Protocol Number: 0103-020

Official Title: A Phase 1/2 Study of HDAC Inhibitor, Mocetinostat,

in Combination With PD-L1 Inhibitor, Durvalumab,

in Advanced or Metastatic Solid Tumors and

Non-Small Cell Lung Cancer

NCT Number: NCT02805660

Document Date: 10 May 2017

MIRATI

T H E R A P E U T I C S

CLINICAL RESEARCH PROTOCOL

DRUG:	Mocetinostat (MGCD0103) and Durvalumab (MEDI4736)
STUDY NUMBER(S):	0103-020
PROTOCOL(S) TITLE:	A Phase 1/2 Study of HDAC Inhibitor, Mocetinostat, in Combination With PD-L1 Inhibitor, Durvalumab, in Advanced or Metastatic Solid Tumors and Non-Small Cell Lung Cancer
IND NUMBER:	128250
SPONSOR:	Mirati Therapeutics, Inc. 9393 Towne Centre Drive, Suite 200 San Diego, California, 92121, USA
ORIGINAL PROTOCOL DATE:	15 January 2016
VERSION NUMBER:	V3.0
VERSION DATE:	10 May 2017

DOCUMENT HISTORY

Document	Version Date	Summary of Changes
Original Protocol Version 1.0	15 JAN 2016	NA
Amendment #1 Version 2.0	26 FEB 2016	At the request of FDA during IND review – Following added to ECG evaluations during study: • Table 1 – Added single ECG to Day 1 of Cycle 3 and higher and at End of Treatment • Table 1 – Added X indicators for triplicate ECGs described in Table 2 for Day 1 of Lead-in Period, Cycle 1 and Cycle 2 • Table 1 and Table 2 – Footnotes updated to indicate manual calculation of QTc intervals using Fridericia's formula for all ECGs • Section 7.3.5 – Clarified calculation of QTc intervals manually using Fridericia's formula Decision making during Phase 1 dose escalation using the modified toxicity probability interval (mTPI) method was made more conservative by using the MTD definition of 0.25 probability of toxicity rather than the original 0.3 probability. The definition of MTD in Section 3.1.3 was updated accordingly. In addition, a few word omissions or typographical errors were corrected.

Amendment #2 Version 3.0	10 MAY 2017	• Study Summary:
		   o Added language for Phase 2 clinical activity evaluable populations and included Predictive Probability Design (similar to Simon design, but allowing for more flexibility in the number of evaluable patients to take a decision on continuing or stopping additional patient enrollment).
		 • Schedule of Assessments (Table 1):
		   o Added optional tumor biopsy for biomarker studies at C2D1
		   o Deleted liver enzyme panel as a separate assessment item as these tests are included in the serum chemistry panel
		   o Clarified language in footnote 7 to allow for collection of safety labs one day prior to the start of Lead-in Day 1 and C1D1 (per Protocol Administrative letter dated 27Jul16)
		   o Added language to footnote 10 noting that tumor biopsy samples will not be collected on subjects in the Phase 1 50 mg cohort (per Protocol Administrative letter dated 28Apr16)
		   o Clarified language in footnote 12 for timing of single lead ECGs versus triplicate ECGs
		   o Updated footnote 13 to allow for use of PET scans for assessment of bone lesions if per standard of care

