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 Escalation and Expansion Phases

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Ensartinib</th>
<th>Durvalumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting</td>
<td>200 mg</td>
<td>1500 mg</td>
</tr>
<tr>
<td>+1</td>
<td>225 mg</td>
<td>1500 mg</td>
</tr>
</tbody>
</table>

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.
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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**
Durvalumab is a human immunoglobulin G1 kappa monoclonal antibody (mAb) directed against human PD-L1. Durvalumab is selective for recombinant PD-L1 and blocks the binding of recombinant PD-L1 to the PD-1 and cluster of differentiation (CD) 80 receptors.

As of the data cutoff dates in the IB (15 Apr 2015 to 18 Sep 2015), a total of 1,910 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,910 subjects, 1,279 received durvalumab monotherapy, 454 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 163 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis / hepatotoxicity, neuropathy / neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in Section 8.3.

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006). Clinical activity has been observed across the 4 studies, and two of the studies have data for NSCLC as detailed below.

**Study CD-ON-MEDI4736-1108:**

Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected subjects, the objective response rate (ORR), based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks ranged from 4.2% in triple-negative breast cancer (n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1 positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC) (n = 3 each, 33.3% each), NSCLC (n = 86; 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22; 18.2%). In the PD-L1 positive subset, disease control rate at 24 weeks was highest in advanced cutaneous melanoma (n = 3; 66.7%), NSCLC (n = 86; 36.0%), HCC and bladder cancer (n = 3 each; 33.3% each), and SCCHN (n = 22; 18.2%).

**Study D4190C00006:**

Of the 102 subjects with advanced NSCLC treated with durvalumab in combination with tremelimumab, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of partial response (PR), 14 (22%) had stable disease (SD), 22 (35%) had progressive disease (PD), and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed complete response (CR) or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.
1.2.2 Ensartinib (X-396)

Ensartinib is briefly described in this section below. Refer to the current IB for complete and current information.

ALK is a highly conserved receptor tyrosine kinase (RTK) first discovered as a fusion with nucleophosmin (NPM) in ALCL. ALK has three structural domains: an extracellular ligand-binding domain, a trans-membrane region, and an intracellular tyrosine kinase domain. It is structurally most similar to leukocyte tyrosine kinase (LTK), and both belong to the insulin-receptor super family. Homo dimerization of ALK leads to trans-phosphorylation and kinase activation. In ALK translocations, the 5' fusion partners provide dimerization domains, permitting ligand-independent activation of the kinase. In addition to NPM in lymphoma, other fusion partners for ALK have been described in NSCLC and in inflammatory myofibroblastic tumors (IMT). Activating mutations in wild-type ALK have also been identified in both familial and sporadic neuroblastoma. Most of these activating mutations occur within the tyrosine kinase domain and are transforming in vitro and in vivo.

The EML4-ALK fusion oncogene is a relatively new molecular target in NSCLC. The ALK fusion arises from an inversion on the short arm of chromosome 2 [Inv (2) (p21p23)] that joins exons 1 to 13 of echinoderm microtubule associated protein-like 4 (EML4) to exons 20 to 29 of ALK. The resulting chimeric protein, EML4-ALK, contains an N terminus derived from EML4 and a C terminus containing the entire intracellular tyrosine kinase domain of ALK. The fusion protein is constitutively active and a driver of cell transformation in cells expressing the fusion protein.

The ALK inhibitor, crizotinib, was the first ALK inhibitor approved (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 is a second generation ALK inhibitor with activity against certain, but not all, crizotinib-resistant mutations. Ensartinib is a potent and selective ALK inhibitor for the treatment of NSCLC in patients with ALK fusion proteins, neuroblastoma in patients with ALK mutation, activation, or amplification, other tumor types with ALK fusion, activating mutation, or amplification, and tumor types with alterations of or dependence on MNNG HOS transforming gene or c-Met (MET). Ensartinib is currently undergoing Phase 1/2 evaluation in subjects with ALK rearranged NSCLC who are either crizotinib naïve or crizotinib resistant as described below. A randomized Phase 3 trial comparing ensartinib to crizotinib in tyrosine kinase inhibitor (TKI) naïve subjects is planned to be initiated in April 2016.

In animal studies, ensartinib induced tumor stasis at well-tolerated doses in xenografts of human EML4-ALK positive NSCLC in nude mice. Human tumor xenografts of the neuroblastoma SH-SY5Y that carry a crizotinib-resistant mutation (F1174L) were growth inhibited by ensartinib. In an intracranial tumor model using SH-SY5Y tumors treated with ensartinib and crizotinib at equivalent doses, a significant increase in life span was observed in mice treated with ensartinib but not in mice treated with crizotinib. Taken together, these non-clinical data supported the potential utility of ensartinib in crizotinib-resistant tumors and the potential use of ensartinib for...
the treatment of NSCLC tumors that have metastasized to the brain. The first-in-human (FIH) study of ensartinib has demonstrated that ensartinib does, in fact, have good activity in ALK positive NSCLC patients who progressed after prior crizotinib and that it has activity against CNS metastases.

The dose escalation phase of the FIH Phase 1/2 study of ensartinib has been completed, and enrollment in the expansion cohort phase is ongoing. In this study, ensartinib is administered once daily, and cycles are approximately 28 days. Subjects have been treated with doses ranging from 25-250 mg once daily (qd). Initially, the study drug was taken without food, although subjects in the last cohort in the dose escalation phase took the drug with food (200 mg with food cohort). Subjects in the expansion cohorts are assigned to take the drug with or without food in Cycle 1; after that, they may take the drug either way.

