2** • Hold D until resolution to ≤ Grade 1 or baseline, and discontinue D permanently if such resolution does not occur within 60 days. **Grade 3** • Hold D. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume D administration at next scheduled dose. Otherwise, discontinue D permanently. **Grade 4** • In general, discontinue D permanently. • For isolated lab results, decision to discontinue should be based on accompanying clinical signs/symptoms and per Investigator's clinical judgment in consultation with the Sponsor.

8.3.2 Durvalumab Dose Modification Not Due to Treatment-related Toxicities

Durvalumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply:

(1) The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 21 days. All resulting protocol deviations should be documented.
(2) If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.

(3) If the dosing interruption is ≤ half the planned dosing interval, the originally planned dose should be given and the next dose(s) should be adjusted in accordance with #1, if necessary.
(4) If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary

8.4 Ensartinib (X-396) Toxicity Management and Dose Modification

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3 or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician.

NOTE: Up to 2 dose reductions (225 to 200 mg; 200 to 150 mg; or 150 to 100 mg) per subject are allowed.

Subjects whose treatment is delayed due to drug-related toxicity will discontinue study drug or will resume treatment when toxicity has improved (as long as the toxicity resolves within 4 weeks) according to the dose modifications below. Treatment with ensartinib will be held in any subject experiencing a DLT as described in Section 3.1.9 at any time during the study.

As noted, dose reductions for toxicity or based on the clinical judgment of the treating physician will be allowed. If persistent toxicity occurs despite the dose reductions, the Investigator should consider removing the subject from the study.

Dose Modifications Due to Drug-Related Hematologic Toxicity

If drug-related hematologic toxicity occurs, treatment with ensartinib should be held (see table below) and re-evaluated in at least 1 week. Absolute neutrophil count (ANC) and platelets should be monitored as is clinically appropriate, but at least weekly, until recovery. For resumption of treatment, see table below. If ANC and/or platelets do not recover within 4 weeks, the subject should be permanently discontinued from trial treatment.

Dose Modifications Due to Drug-related Hematologic Toxicities

Event	Ensartinib Dose [c]
Neutropenia (ANC)	
ANC <0.5 x 10^9/L (Grade 4)	Hold dose [a] until recovery to ≤ Grade 2 [ANC ≥1.0 x 10^9/L], then resume ensartinib at one lower dose level [b].
Recurrence of ANC <0.5 x 10^9/L (Grade 4)	Hold dose [a] until ANC recovery to ≤ Grade 2 [ANC ≥1.0 x 10^9/L], then resume ensartinib at one lower dose level [b].
Thrombocytopenia	
Platelets <50 x 10^9/L (Grade 3)	Hold dose [a] until improvement to Platelets ≥75 x 10^9/L • If resolved in ≤5 days, then resume without a dose reduction [b]. • If resolved in >5 days but <4 weeks, then resume dose at one lower dose level [b].

[a] Hold ensartinib treatment; do at least weekly CBC with differential until toxicity resolves (ANC recovery ≥1.0 x 10^9/L and Platelets ≥75 x 10^9/L).

[b] Re-treatment criteria = ANC recovery ≥1.0 x 10^9/L and Platelets ≥75 x 10^9/L. Dose reduction(s) (up to 2 per subject): 225 to 200 mg; 200 to 150 mg; or 150 to 100 mg.

[c] Any subjects who require a treatment delay of more than 4 weeks due to treatment-related toxicity will be discontinued from trial treatment.

Dose Modifications Due to Drug-Related Non-Hematologic Toxicities

Grade 3 or 4 Non-Hematologic Toxicity

The dose reduction guidelines for drug-related non-hematologic toxicities are shown in the table below. If a Grade 3 non-hematologic toxicity that is expected to be manageable and reversible with dose reduction occurs, treatment with ensartinib should be held until the toxicity resolves to ≤ Grade 1. If the Grade 3 non-hematologic toxicity lasts longer than 7 days, study drug will be discontinued. Subjects with Grade 3 non-hematologic toxicity lasting ≤7 days that does not resolve to ≤ Grade 1 within 4 weeks should also be removed from the trial treatment. If a Grade 4 non-hematologic toxicity occurs, study drug will be discontinued.