Document	Version Date	Summary of Changes
Amendment #2 Version 3.0 (cont'd)		• Introduction and Rationale: 　○ Updated mocetinostat clinical data section for consistency with most recent version of mocetinostat Investigator's Brochure (v9.0) 　○ Updated durvalumab clinical data section and adverse events of special interest for consistency with most recent version of durvalumab Investigator's Brochure (v10.0) • Study Design: 　○ Added language for Phase 2 clinical activity evaluable population and included Predictive Probability Design (similar to Simon design, but allowing for more flexibility in the number of evaluable patients to take a decision on continuing or stopping additional patient enrollment) (page 52) • Inclusion Criteria: 　○ Inclusion criteria #2 updated to include patients that have received either a platinum-based chemotherapy or an immunotherapy regimen based on changing standard of care for first line therapy 　○ Inclusion criteria #2.b.ii deleted to exclude patients with tumors that test positive for EGFR mutation or ALK fusion • Exclusion Criteria: 　○ Added Exclusion for Patients with any history of tumors that test positive for *EGFR, ROS1, ALK* mutations or *ALK* fusions or any other mutations for which there are tyrosine kinase inhibitors available or under development 　○ Revised Exclusion #12 to include patients with a history of chronic hepatitis C that is no longer present 　　Revised Exclusion #17.c to allow for assessment from one ECG reading, as per Schedule of Assessments 　○ Revised Exclusion #19 to note that subjects with active brain metastases are exclusionary. Subjects are eligible if brain metastases are adequately treated and subjects are neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment without the use of corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) • Study Treatment: 　○ Updated Section 5.1.1 to add capsule strengths of 10 mg and 25 mg for mocetinostat study drug treatment (per Protocol Administrative Letter dated 05Jul16) 　○ Updated Section 5.1.6 to provide further direction around mocetinostat administration and vomiting, as well as mocetinostat administration around PK sampling

Document	Version Date	Summary of Changes

Amendment #2
Version 3.0 (cont'd)
		• Study Treatment (cont'd):
		   o Updated Section 7.2 to allow for use of positron emission tomography (PET) scans for assessment of bone lesions if per standard of care
		   o Added Section 9.3.2 to define the Phase 2 Clinical Activity Evaluable Population
		   o Revised Section 5.1.8, Table 9, Table 10, Table 11 and Appendix 4 to include updated toxicity management guidelines for durvalumab (per Protocol Administrative letter dated 07Sep16)
		   o In Table 13 clarified that Gamma glutamyltransferase is collected at Screening, C1D1, and as clinically indicated
		   o Addressed clerical errors and made minor clarifications of language

STUDY SUMMARY

Title:
Phase 1/2 Study of HDAC Inhibitor, Mocetinostat, in Combination With PD-L1 Inhibitor, Durvalumab, in Advanced or Metastatic Solid Tumors and Non-Small Cell Lung Cancer

Rationale:
Advanced tumors evade host immune responses by down regulation of major histocompatibility complex (MHC) molecules and tumor antigens and by creating an immune suppressive microenvironment around the tumor. Histone deacetylases (HDACs) have been implicated in the epigenetic regulation of innate and adaptive immunity. Increasing evidence supports the proposal that spectrum-selective inhibitors of class I HDACs can reverse immune evasion and elicit antitumor host response through immunostimulatory mechanisms. The immunomodulatory properties of class I HDAC inhibitors are reported to be mediated through multiple mechanisms including: 1) induction of programmed cell death ligand 1 (PD-L1) expression on the tumor cell surface, 2) induction of tumor associated antigens (TAAs) and MHC Class I and Class II molecules on tumor cells, 3) induction of immunogenic cell death via activation and cross-presentation of tumor antigens by antigen presenting cells (APCs), 4) enhanced function of T effector cells, and 5) decreased function of immunosuppressive cell subsets including T regulatory (Treg) cells and myeloid-derived suppressor cells (MDSCs). In addition, HDAC inhibitors are associated with anticancer effects through inhibiting cell cycle progression and inducing apoptosis in tumor. The combination of a class I HDAC inhibitor with an anticancer immunotherapy has the potential to enhance activity over that observed with either agent alone.

Mocetinostat is a spectrum-selective Class I/IV HDAC inhibitor specifically targeting HDACs 1, 2, 3 and 11. Class I and IV HDACs are of particular interest from an immunostimulatory and immune priming perspective.

Durvalumab is a human monoclonal antibody (MAb) that inhibits binding of PD-L1 to programmed cell death 1 (PD-1) and CD80 expressed on host immune effector cells, preventing immune suppression signaling. Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors or hematological malignances.