Based on data in the database as of March 2016, the total number of subjects enrolled to date is 63. Of the 63 subjects in the study, 35 have received a dose of ≥ 200 mg. There are 16 subjects continuing on treatment, the longest being for 41+ cycles. For the study as a whole, as well as those receiving ≥ 225 mg, the drug has generally been well tolerated.

Two subjects (100 mg and 250 mg) died during the study, related to disease progression; there were no drug-related deaths. Eight subjects discontinued for an adverse event (AE), two of which were considered by the Investigator to be related to study drug. One was hyperbilirubinemia and abdominal pain (200 mg) and the other was thrombotic microangiopathy (TMA; 25mg). The latter was considered by the Investigator to be an idiosyncratic reaction possibly related to the study drug, but the Sponsor considered it unlikely related to study drug and more likely related to other factors.

Five serious AEs (SAEs) considered drug-related by the Investigator have been reported to date from 4 subjects: the TMA described above, peripheral edema and fluid overload (200 mg), and erythematous rash (2 subjects; 225 mg and 250 mg).

The most frequent drug-related adverse events (AEs) are rash, nausea, fatigue, vomiting, and pruritis. The most prominent toxicity is skin toxicity, which is easily managed with topical treatment and, for the more severe events, holding study drug until improvement and then resuming treatment at a reduced dose of study drug. The frequency of gastrointestinal AEs, particularly diarrhea, appears to be relatively low for ensartinib, as is the frequency of transaminase elevations. Minimal QTc (corrected QT interval) prolongation has been observed to date; this has been reported as a related AE (Grade 2) in one subject.

With respect to preliminary efficacy in ALK positive NSCLC, an overall response rate of 57% (20/35 subjects) has been observed to date in all evaluable subjects treated at doses ≥ 200 mg, with a median duration of response of approximately 9.5+ months.

Looking at subpopulations of these subjects, 8 evaluable ALK TKI naïve subjects have been enrolled to date at doses ≥200 mg, resulting in a response rate of 88% (7/8 subjects) in the ALK TKI naïve subjects. The only one having progressive disease as the best response to ensartinib was borderline ALK positive. Although there have been few ALK TKI naïve subjects treated to date, good responses have also been observed in subjects who have failed prior crizotinib but have not received another ALK TKI (overall response rate of 58%; 11/19 subjects), with a median duration of response of approximately 5.5 months. Eight subjects have received a prior second...
generation ALK TKI, with or without prior crizotinib. Two of these subjects have had responses, and one had stable disease on ensartinib. Responses have also been reported in subjects with CNS metastases: of the 8 subjects, 4 (50%) had objective responses and 3 had stable disease.

In summary, ensartinib is a potent second generation ALK inhibitor that is demonstrating activity in subjects with ALK positive NSCLC who are either crizotinib-naïve or who have progressed after prior crizotinib; and responses have been observed in subjects with CNS metastases and in subjects who received another second generation ALK inhibitor. To date, the drug has been generally well tolerated, with skin toxicity as the most prominent adverse event. The clinical data support the further evaluation of ensartinib in the clinic.
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. The addition of checkpoint inhibitor therapy could capitalize on this immunologic priming effect of targeted therapies for a potentially marked synergistic efficacy.

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. 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, 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, while inhibition of CSF1R modulates the tumor microenvironment including tumor-associated macrophages and myeloid-derived suppressor cells. 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.

Data from Study D4190C00006 (Phase 1 trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. For further information on PK observations in Study 006, please see the current IB.

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen. A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W. Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by the area under the concentration-time curve (AUC) at 4 weeks. Median maximum concentration (Cmax) is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median Cmin is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar AUC and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.
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

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40–120 kg. Simulation results demonstrate that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others.\(^{25-28}\) Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, Zhang et al. investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK/PD parameters.\(^{27}\)

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, it was considered feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W) or 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is recommended.

This dosing of durvalumab is recommended only for subjects with > 30 kg body weight due to endotoxin exposure. Subjects with a body weight \(\leq 30\) kg are not eligible for enrollment in the current study. If a subject's body weight drops to \(\leq 30\) kg while on the study, the durvalumab dose will be weight based as long as the body weight remains \(\leq 30\) kg (see Section 6.1.3).

2.3 Rationale for Amendment 2

Xcovery, the developer of ensartinib, has treated over 100 subjects in the Phase 2 program and has a randomized Phase 3 ongoing. An analysis of the subjects who reported drug-related rash in the Phase 2 study by severity and by duration indicated that 57 subjects developed rash; the majority (52/57 subjects) in the first month of treatment. Of these, the maximum grade was Grade 2 or 3 in 24 subjects. In this subset with grade 2 or higher rash, 19 subjects developed rash within the first 28 days, 3 between days 34 and 39 and one on day 47. One additional subject developed rash on day 544. Based on these data, it was decided that a run-in period of 1 cycle Instead of 2 cycles) for ensartinib would be sufficient.
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:

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

3.1.7 Treatment Schema

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

<table>
<thead>
<tr>
<th>Dosing Schedule:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Period</strong></td>
</tr>
<tr>
<td>Run-in Period: see Section 3.1.7.1</td>
</tr>
<tr>
<td>Combination Treatment</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Ensartinib</th>
<th>Durvalumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>150 mg</td>
<td>1500 mg</td>
</tr>
<tr>
<td>Starting</td>
<td>200 mg</td>
<td>1500 mg</td>
</tr>
<tr>
<td>+1</td>
<td>225 mg</td>
<td>1500 mg</td>
</tr>
</tbody>
</table>
Dose Escalation and De-Escalation Schema (3 + 3 Design)

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 durvalumab 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 downgrades 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 downgrades 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 ≤ 7 days.
   • 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).
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:
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

<table>
<thead>
<tr>
<th>Length of Study per subject:</th>
<th>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)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment Period:</td>
<td>24 months</td>
</tr>
<tr>
<td>Length of Study:</td>
<td>41 months</td>
</tr>
<tr>
<td>Length of Survival Post Study Follow-up</td>
<td>Up to 5 years from initiation of treatment</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Screening / Baseline</th>
<th>Enzalutamide (Run-In) (Cycle -1)</th>
<th>Treatment (4 weeks/cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cycle 1</td>
</tr>
<tr>
<td>Cycle Day</td>
<td>Up to 28 days before Tx start</td>
<td></td>
<td>1 (±3)</td>
</tr>
<tr>
<td>Cumulative Study Day</td>
<td>-28 -14</td>
<td>1</td>
<td>15</td>
</tr>
</tbody>
</table>

### Treatment

- **Durvalumab** (1500 mg)
  - X
- **Ensartinib (X-396)** (oral; see Sections 3.1.7.1 and 3.1.7.2)
  - Daily

### Tumor & Disease Assessments

- Disease Staging (date/stage at 1st diagnosis and at study entry)
  - X
- Disease Assessment by irRECIST/RECIST
  - X

### Study Procedures & Examinations

- Eligibility Assessment and Informed Consent (IC)
  - X
- Demographics (incl. DoB; sex; height; race; ethnicity)
  - X
- Medical history
  - X
- Physical Exam (incl. weight and ECOG Perf Status)
  - X
- 12-Lead ECG
  - X
- Vital Signs (T, HR, BP, RR)
  - X
- Concomitant Medications / Procedures
  - X
- Adverse Events (starting or worsening after IC)
  - X
- Blood Hematology (CBC, differential, platelets)
  - X
- Chemistry (glucose, BUN, creat., Na, K, Cl, CO₂, Ca, Mg, total protein, albumin, Tbilii., AST, ALT, ALP, LDH)
  - X
- AST, ALT, ALP, and Tbil
  - X
- Chemistry cont. (Free T3, Free T4, TSH)
  - X
- Chemistry cont. (Amylase and lipase)
  - X
- Testosterone (males only)
  - X
- Urinalysis
  - X
- Coagulation parameters (PT, aPTT, INR)
  - X
- Serum pregnancy test (Urine test only pre-dose on first day of ensartinib and first day of combination drug)
  - Up to 1 week before Tx start
- Whole blood for (PBMC and plasma) for flow cytometry and biological assays
  - X
- Blood for Biomarker analyses
  - X

### Biopsy

- Biopsy (or FFPE slides) for tumor microenvironment
  - X

### Long Term Follow-up

- Overall Survival
- Progression Free Survival
### 3.2.1 - Flowchart for Subjects who Proceed with Combination Therapy after Run-in (cont.)

<table>
<thead>
<tr>
<th>Study Week</th>
<th>Cycle 7</th>
<th>Cycle 8</th>
<th>Cycle 9</th>
<th>Cycle 10</th>
<th>Cycle 11</th>
<th>Cycle 12</th>
<th>Optional Study Treatment Extension</th>
<th>On Study Follow-up</th>
<th>Post Study Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
<td>29</td>
<td>33</td>
<td>37</td>
<td>41</td>
<td>45</td>
<td>Last Study Drug Dose +28 (±4) days</td>
<td>Last Study Drug Dose +56 (±8) days</td>
<td>Last Study Drug Dose +91 (±12) days</td>
</tr>
<tr>
<td>Cycle Day</td>
<td>1 (±3)</td>
<td>1 (±3)</td>
<td>1 (±3)</td>
<td>1 (±3)</td>
<td>1 (±3)</td>
<td>1 (±3)</td>
<td></td>
<td>End of Study</td>
<td>Everything post initiation of treatment</td>
</tr>
<tr>
<td>Cumulative Study Day</td>
<td>169</td>
<td>197</td>
<td>225</td>
<td>253</td>
<td>281</td>
<td>309</td>
<td>Q8W starting on Week 49 or SOC</td>
<td>Q8W starting 8 weeks after last disease assessment</td>
<td></td>
</tr>
</tbody>
</table>

#### Treatment
- **Durvalumab** (1500 mg)
- **Ensartinib (X-396)** (oral; see Sections 3.1.7.1 and 3.1.7.2)

#### Tumor & Disease Assessments
- Disease Staging (date/stage at 1st diagnosis and at study entry)
- Disease Assessment by iRECIST/RECIST