Specific Recommendations for Rash:

To date, the most common drug-related adverse event with ensartinib has been rash, primarily Grade 1-2. Although different types of rash have been reported (rash, erythema, erythematous rash, follicular rash, macular rash, maculopapular rash, pruritic rash, acneiform dermatitis, exfoliative rash, pustular rash), the predominant type of rash seems to be the erythematous rash, described sometimes as a sunburn-type rash (however, it does not appear to be phototoxicity). Some of these have been Grade 3, generally with pruritus and sometimes with peeling. It has begun as early as Cycle 1 Day 4 and in other cases not until Cycle 2.

Based on the experience to date, the recommendations for treating rashes considered related to ensartinib are as follows. For Grade 3 rash, hold ensartinib until resolution to ≤ Grade 1, then resume treatment at a reduced dose. For Grade 1-2 rashes, topical corticosteroids may be used, if appropriate. If it is felt that short-term courses of oral corticosteroids are needed, it is suggested that the dose of ensartinib be held until improvement to ≤ Grade 1, then resume ensartinib at a reduced dose. Of course, the Investigator should treat the subject as he/she feels is most appropriate, including the use of allowed concomitant medications and holding and/or reducing the dose of ensartinib.

Specific Recommendations for Nausea, Vomiting and Diarrhea:

For subjects with Grade 3 nausea, vomiting, and/or diarrhea, ensartinib should be held and supportive care initiated. If the Grade 3 toxicity lasts ≤7 days, subjects may restart ensartinib at a reduced dose when toxicity returns to ≤ Grade 1. If the subject has recurrent Grade 3 toxicity despite supportive care, the subject will restart ensartinib at the next lower dose level once toxicity has resolved to ≤ Grade 1.

Specific Recommendations for Liver Function Test Abnormalities:

For subjects with Grade 3 liver enzyme elevations (AST/ALT), ensartinib should be held until the values recover to ≤ Grade 1. Subjects with an elevation of ALT ≥3 x ULN in conjunction with a bilirubin ≥2 x ULN may remain in the study if a correctable, non-drug related cause of the liver test evaluations can be documented; otherwise, the subject must be discontinued from the trial.

Specific Recommendations for Pneumonitis:

For pneumonitis of any grade not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect, or other treatment, trial treatment must be discontinued.

Dose Modifications for Drug-related Non-Hematologic Toxicities

Toxicity Grade	Ensartinib Dose
Grade 0, 1, or 2	None
Grade 3 and expected to be manageable and reversible with dose reduction	Hold [a]
If toxicity remains Grade 3 toxicity for longer than 7 days	Discontinue study drug
If Grade 3 toxicity lasts ≤7 days and resolves to ≤ Grade 1	Reduce one dose level [c]
Grade 3 and not expected to be manageable and reversible with dose reduction (e.g., cardiac failure)	Discontinue study drug
Recurrence of Grade 3 toxicity	Reduce one dose level or discontinue treatment [a, c]
Elevated ALT ≥3 x ULN in conjunction with a bilirubin ≥2 x ULN, and no correctable, non-drug related cause	Discontinue study drug
Grade 4	Discontinue study drug
Pneumonitis of any grade [b]	Discontinue study drug

[a] Ensartinib should be held until toxicity resolves to ≤ Grade 1. Any subject who develops toxicity that does not resolve to ≤ Grade 1 within 4 weeks should be removed from the trial treatment.

[b] For pneumonitis of any grade not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect, or other treatment, discontinue study drug.

[c] Dose reduction(s) (up to 2 per subject): 225 to 200 mg; 200 to 150 mg; or 150 to 100 mg

Other Dose Modifications

If the subject misses a dose of study medication, the subject should take the dose as soon as possible, but not less than 12 hours before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking the study medication, the subject should be instructed not to retake the dose. Subjects should take the next scheduled dose of study medication. If vomiting persists, the subject should contact the Investigator. No routine prophylactic antiemetics will be given. However, antiemetics may be administered with nausea and vomiting when they occur, and may be given prophylactically afterwards.