Rationale (cont'd):	In this study, the treatment regimen will begin with a 7-Day Lead-in Period of mocetinostat followed by start of the combination regimen of mocetinostat and durvalumab. The Recommended Phase 2 Dose (RP2D) of mocetinostat will be established in the Phase 1 dose escalation segment, followed by evaluation of the clinical activity of the combination regimen in patients having NSCLC.
Target Population:	Phase 1: Patients with advanced solid tumors.
	Phase 2: Patients with advanced or metastatic NSCLC, who have received prior treatment with at least one platinum-containing doublet chemotherapy regimen for advanced/metastatic disease.
Number in Trial:	Phase 1: Approximately 24 patients.
	Phase 2: As many as 261 patients.
Primary Objectives:	• To determine the Recommended Phase 2 Dose (RP2D) of mocetinostat administered in combination with full dose durvalumab.
	• To evaluate the clinical activity of mocetinostat in combination with durvalumab in cohorts of patients with NSCLC having differing tumor expression of PD-L1 or prior tumor responsiveness to treatment with checkpoint inhibitors.
Secondary Objectives:	• To evaluate the safety and tolerability of mocetinostat in combination with durvalumab in the selected population.
	• To evaluate secondary efficacy endpoints with mocetinostat in combination with durvalumab treatment in the selected population.
	• To evaluate mocetinostat and durvalumab pharmacokinetics (PK).
	• To evaluate the incidence of anti-drug antibodies (ADA) to durvalumab.
	• To evaluate the effect of mocetinostat during the Lead-in Period on tumor cell PD-L1 expression.

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Primary
Endpoints:

• Incidence of Dose Limiting Toxicities (DLTs) occurring during the first 28-day cycle of combination treatment.

• Objective Response Rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Secondary
Endpoints:

• Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events and laboratory abnormalities.

• Secondary efficacy endpoints:

  o Duration of Response (DR);

  o Clinical Benefit Rate (CBR);

  o Progression-Free Survival (PFS);

  o 1-Year Survival Rate; and

  o Overall Survival (OS).

• Blood plasma MGCD0103 and MEDI4736 concentrations.

• Anti-drug antibody (ADA) detected in blood.

• Tumor PD-L1 expression.

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Study Design: Study 0103-020 is an open-label Phase 1/2 evaluation of mocetinostat in combination with durvalumab. The Phase 1 segment will define the RP2D of mocetinostat to be used in combination with the full dose regimen of durvalumab; eligible patients will have an advanced solid tumor disease that is not amendable to curative treatment. The Phase 2 segment will evaluate the clinical activity of mocetinostat in combination with durvalumab, as assessed by ORR in accordance with RECIST 1.1., in patients with locally advanced, unresectable or metastatic NSCLC who have previously received at least one platinum-containing doublet chemotherapy regimen for advanced disease. Patients who have previously received treatment with checkpoint inhibitors may be in enrolled in the Phase 1 assessment and will be enrolled into dedicated cohorts in the Phase 2 assessment. Secondary objectives include secondary efficacy endpoints, PK, incidence of ADA and change in tumor PD-L1 expression.

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████████████████████████   The Schedule of Assessments to be performed in the study is presented in Table 1. Triplicate ECG assessments, PK, and ADA collection time points are presented in Table 2.

The treatment regimen to be evaluated in this study includes a 7-Day Lead-in Period of mocetinostat single agent administered three times weekly (TIW, e.g., Monday, Wednesday and Friday) followed by administration of the combination regimen with durvalumab. The RP2D dose of mocetinostat will be established in successive dose escalation cohorts in the Phase 1 study and utilized in the Phase 2 study. The dose and regimen of durvalumab to be used throughout the study is 1500 mg on Day 1 of each 28-day cycle (i.e., Q4W). Guidelines for adverse event management and associated treatment modifications of each agent are provided in Section 5.

The dose escalation phase of the study will employ the modified toxicity probability interval (mTPI [Ji-2013]) method. The mocetinostat dose levels planned for evaluation include 50, 70, and 90 mg TIW, depending on safety observations. In addition, if necessary, dose de-escalation of mocetinostat to 40 mg TIW may be undertaken.