#### Study Procedures & Examinations
- Eligibility Assessment and Informed Consent (IC)
- Demographics (incl. DoB; sex; height; race; ethnicity)
- Medical history
- Physical Exam (incl. weight and ECOG Perf Status)
- 12-Lead ECG
- Vital Signs (T, HR, BP, RR)
- Concomitant Medications / Procedures
- Adverse Events (starting or worsening after IC)
- Specimens for Routine Laboratory Procedures
- Blood Hematology (CBC, differential, platelets)
- Chemistry (glucose, BUN, creat., Na, K, Cl, CO2, Ca, Mg, total protein, albumin, Tbili., AST, ALT, ALP, LDH)
- AST, ALT, ALP, and Tbili.
- Chemistry cont. (Free T3, Free T4, TSH)
- Chemistry cont. (Amylase and lipase)
- Testosterone (males only)
- Urinalysis
- Coagulation parameters (PT, aPTT, INR)
- Serum pregnancy test (Urine test only pre-dose on first day of ensartinib and first day of combination drug)
- Specimens for Other Peripheral Blood Assays
- Whole blood for (PBMC and plasma) for flow cytometry and biological assays
- Blood for Biomarker analyses
- Tumor Biopsy
- Biopsy (or FFPE slides) for tumor microenvironment

#### Study Week
- Study Week 37
- Study Week 41
- Study Week 45
- Study Week 25

#### Overall Follow-up
- End of Study
  - Q8W starting 8 weeks after last disease assessment

#### Post Study Follow-up
- Overall Survival
- Progression Free Survival

---

**SOP-C01-TMP-3 version 3**  
**LUD2014-012-ALK Protocol Amendment 2 (Final, 14-AUG-2017)**
### Footnotes for Flowchart 3.2.1

<table>
<thead>
<tr>
<th>a:</th>
<th>Pre durvalumab dose, when applicable. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>b:</td>
<td>Full physical examination at baseline; targeted physical examination at other timepoints</td>
</tr>
<tr>
<td>c:</td>
<td>Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.</td>
</tr>
<tr>
<td>d:</td>
<td>Coagulation tests: prothrombin time, aPTT and INR – only performed at Screening and as clinically indicated.</td>
</tr>
<tr>
<td>e:</td>
<td>Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.</td>
</tr>
<tr>
<td>f:</td>
<td>See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.</td>
</tr>
<tr>
<td>g:</td>
<td>See Section 6.4 for assessment of vital signs before/during/after durvalumab.</td>
</tr>
<tr>
<td>h:</td>
<td>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.</td>
</tr>
<tr>
<td>i:</td>
<td>If subjects are ALK inhibitor naïve, either archival tissue or pre-treatment biopsy will be acceptable. See Section 4.3.1.1 for details.</td>
</tr>
<tr>
<td>j:</td>
<td>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.</td>
</tr>
<tr>
<td>k:</td>
<td>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.</td>
</tr>
<tr>
<td>l:</td>
<td>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.</td>
</tr>
</tbody>
</table>
3.2.2 Flowchart for Subjects who Continue Treatment with Ensartinib (X-396) Monotherapy after Run-in

<table>
<thead>
<tr>
<th>3.2.2 - Flowchart for Subjects who Continue Treatment with Ensartinib (X-396) Monotherapy after Run-in (and do not proceed with Combination Therapy)(^a)</th>
<th>Post Run-in Monotherapy(^a)</th>
<th>Ensartinib On Study Follow-up</th>
<th>Post Study Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td>Last dose of Ensartinib + 30 days</td>
</tr>
<tr>
<td>Ensartinib (X-396) – oral</td>
<td>daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tumor &amp; Disease Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Assessment by RECIST</td>
<td>Q8W</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Study Procedures &amp; Examinations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam (incl. weight and ECOG Perf Status)</td>
<td>Q4W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>12-Lead ECG</td>
<td>Q8W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vital Signs (T, HR, BP, RR)</td>
<td>Q4W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medication / Procedure</td>
<td>Q4W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events (starting or worsening after IC)</td>
<td>Q4W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Specimens for Routine Laboratory Procedures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood Hematology (CBC, differential, platelets)</td>
<td>Q4W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Chemistry (glucose, BUN, creat., Na, K, Cl, CO(_2), Ca, Mg, total protein, albumin, Tbilii., AST, ALT, ALP, LDH)</td>
<td>Q4W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Q8W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Serum pregnancy test</td>
<td>Q8W</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Long Term Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Survival</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression Free Survival</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\): 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

<table>
<thead>
<tr>
<th>Primary Objective [Endpoints]</th>
<th>Phase 1 Dose Escalation Phase:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommended Combination Dose (RCD)</td>
</tr>
<tr>
<td></td>
<td>Safety and Tolerability [CTCAE 4.03, including DLTs and RCD]</td>
</tr>
<tr>
<td></td>
<td>Expansion Phase:</td>
</tr>
<tr>
<td></td>
<td>Safety and Tolerability [CTCAE 4.03]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Objectives [Endpoints]</th>
<th>Dose Escalation and Expansion Phases (all subjects):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical Efficacy by irRECIST and RECIST 1.1 [PFS rate and ORR at 8 and 24 weeks, overall best response, DCR, DoR, OS]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exploratory Objectives [Endpoints]</th>
<th>Dose Escalation and Expansion Phases (all subjects):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biologic Activity [Effects on Tumor Microenvironment, Immune Response]</td>
</tr>
</tbody>
</table>

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 25th percentile, Median, and 75th 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:

1. 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.

2. 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.

3. Willing to provide a fresh pre-treatment biopsy; however, if subject is ALK inhibitor naïve, either archival or pre-treatment biopsy will be acceptable.