8.5 RECIST 1.1 and irRECIST Guidelines

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were revised in 2009 as RECIST 1.1.(29) These guidelines have been the widely accepted criteria to assess response and progression in solid tumors; however, limitations have been noted in the use of RECIST 1.1 for immunotherapy trials. With immunotherapeutic agents, clinical trials have shown that complete response, partial response, or stable disease status can still be achieved after an initial increase in overall tumor burden, and regression of initial lesions may occur despite development of new lesions. The Immune-related Response Criteria (irRC) were developed to address the need for response criteria in an immunotherapy setting.(30) The main difference with irRC was that it considered the subject's total tumor burden at each subsequent assessment and required confirmation of suspected disease progression with subsequent imaging, approximately four weeks later. In addition, a greater number of lesions (10 vs. 5) were measured in a bidimensional manner instead of unidimensionally as in RECIST 1.1. In 2013, Nishino et al. demonstrated that immune-related response criteria using unidimensional measurements were highly concordant with the bidimensional results of irRC, but with less measurement variability.(31) Based on these findings and in order to utilize both the established criteria of irRC and RECIST 1.1, the two systems have been adapted, modified, and combined into the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).(32) The adapted irRECIST criteria are modifications to the irRC, incorporating the findings of Nishino et al. and the advantages of RECIST 1.1 while overcoming the shortcomings of each of the other guidelines.

The guidelines for RECIST 1.1 are summarized below, followed by a summary for irRECIST.

RECIST 1.1

The following section outlines the RECIST 1.1 guidelines as published (29) and as summarized by National Cancer Institute for CTEP-involved clinical trials**.**

I. Disease Parameters for RECIST 1.1

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the Investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

NOTE for irRECIST: During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

NOTE for irRECIST:
Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.
Brain lesions detected on brain scans can be considered as both target or non-target lesions depending on the protocol definition.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, 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. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any non-measureable as well as measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

II. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. 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. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, 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. It is beyond the scope of the RECIST guidelines 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.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the 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 and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to

the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.(33-35) In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.(36)

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

III. Response Criteria for RECIST 1.1

A. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

B. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

C. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

1. For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

2. For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an end-point for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

D. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

irRECIST

Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. (32) are presented below.

I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1. One new definition is added: If a subject has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the total measured tumor burden (TMTB). irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow the inclusion of subjects with no visible disease.

II Follow-up Assessments in irRECIST

A. Follow-up recording of target and new measurable lesions

A key difference in irRECIST is that the appearance new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow-up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

B. Follow-up non-target assessment

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

C. Follow-up for New Non-Measurable Lesions

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.

III Overall Assessments for irRECIST

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment, the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB).

Overall Assessments by irRECIST	
Complete Response (irCR)	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions • If new measurable lesions appear in subjects with **no target lesions at baseline**, irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation • irRECIST can be used in the **adjuvant setting**, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response. • Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.
Stable Disease (irSD)	Failure to meet criteria for irCR or irPR in the absence of irPD
Progressive Disease (irPD)	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response. • In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression. • IrPD may be assigned for a subject with multiple **new non-measurable lesions** if they are considered to be a sign of unequivocal massive worsening
Other	**irNE:** used in exceptional cases where insufficient data exist. **irND:** in adjuvant setting when no disease is detected **irNN:**, no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD

8.6 Exploratory Assessment of Correlative Immunologic Research

Please refer to the Study Laboratory Manual for information on testing to be done and instructions on specimen handling and logistics.

8.7 Drugs with Known Risk of Torsades de Pointes

The following list is taken from www.crediblemeds.org (17 Dec 2015). This may not be a comprehensive list. For more details and periodic updates, see www.crediblemeds.org.