Study Design (cont'd):

The Phase 2 study will enroll patients with NSCLC into one of the following 4 population cohorts:

Cohort 1 – Patients naïve to treatment with immunotherapy, having tumor with no/low PD-L1 expression.

Cohort 2 – Patients naïve to treatment with immunotherapy, having tumor with high PD-L1 expression.

Cohort 3 – Patients previously treated with an anti-PD-L1 or anti-PD-1 agent with clinical benefit response followed by progression of disease.

Cohort 4 – Patients previously treated with an anti-PD-L1 or anti-PD-1 agent with progression of disease ≤ 16 weeks after initiation of treatment.

Tumor PD-L1 expression will be determined by the PD-L1 (SP263) CDx assay. No/low PD-L1 expression is defined as positivity < 25% of tumor cells; high PD-L1 expression is defined as positivity ≥25% of tumor cells. Tumor samples used to establish PD-L1 expression for eligibility must have been collected after the most recent systemic therapy.

The sample sizes for the populations to be enrolled in the Phase 2 portion of the study are based on Predictive Probability Design, which allows for flexibility in the number of patients to be included at first stage in order to ensure that sufficient number of evaluable patients are available for decision to continue or to stop enrollment of additional patients.

- Cohorts 1, 3 and 4: Stage 1 of enrollment will include a minimum of 9 evaluable patients. With exactly 9 evaluable patients at Stage 1, if at least 1 patient has an Objective Response, 8 additional evaluable patients will be enrolled, for a total sample size of 17 evaluable patients. If at least 3 Objective Responses are observed, further investigation may be warranted.

- Cohort 2: Stage 1 of enrollment will include approximately 17 evaluable patients. With exactly 17 evaluable patients at Stage 1, if at least 5 patients have Objective Responses, 27 additional evaluable patients will be enrolled, for a total sample size of 44 evaluable patients. If at least 18 Objective Responses are observed, further investigation may be warranted.

Study Design (cont'd):

The exact stopping rules for all cohorts will be calculated based on the Predictive Probability Design, once the exact number of patients evaluable at Stage 1 is known. The aim is to get a minimum of 9 evaluable patients at Stage 1 for cohorts 1, 3 and 4 and about 17 evaluable patients at Stage 1 for cohort 2.

The populations included in Cohorts 3 and 4, who have had progression of disease during or following treatment with a checkpoint inhibitor, represent a potential unmet medical need. For this reason, if results in Stage 2 of enrollment are of high interest, enrollment may be expanded to as many as 100 patients total in each cohort to narrow the 95% Confidence Interval (CI) around the ORR point estimate and more fully characterize the secondary endpoints in the population of interest.

In order to be part of the clinical activity evaluable population, the patient must have at least one on-study disease assessment or discontinue from treatment for PD prior to this assessment. Patients who discontinue treatment prior to the first on-study disease assessment for an AE, toxicity, or withdraw consent are considered non-evaluable for disease assessment. These patients will not be part of the clinical activity evaluable population.

Disease response and progression as documented by the investigator in the Case Report Form (CRF) will be the basis for patient management and study expansion decision making. Unconfirmed objective responses recorded in the CRF may be used as the initial basis for expansion of study enrollment; however, follow-up evaluations on patients with unconfirmed responses must continue to support the decision to continue to the full number of patients to be included in the next stage. Central radiology review for disease response and progression may be added to the study during Stage 2. If this occurs, central review of all radiologic assessments performed in the study will be expected (including retrospective review of patients enrolled in Stage 1), and central radiology review for disease response will be the basis for the primary statistical analyses to estimate the objective response rate and its confidence interval, as well as the duration of response and PFS.

Table 1: Schedule of Assessments

The Schedule of Assessments provides an overview of the protocol visits and procedures. Refer to Section 7 for detailed information on each assessment. Additional, unplanned assessments should be performed as clinically indicated, including for the purpose of fully evaluating adverse events.