4. 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).

5. 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>
<thead>
<tr>
<th>Parameter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<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/mm³</td>
</tr>
<tr>
<td>Serum creatinine, or Creatinine Clearance</td>
<td>≤ 1.5 x 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 x 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>
</tbody>
</table>

6. ECOG Performance Status ≤ 2.

7. Age ≥ 18 years.

8. Able and willing to provide valid written informed consent.
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 may not 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 highly effective 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
The 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 Methods of Contraception

<table>
<thead>
<tr>
<th>Barrier/Intrauterine Methods</th>
<th>Hormonal Methods</th>
</tr>
</thead>
</table>
| • 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 intravaginal 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”*: 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.


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 m², 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

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>MedImmune</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expiration/Retest Date</td>
<td>Expiration/retest dates are documented in the QA Disposition of Investigational Medicinal Product (IMP) Report.</td>
</tr>
<tr>
<td>Container Description</td>
<td>Type: Single use vial, Material: Glass, Size: 10 mL</td>
</tr>
<tr>
<td>Formulation</td>
<td>Liquid solution containing 500 mg durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, at pH 6.0.</td>
</tr>
<tr>
<td>Active Ingredient Content</td>
<td>Mass/Weight: 500 mg, Volume: 10mL, Concentration: 50 mg/mL</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>2°C–8°C (36°F–46°F) Do not freeze</td>
</tr>
<tr>
<td>Labeling</td>
<td>Product name, lot number, route of administration, and storage conditions</td>
</tr>
</tbody>
</table>

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:
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.
- 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.
6.2 Ensartinib (X-396)

6.2.1 Study Drug Information

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Xcovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expiration/Retest Date</td>
<td>Expiration/retest dates are documented on the Certificate of Analysis and/or stability certification.</td>
</tr>
<tr>
<td>Container Description</td>
<td>Type: Bottle</td>
</tr>
<tr>
<td>Formulation</td>
<td>Dry blend in capsule</td>
</tr>
<tr>
<td>Active Ingredient Content</td>
<td>Mass/Weight: 25 or 100 mg</td>
</tr>
<tr>
<td>Storage Conditions</td>
<td>Room temperature, 15°C to 30°C (59°F to 86°F)</td>
</tr>
<tr>
<td>Labeling</td>
<td>Product name, lot number, route of administration, and storage conditions</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensartinib (25 mg capsules)</td>
<td>1,000 bottles (30 capsules/bottle)</td>
</tr>
<tr>
<td>Ensartinib (100 mg capsules)</td>
<td>1,000 bottles (30 capsules/bottle)</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>350 kits (4 vials/kit)</td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Vital Signs Assessment on Study Drug Administration Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Durvalumab</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Vital Signs Assessment on study drug administration days (after first 4 doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Durvalumab</td>
</tr>
</tbody>
</table>

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,
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.

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:**
Senior Manager, Drug Safety
Clinical Trials Management
Ludwig Institute for Cancer Research
666 3rd Ave, 28th Floor
New York, New York 10017

**Primary Sponsor Contact:**
Director
Clinical Trials Management
Ludwig Institute for Cancer Research
666 3rd Ave, 28th Floor
New York, New York 10017

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)**
that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an AE being an irAE, the Investigator should promptly contact the Medical Monitor.

If an AESI also meets SAE criteria, the event will be reported as an SAE per Section 7.1.6.

AESIs observed with durvalumab and those considered AESIs for the purpose of this study are listed below. Further information on these AESIs (e.g. presenting symptoms) can be found in the current version of the durvalumab (MEDI4736) Investigator's Brochure (IB). Guidelines for the management of subjects experiencing toxicities for durvalumab can be found in Section 8.3 and in the following Medimmune guideline:

"Medimmune's Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)."

- **Colitis/Gastrointestinal disorders**
  Diarrhea and colitis are the most commonly observed treatment-emergent AEs following dosing with study medications. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome, if not properly managed.

- **Pneumonitis/Interstitial lung disease (ILD)**
  Adverse events of pneumonitis have been observed with anti-PD-1, and anti-PD-L1 antibodies (see IB). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Typically, pulmonary consultation is required.

- **Hepatic Function Abnormality (Hepatitis, hepatotoxicity)**
  Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (see IB). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin. Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a concurrent or pre-existing disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Cases where a subject shows an AST or ALT ≥ 3 x ULN or total bilirubin ≥ 2 x ULN may need to be reported as SAEs. These cases should be...
reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

- **Neurotoxicity (Neuropathy / neuromuscular toxicity)**
  Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis.

- **Endocrine Disorders**
  Immune-mediated endocrinopathies include hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism, diabetes insipidus, and Type 1 diabetes mellitus.
  **Type 1 diabetes mellitus:**
  For subjects with suspected diabetes mellitus, Investigators should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin.

- **Dermatitis/Rash**
  Prompt treatment with steroids (topical or systemic based on severity) is important as per current established toxicity management guidelines.

- **Nephritis and increases in serum creatinine**
  A consult with a Nephrologist should be done as well as monitoring for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.). Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, etc.). Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.

- **Pancreatic Disorders**
  Immune-mediated pancreatitis includes autoimmune pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase).

- **Hypersensitivity and Infusion Reactions**
  Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (see IB). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies (MAbs) can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

- **Other inflammatory responses**
  that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.