Amiodarone (Cordarone® and others)	Halofantrine (Halfan®)
Anagrelide (Agryline® and others)	Haloperidol (Haldol® (US & UK) and others)
Arsenic trioxide (Trisenox®)	Ibutilide (Corvert®)
Astemizole (Hismanal®)	Levofloxacin (Levaquin® and others)
Azithromycin (Zithromax® and others)	Levomeprazine (Nosinan®, Nozinan®, Levoprome®)
Bepridil (Vascor® and others)	Levomethadyl (Orlaam®)
Chloroquine (Aralen®)	Mesoridazine (Serentil®)
Chlorpromazine (Thorazine® and others)	Methadone (Dolophine® and others)
Cilostazol (Pletal®)	Moxifloxacin (Avelox® and others)
Ciprofloxacin (Cipro® and others)	Ondansetron (Zofran® and others)
Cisapride (Propulsid®)	Oxaliplatin (Eloxatin®)
Citalopram (Celexa® and others)	Papaverine HCl
Clarithromycin (Biaxin® and others)	Pentamidine (Pentam®)
Cocaine (Cocaine)	Pimozide (Orap®)
Disopyramide (Norpace®)	Probucol (Lorelco®)
Dofetilide (Tikosyn®)	Procainamide (Pronestyl® and others)
Domperidone (Motilium® and others)	Propofol (Diprivan® and others)
Donepezil (Aricept®)	Quinidine (Quinaglute® and others)
Dronedarone (Multaq®)	Sevoflurane (Ulane® and others)
Droperidol (Inapsine® and others)	Sotalol (Betapace® and others)
Erythromycin (E.E.S.® and others)	Sparfloxacin (Zagam®)
Escitalopram (Cipralex® and others)	Sulpiride (Dogmatil® and others)
Flecainide (Tambocor® and others)	Terfenadine (Seldane®)
Fluconazole (Diflucan® and others)	Thioridazine (Mellaril® and others)
Gatifloxacin (Tequin®)	Vandetanib (Caprelsa®)
Grepafloxacin (Raxar®)	

8.8 ECOG Performance Status

Eastern Cooperative Oncology Group Performance Status

Grade	ECOG PS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all 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 any self-care. Totally confined to bed or chair
5	Dead

Reference: (37)

8.9 List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration time curve
CD	Cluster of differentiation
CI	confidence intervals
Cmax	peak concentration
Cmin	trough concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal Cancer
CRF	Case report form
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DC	Dendritic cell
DCR	Disease control rate
DLT	dose-limiting toxicity
DoR	Duration of Response
ECLA	Electrochemiluminescence assay
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose (FDG)-positron emission tomography (PET)
FNA	Fine needle aspiration
EML4	Echinoderm microtubule associated protein-like 4
FFPE	Formalin-fixed paraffin-embedded
FIH	First in human
GCP	Good Clinical Practice
GMP	Good manufacturing practice
HCC	hepatocellular carcinoma
HDT	High dose therapy
HLA	Human Leukocyte Antigen
IB	Investigator Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGSF	Immunoglobulin superfamily
IHC	Immunohistochemistry
IL	interleukin
IMiD	Immune modulatory drug
IMT	inflammatory myofibroblastic tumors
IND	Investigational new drug
irAE	Immune-related adverse event
irRC	irRC immune-related response criteria
IV (i.v.)	intravenous
IRB	Institutional Review Board
LICR	Ludwig Institute for Cancer Research
LTK	leukocyte tyrosine kinase
mAb	Monoclonal antibody
MDSC	myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Meso Scale Discovery
MET	MNNG HOS transforming gene or c-Met
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPM	nucleophosmin
NSCLC	Non-small cell lung cancer
NK	Natural killer
ORR	Objective Response Rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PFS	Progression free survival
PD	Pharmacodynamics
PK	Pharmacokinetics
p.o.	By mouth
PD	Progressive disease
PR	Partial response
Q4W	Every 4 weeks
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RCC	Renal cell carcinoma

RCD	Recommended combination dose
RTK	receptor tyrosine kinase
SAE	Serious Adverse Event
SCCHN	squamous cell carcinoma of the head and neck
SD	Stable disease
SOC	Standard of care
TIL	tumor-infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
TMA	thrombotic microangiopathy
TME	tumor microenvironment
TMTB	Total Measured Tumor Burden
ULN	Upper limit of normal
WFI	Water for Injection

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