Assessments	Screen/ Baseline Within 28 days	7-Day Mocetinostat Lead-In Period Day 1	Mocetinistat + Durvalumab					End of Treatment[15]	
			Cycle 1		Cycle 2 and 3		≥Cycle 4	End of Treatment/ Withdrawal	Post Treatment Follow Up
			Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)		
Study Participation Informed Consent[1]	Before study specific assessments								
Tumor PD-L1 Expression Testing[2]	X		X					X	
Medical History, Disease History, Prior Therapy	X								
ECOG Performance Status	X								
Physical Exam[3]	X							X	
Abbreviated Physical Exam[3]		X	X	X	X	X	X		
Vital Signs[4]	X	X	X	X	X	X	X	X	
Pregnancy Test[5]	X	As clinically indicated							
Hematology[6,7]	X	X	X	X	X	X	X	X	

Table 1:   Schedule of Assessments – During Study (Continued)

Assessments	Screen/ Baseline Within 28 days	7-Day Mocetinostat Lead-In Period Day 1	Mocetinistat + Durvalumab Cycle 1 Day 1	Cycle 1 Day 15 (± 2 days)	Cycle 2 and 3 Day 1 (± 2 days)	Cycle 2 and 3 Day 15 (± 2 days)	≥Cycle 4 Day 1 (± 2 days)	End of Treatment[15] End of Treatment/ Withdrawal	End of Treatment[15] Post Treatment Follow Up
Coagulation[6,7]	X	As clinically indicated							
Urinalysis[6,7]	X		X		X		X		
Serum Chemistry[6,7]	X	X	X	X	X	X	X	X	
Thyroid Function Test[6,7]	X		X		X		X		
Blood for Pharmcokinetics[8]		See Table 2							90 Days
Blood for Anti-Drug Antibody[9]		See Table 2							90 Days
Biopsy of tumor for Biomarker Studies[10]	X		X		X[10]			X	
Blood Samples for Biomarker Studies[11]	X	X	X	X[11]	11				
Single 12-Lead ECG[12]	X				Cycle 3		X	X	
Triplicate 12-Lead ECG[12]		X, See Table 2	X		Cycle 2				
Echocardiogram	X			X	X		X	X	

Table 1: Schedule of Assessments – During Study (Continued)

Assessments	Screen/ Baseline	7-Day Mocetinostat Lead-In Period	Mocetinistat + Durvalumab					End of Treatment[15]	
			Cycle 1		Cycle 2 and 3		≥Cycle 4		
	Within 28 days	Day 1	Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	End of Treatment/ Withdrawal	Post Treatment Follow Up
Disease Evaluation[13]	X		Q 8 weeks Starting from Cycle 1, Day 1 until Week 49 (~1 year) and then Q 12 weeks						
Mocetinostat Dispensing and/or Reconciliation		X	X		X		X		
Durvalumab Administration			X		X		X		
Adverse Events[14] and Concomitant Medications	SAEs only	Throughout							SAEs only for 90 Days
Long Term Follow-up[16]									X

1 Study Participation Informed Consent: May be performed prior to 28 days before first dose of study treatment and must be completed prior to study specific assessments.
2 Tumor Testing for PD-L1 Expression: Required test for patients enrolling in Cohorts 1 and 2; encouraged for patients enrolling in Phase 1 or Phase 2 Cohorts 3 and 4. Biopsy may precede informed consent if performed as Standard of Care (SOC) or to assess eligibility for a different clinical trial. In Cohorts 1 and 2, the sample tested must have been collected following completion of the most recent systemic treatment regimen.
3 Physical Examinations: A complete physical examination required at Screening and End of Treatment only. Height will be recorded at screening only. All other evaluations will be symptom-directed, abbreviated evaluations.
4 Vital Signs: Weight, temperature, blood pressure, and pulse rate to be assessed prior to dosing as indicated. In addition, blood pressure and pulse rate will be assessed every 30 minutes (± 5 minutes) between the start and end of durvalumab infusions and, for the first infusion, for 1 hour post infusion. If the Durvalumab infusion period lasts 60 minutes, the first BP and pulse assessment should be made 30 minutes into the infusion and 30 minutes later at the end. If the infusion period lasts longer than 60 minutes, BP and pulse assessment should continue to be made at 30-minute (± 5 minutes) intervals.