Guidelines for the management of subjects experiencing toxicities for durvalumab can be found in Section 8.3. Guidelines for ensartinib can be found in Section 8.4.
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

<table>
<thead>
<tr>
<th>Issue</th>
<th>Issue date</th>
<th>Summary of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Issue</td>
<td>21-JUL-2016</td>
<td>not applicable</td>
</tr>
<tr>
<td>Amendment 1</td>
<td>11-NOV-2016</td>
<td></td>
</tr>
</tbody>
</table>
subsequent infusions may be administered at 50% of the initial rate.

Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the Investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. See Section 8.3.1.

b. The following sentence was updated (changes in bold): “Investigational product(s) must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein or central line.”

c. The following sentence was modified: “Since the compatibility of durvalumab with other IV medications and solutions, other than normal saline (0.9% [w/v] Sodium Chloride for Injection), is not known, the Durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.”

d. The following sentence was changed FROM: “If durvalumab administration has to be delayed, temporally interrupted or the infusion rate decreased, or if administration time exceeds these limits, a new dose must be prepared from new vials.” TO: “Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.”

10. Section 7.1.6 (Expedited Serious Adverse Event (SAE) Reporting Requirements): The following sentence was added “Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement.” This is per current protocol language.

11. Section 8.3.1 (Durvalumab Dose Modification Due to Toxicity): table was updated according to current Medimmune guidelines, dated 19Aug2016.

12. Section 8.3.2 (Durvalumab Dose Modification Not Due to Treatment-related Toxicities). The section was updated for clarification and to provide consistency with other protocols. Changed FROM: “(1) If the subject misses 2 consecutive planned doses, the subject should be discontinued from treatment. (2) If the dosing interruption is ≤ half the planned dosing interval, the originally planned drug administration should be given. The respective protocol deviation should be documented. (3) If the dosing interruption is greater than half the planned dosing interval, the dosing should be skipped and the next scheduled drug administration should be performed. The respective protocol deviation should be documented.” TO: “(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.”
Amendment 2  
Issue date: 14-AUG-2017  
Summary of Changes:

1. Per rationale provided in Section 2.3, the Run-in period for ensartinib monotherapy was changed from 2 cycles to 1 cycle. This change was made in the Synopsis and Sections 3.1, 3.1.7, 3.1.7.1, 3.1.15, and 3.2. Section 2.3 was added.

2. Per current Medimmune recommendations, the language was updated for durvalumab dosing of subjects whose body weight drops to ≤ 30 kg while on the study; in these cases, durvalumab dose will be weight based. Previously a fixed dose of 600 mg was recommended for ≤ 30 kg. This change was made in the Synopsis and Sections 2.2.3, 3.1.7.2, and 6.1.3. The following clarification was added in Sections 3.1.7.2 and 6.1.3: “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.”

3. Section 3.1.16, On Study and Post Study Follow-up.
   a. The 3rd paragraph was clarified (changes in bold): “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.”
   b. The following paragraph was added before the last paragraph: “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.”

4. Section 3.2.1, Flowchart
   a. Deleted Run-in Cycle -2, per changes described in point #1. Cumulative study days for Cycle -1 were corrected to -28 for Week -4 and -14 for Week -2.
   b. An additional column was added to indicate that testing described in footnote J occurs in Study Week 3.
   c. Footnote h was updated to indicate that the post ensartinib biopsy may be taken up to 14 days prior to start of durvalumab (changed from 28 days). This was done per the change of ensartinib monotherapy from 2 cycles to 1 cycle.
   d. Footnote h was updated to clarify timing of optional tumor biopsies (see changes to Section 4.1.3.1.)
   e. Optional tumor biopsy was removed from Cycle 12 per change to Section 4.3.1.1.
   f. Screening window was changed from 1 month to 28 days (for clarification and agreement with cycles).

5. Section 3.2.2 Flowchart
   a. Third column was relabeled as Ensartinib On Study Follow-up to distinguish it from the On Study Follow-up in Section 3.2.1.
   b. The Post Study Follow-up column was added; long term follow-up assessments were added.
   c. Note was clarified to indicate (changes in bold) “It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing at every assessment point.”
6. Section 4.3.1.1 (Tumor Microenvironment)
   a. First sentence was updated (changes in bold): "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 28 days prior to initiation of durvalumab)." This was done per the change of ensartinib monotherapy from 2 cycles to 1 cycle.
   b. 4th sentence was updated to clarify timing of optional tumor progressions (changes in bold): Optional core biopsies will be obtained at the time of tumor progression or at the end of the study completion of treatment from subjects who consent to this procedure.

7. Section 5.1, Inclusion Criterion #4 was changed FROM: "Subjects with treated brain metastases must have been treated with surgery and/or radiation therapy ≥ 21 days pre-study and must be clinically stable with no requirement for steroids." TO: "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)." The change was implemented to provide requirement clarification for subjects receiving surgery vs those receiving radiation therapy and to further clarify the requirement for symptomatic vs asymptomatic subjects.

8. Section 5.2, Exclusion Criteria:
   a. #1 was clarified (changes in bold): "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.
   b. #4: Start of study drug was changed from Day -57 to -28. This was based on change of run-in.

9. Section 5.3.1, Non-permitted Concomitant Therapies; Start of study drug was changed from Day -57 to -28. This was based on change of run-in.