5   Pregnancy Test: If the patient is a woman of childbearing potential, negative serum or urine pregnancy test performed by the local laboratory at screening will be required. The informed consent process must include discussion of the risks associated with pregnancy and adequate contraception methods. Additional pregnancy testing may be necessary if required by local practices or regulations, or if potential pregnancy is suspected.

6   Selected Lead-In, Day 1 Assessments: Repeat assessment not required if screening assessment performed within 7 days before the first dose.

7   Safety Laboratory Assessments: Hematology, coagulation, chemistry and thyroid function evaluations (see Section 7.3.4) will be performed by local laboratories. For scheduling convenience, these assessments may be performed one day prior to the visit at the start of the 7-day Lead-in Period and Cycle 1 Day 1.

8   Pharmacokinetic Samples: Blood samples to be collected following ECGs and assessment of vital signs as scheduled in Table 2. In addition, in the event of a Serious Adverse Event (SAE), unscheduled PK blood samples should be drawn for each study treatment as soon as possible.

9   Anti-Drug Antibody Samples: Blood samples to be collected as scheduled in Table 2.

10   Tumor Biopsy for Biomarker Studies: Consent for serial sampling of tumor tissue (preferably the same lesion) is requested but is not mandatory for study entry. The tumor biopsy used to determine eligibility may be used for the baseline assessment. Four collection timepoints are scheduled: baseline, C1D1, C2D1, and EOT. Markers of interest in tumor tissue include PD-L1 expression, CD8+ tumor infiltrating lymphocytes (TILs), natural killer cells (NK-cells), T regulatory cells (Tregs), and myeloid derived suppressor cells (MDSCs). Tumor biopsy tissue samples will not be collected on subjects in the Phase 1 50 mg cohort, and are optional for subjects in all other cohorts.

11   Blood Samples for Biomarker Studies: Blood samples for biomarker studies will not be collected on subjects in the Phase 1 50 mg cohort, but will be required for subjects in all other cohorts. At the beginning of the study, sampling will be scheduled on Cycle 1 Day 15. During the study, emerging data may indicate that quality of information gained from the assessment should improve with increased duration of combination treatment If so, the sample may be moved to Cycle 2 Day 1 and communicated to Investigators by Administrative Letter. Markers of interest in circulation include circulating PD-L1, Tregs, MDSCs, NK-cells, flow cytometry for T- and B-cell including CD4, CD8 and Ki67, and selected cytokines including CD8A, GZMB, IFNγ, CXCL9, CXCL10, CXCL11, and TBX21.

12   ECGs: Single 12-lead ECGs are to be performed at screening and at points not accompanied by PK sampling, with the exception of C3D1, C4D1 and C7D1. On days when PK samples are being collected, the single ECG should be performed prior to the blood draw. Triplicate ECGs are to be performed to as noted in Table 2. Assessments will include an evaluation of rhythm, heart rate, and PR, QRS, QT, and QTc intervals (Fridericia's formula). Respiration rate should be recorded during each ECG assessment.

13   Disease Evaluations: To be performed at screening (28 day window allowed) and every 8 weeks (± 10 days window) from C1D1 for all other assessments except screening until Week 49 (~1 year) and then every 12 weeks. At screening/baseline, assessments are to include CT with contrast of the chest, abdomen and pelvis, as well as brain Magnetic Resonance Imaging (MRI) with and without gadolinium or Computed Tomography Scan (CT) with contrast, a whole body bone scan and evaluation of any superficial lesions. Subsequent disease assessments should include all sites of disease identified at baseline or suspected to have developed; bone scans may be performed at one-half the frequency of other radiology evaluations and should be performed during assessment for confirmation of disease response. For those sites that routinely use PET scans for assessment of bone lesions in lieu of skeletal scintigraphy, PET scans may be used on-study, with the same modality planned throughout the study for any given patient. More detailed guidance on exceptional circumstances is provided in the protocol.