10. Sections 6.1.1 (Study Drug Information), 6.1.2 (Durvalumab Investigational Product Inspection), 6.1.3 (Durvalumab Preparation) and 6.1.4 (Durvalumab Administration): Sections were clarified and/or reorganized per current Medimmune recommendations and to maintain consistency with current protocols.

11. Section 7.1.8 (AESIs): section was updated and descriptions of AESIs were expanded per current Medimmune recommendations. Diabetes insipidus was added to endocrine disorders. The following bullet was added:

   • Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.

12. Section 8.3.1 (Durvalumab Dose Modification due to toxicity)
   a. added myocarditis to Pneumonitis/ILD bullet in Grades 1, 2, and 3.
   b. For Infusion related reactions Grades 1 and 2, the phrase "total infusion time not to exceed 4 hours." was deleted per Medimmune current guidelines.

13. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.
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:

"MedImmune's Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)."

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.

<table>
<thead>
<tr>
<th>Durvalumab (D) Dose Modification Due to Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Note:</strong> If D dosing is held temporarily until resolution of the event as per instructions below, treatment should resume at the next scheduled treatment date.</td>
</tr>
</tbody>
</table>

**Immune-related Adverse Events (irAEs)**

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, permanently discontinue D 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** immediately 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

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

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

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

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. 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. 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. 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). 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 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 \( \geq 15 \text{ mm} \) 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 \( <10 \text{ mm} \) or pathological lymph nodes with \( \geq 10 \text{ to } <15 \text{ mm} \) 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. 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.

**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)

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
<th>Best Overall Response when Confirmation is Required*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
<td>&gt;4 wks. Confirmation**</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Non-CR/Non-PD/Not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-CR/Non-PD/Not evaluated</td>
<td>No</td>
<td>SD</td>
<td>documented at least once &gt;4 wks. from baseline**</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>PD***</td>
<td>Yes or No</td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

* 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)

<table>
<thead>
<tr>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>Non-CR/Non-PD*</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>No</td>
<td>not evaluated</td>
</tr>
<tr>
<td>Unequivocal PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

* ‘Non-CR/Non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint 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.
### 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).

<table>
<thead>
<tr>
<th>Overall Assessments by irRECIST</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response</strong> (irCR)</td>
<td>Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to &lt; 10 mm in short axis.</td>
</tr>
</tbody>
</table>
| **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](http://www.crediblemeds.org) (17 Dec 2015). This may not be a comprehensive list. For more details and periodic updates, see [www.crediblemeds.org](http://www.crediblemeds.org).

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Cordarone* and others</td>
</tr>
<tr>
<td>Anagrelide</td>
<td>Agryline* and others</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>Trisenox*</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Hismanal*</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Zithromax* and others</td>
</tr>
<tr>
<td>Bepridil</td>
<td>Vascor* and others</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Aralen*</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine* and others</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Pletal*</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Cipro* and others</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Propulsid*</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Celexa* and others</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Biaxin* and others</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Norpace*</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Tikosyn*</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Motilium* and others</td>
</tr>
<tr>
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<td>Aricept*</td>
</tr>
<tr>
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<td>Multaq*</td>
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<tr>
<td>Droperidol</td>
<td>Inapsine* and others</td>
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<tr>
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<td>E.E.S.* and others</td>
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<tr>
<td>Escitalopram</td>
<td>Cipralex* and others</td>
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<tr>
<td>Flecainide</td>
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<tr>
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<tr>
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<td>Tequin*</td>
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<tr>
<td>Grepafloxacin</td>
<td>Raxar*</td>
</tr>
<tr>
<td>Halofantrine</td>
<td>Halfan*</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol* (US &amp; UK) and others</td>
</tr>
<tr>
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<td>Corvert*</td>
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<tr>
<td>Levofloxacin</td>
<td>Levaquin* and others</td>
</tr>
<tr>
<td>Levomeprazine</td>
<td>Nosinan®, Nozinan®, Levoprome*</td>
</tr>
<tr>
<td>Levomethadyl</td>
<td>Orlaam*</td>
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<tr>
<td>Mesoridazine</td>
<td>Serentil*</td>
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<tr>
<td>Methadone</td>
<td>Dolophine* and others</td>
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<tr>
<td>Moxifloxacin</td>
<td>Avelox* and others</td>
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<tr>
<td>Ondansetron</td>
<td>Zofran* and others</td>
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<tr>
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<td>Eloxatin*</td>
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<td>Papaverine HCl</td>
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<tr>
<td>Pentamidine</td>
<td>Pentam*</td>
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<tr>
<td>Pimozide</td>
<td>Orap*</td>
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<tr>
<td>Probucol</td>
<td>Lorelco*</td>
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<tr>
<td>Procainamide</td>
<td>Pronestyl* and others</td>
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<tr>
<td>Propofol</td>
<td>Diprivan* and others</td>
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<tr>
<td>Quinidine</td>
<td>Quinaglute* and others</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>Ulane* and others</td>
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<tr>
<td>Sotalol</td>
<td>Betapace* and others</td>
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<tr>
<td>Sparfloxacin</td>
<td>Zagam*</td>
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<td>Sulpiride</td>
<td>Dogmatil* and others</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Seldane*</td>
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<tr>
<td>Thioridazine</td>
<td>Mellaril* and others</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Caprelsa*</td>
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### 8.8 ECOG Performance Status

Eastern Cooperative Oncology Group Performance Status

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG PS</th>
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<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>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</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
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</table>