14   Adverse Events: SAEs will be reported from the time of informed consent until 90 days after the last administration of mocetinostat or durvalumab. Adverse events will be reported from the first day of study treatment until at least 28 days after last dose of study drug, and until resolution or stabilization of acute AEs and/or ongoing SAEs. After the 90-day SAE observation period, post-treatment follow-up may be performed by remote contact (e.g., telephone call).

15   End of Treatment: Assessments that have been completed in the previous 4 weeks do not need to be repeated (8 or 12 weeks for tumor assessments in accordance with schedule).

16   Long Term Follow-up: Blood samples for MEDI4736 PK and ADA will be collected approximately 90 days after the last infusion of durvalumab. Survival status and subsequent therapies will be collected during long term follow-up every 2 months (±14 days) from the date the subject was discontinued from study treatment until death or lost to follow-up. Follow-up beyond 90 days after last treatment may be performed by telephone contact.

Table 2: Schedule of Triplicate ECG, PK and ADA Assessments

| Nominal Cycle Day | Mocetinostat [1] | | Durvalumab [1,2] | |
	Triplicate ECG [3]	PK Sample [5,6,7]	PK Sample [5,6]	ADA Sample [6]
Lead-In Day 1	Pre-[4] and post-dose (1 hour only)	Phase 1: Pre- and post-dose (1, 3 and 7 hour) Phase 2: Pre- and post-dose (1 hour)		
Cycle 1 Day 1 (Day 1, Week 1)	Pre- and post-dose (1 hour only)	Phase 1: Pre- and post-dose (1, 3 and 7 hour) Phase 2: Pre- and post-dose (1 hour)	Pre-dose and end-of-infusion	Pre-dose
Cycle 1 Day 15 (Day 15, Week 3)		Pre- and post-dose (1 hour)	Pre-mocetinostat dose	
Cycle 2 Day 1 (Day 29, Week 5)	Pre- and post-dose (1 hour)	Pre- and post-dose (1 hour)	Pre-dose	Pre-dose
Cycle 3 Day 1 (Day 57, Week 8)		Pre- and post-dose (1 hour)	Pre-dose	
Cycle 4 Day 1 (Day 85, Week 13)			Pre-dose and end-of-infusion	Pre-dose
Cycle 7 Day 1 (Day 169, Week 25)		Pre-dose	Pre-dose	Pre-dose
Long Term Follow-up			90-days after last dose	90-days after last dose

1. On days mocetinostat and durvalumab are both administered and scheduled for PK assessment, mocetinostat dosing and sampling should precede durvalumab dosing. The 1 hour post-dose mocetinostat PK sample and the pre-dose durvalumab PK sample can be drawn at the same time, but separate samples for each must be collected as outlined in the Covance Lab Manual.
2. The typical durvalumab infusion duration is 1-hour. End-of-infusion samples are to be collected within 5 minutes from the contralateral arm.
3. ECGs should be taken in triplicate, with readings at least 2 minutes apart. QTc should be manually calculated using Fridericia's formula.
4. On Lead-In Day 1, two sets of triplicate ECGs should be done within 1 hour prior to dosing (e.g., at 20-30 minute intervals) to firmly establish the baseline. In general, ECGs should be performed prior (within -30 to -5 minutes) to the respective PK blood collection.
5. Scheduled vital signs and triplicate ECGs precede PK sample collection in all cases.
6. Pre-dose sample allowable window up to 30 minutes prior to dose in all cases.
7. Allowable windows for mocetinostat post-dose samples are plus or minus 30 minutes for 1 hour post-dose and plus or minus 1 hour for 3 and 7 hour samples.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ADA	Anti-drug Antibodies
AE	Adverse Event
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cells
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography Scan
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EIU	Exposure In-Utero
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDAC	Histone Deacetylases
HDACi	Histone Deacetylase Inhibitor
HDPE	High-Density Polyethlyene
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	International Normalized Ration
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IUD	Intrauterine Device
IV	Intravenous
MAb	Monoclonal Antibody
MDSC	Myeloid-derived Suppressor Cell
MDSCs	Myeloid-Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHC	Major Histocompatibility Complex
mITT	Modified Intent-to-Treat
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
NCI	National Cancer Institute
NE	Not Evaluable
NK	Natural Killer
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Objective Progression of Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PTT	Partial Thromboplastin Time