Reference: (37)
8.9 List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AESI</td>
<td>adverse event of special interest</td>
</tr>
<tr>
<td>ALCL</td>
<td>Anaplastic large cell lymphoma</td>
</tr>
<tr>
<td>ALK</td>
<td>Anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the concentration time curve</td>
</tr>
<tr>
<td>CD</td>
<td>Cluster of differentiation</td>
</tr>
<tr>
<td>CI</td>
<td>confidence intervals</td>
</tr>
<tr>
<td>Cmax</td>
<td>peak concentration</td>
</tr>
<tr>
<td>Cmin</td>
<td>trough concentration</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal Cancer</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CTC</td>
<td>Circulating tumor cell</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Cytotoxic T lymphocyte-associated antigen 4</td>
</tr>
<tr>
<td>DC</td>
<td>Dendritic cell</td>
</tr>
<tr>
<td>DCR</td>
<td>Disease control rate</td>
</tr>
<tr>
<td>DLT</td>
<td>dose-limiting toxicity</td>
</tr>
<tr>
<td>DoR</td>
<td>Duration of Response</td>
</tr>
<tr>
<td>ECLA</td>
<td>Electrochemiluminescence assay</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
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<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>fluorodeoxyglucose (FDG)-positron emission tomography (PET)</td>
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<tr>
<td>FNA</td>
<td>Fine needle aspiration</td>
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<tr>
<td>EML4</td>
<td>Echinoderm microtubule associated protein-like 4</td>
</tr>
<tr>
<td>FFPE</td>
<td>Formalin-fixed paraffin-embedded</td>
</tr>
<tr>
<td>FIH</td>
<td>First in human</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good manufacturing practice</td>
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<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
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<tr>
<td>HDT</td>
<td>High dose therapy</td>
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<tr>
<td>HLA</td>
<td>Human Leukocyte Antigen</td>
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<tr>
<td>IB</td>
<td>Investigator Brochure</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
<td>------------</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>IGSF</td>
<td>Immunoglobulin superfamily</td>
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<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
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<tr>
<td>IL</td>
<td>interleukin</td>
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<tr>
<td>IMiD</td>
<td>Immune modulatory drug</td>
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<tr>
<td>IMT</td>
<td>inflammatory myofibroblastic tumors</td>
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<tr>
<td>IND</td>
<td>Investigational new drug</td>
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<tr>
<td>irAE</td>
<td>Immune-related adverse event</td>
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<tr>
<td>irRC</td>
<td>irRC immune-related response criteria</td>
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<tr>
<td>IV (i.v.)</td>
<td>intravenous</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>LICR</td>
<td>Ludwig Institute for Cancer Research</td>
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<tr>
<td>LTK</td>
<td>leukocyte tyrosine kinase</td>
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<tr>
<td>mAb</td>
<td>Monoclonal antibody</td>
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<tr>
<td>MDSC</td>
<td>myeloid derived suppressor cells</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<td>MSD</td>
<td>Meso Scale Discovery</td>
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<tr>
<td>MET</td>
<td>MNNG HOS transforming gene or c-Met</td>
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<tr>
<td>MTD</td>
<td>maximum tolerated dose</td>
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<tr>
<td>NCI CTCAE</td>
<td>National Cancer Institute Common Terminology Criteria for Adverse Events</td>
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<td>NPM</td>
<td>nucleophosmin</td>
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<tr>
<td>NSCLC</td>
<td>Non-small cell lung cancer</td>
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<tr>
<td>NK</td>
<td>Natural killer</td>
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<tr>
<td>ORR</td>
<td>Objective Response Rate</td>
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<tr>
<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>PBMC</td>
<td>Peripheral blood mononuclear cell</td>
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<tr>
<td>PD</td>
<td>Progressive disease</td>
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<tr>
<td>PD-1</td>
<td>Programmed death-1</td>
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<tr>
<td>PD-L1</td>
<td>Programmed death ligand 1</td>
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<tr>
<td>PFS</td>
<td>Progression free survival</td>
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<td>Pharmacodynamics</td>
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<td>Pharmacokinetics</td>
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<td>p.o.</td>
<td>By mouth</td>
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<td>PD-Pharma</td>
<td>Progressive disease</td>
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<td>PR</td>
<td>Partial response</td>
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<td>Q4W</td>
<td>Every 4 weeks</td>
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<td>Response Evaluation Criteria in Solid Tumors</td>
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<td>Renal cell carcinoma</td>
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<td>Definition</td>
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<tr>
<td>RCD</td>
<td>Recommended combination dose</td>
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<td>receptor tyrosine kinase</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SCCHN</td>
<td>squamous cell carcinoma of the head and neck</td>
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<tr>
<td>SD</td>
<td>Stable disease</td>
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<td>SOC</td>
<td>Standard of care</td>
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<tr>
<td>TIL</td>
<td>tumor-infiltrating lymphocyte</td>
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<td>TKI</td>
<td>tyrosine kinase inhibitor</td>
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<td>TMA</td>
<td>thrombotic microangiopathy</td>
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<td>TME</td>
<td>tumor microenvironment</td>
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<tr>
<td>TMTB</td>
<td>Total Measured Tumor Burden</td>
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<td>ULN</td>
<td>Upper limit of normal</td>
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<tr>
<td>WFI</td>
<td>Water for Injection</td>
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9 References