QTc	Corrected QT Interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	Standard of Care
TAA	Tumor Associated Antigens
TIW	Three Times Weekly
Treg	T Regulatory Cells
ULN	Upper Limit of Normal
WBC	White Blood Cell
WOCBP	Women of Child Bearing Potential

1   INTRODUCTION AND RATIONALE

1.1   Disease and Therapeutic Strategy

1.1.1   *Non-Small Cell Lung Cancer*

Lung cancer remains the leading cause of cancer-related death in the United States (US). Approximately 221,200 new cases of lung cancer are expected to be diagnosed in the US in 2015, and approximately 158,040 deaths will be attributed to lung cancer (Cancer Facts and Figures-2015). Non-small cell lung cancer (NSCLC) accounts for approximately 83% of lung cancer cases (Cancer Facts and Figures-2015), of which approximately half are classified as adenocarcinoma of the lung; squamous cell carcinoma accounts for approximately one-third of NSCLC cases and large cell carcinoma is less frequently diagnosed.

In 1995, the use of cisplatin-based chemotherapy was reported to lead to modest improvement in survival in patients with advanced NSCLC as compared to best supportive care, with a 27% reduction in death as reported in a meta-analysis of 11 trials (NSCLC Collaborative Group-1995). Subsequently, other chemotherapeutic agents have been reported to be active in NSCLC, leading to a comparison of 4 platinum-based doublets in the first-line treatment setting, all of which demonstrated similar activity (Schiller-2002). The importance of histology in the selection of first-line treatment for NSCLC was later described in the development of bevacizumab and pemetrexed. In a Phase 3 clinical trial, treatment with bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), demonstrated an improvement in survival when added to doublet chemotherapy, specifically in patients with non-squamous NSCLC (Sandler-2006). Similarly, treatment with pemetrexed, an antifolate chemotherapeutic agent, resulted in an improvement in survival when used as part of a chemotherapy doublet in patients non-squamous NSCLC, but with a probable decrease in survival among patients with squamous cell NSCLC (Scagliotti-2008). Based on the results of these and other trials, platinum-based chemotherapy doublets, with or without bevacizumab in selected patients, remain a standard of care for most patients with advanced NSCLC in the first-line treatment setting.

Effective options are limited however for patients with advanced NSCLC whose disease progresses after first-line treatment. Over the past few years there has been increasing interest in treating cancer with immunotherapy, in particular manipulating the anticancer host immune response with human monoclonal antibodies (MAbs).

Nivolumab, a fully human IgG4, PD-1 receptor antagonist, was evaluated in a Phase 3 clinical trial of patients with squamous cell carcinoma of the lung with disease progression during or after first-line chemotherapy. This study demonstrated a significant improvement in survival compared with docetaxel, with a hazard ratio (HR) of 0.59 (95% CI: 0.44, 0.79, p<0.001) (Brahmer-2015). A similar Phase 3 trial of patients

with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy demonstrated an improvement in survival with nivolumab over docetaxel (HR 0.73, 96% [sic] CI 0.59, 0.89, p=0.002) (Borghaei-2015). Opdivo® (nivolumab) was approved by the FDA in for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Nivolumab was approved in the US in March 2015 for squamous NSCLC and October 2015 for non-squamous NSCLC.

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. In a large international Phase 1 clinical trial, pembrolizumab was given to 495 patients with advanced NSCLC to evaluate safety, side-effect profile, and antitumor activity (Garon-2015). Patients (some of whom had received previous therapy and some of who had not) were treated with various doses and regimens of pembrolizumab. Pembrolizumab had an acceptable side-effect profile and showed anti-tumor activity. Among all patients, the objective response rate was 19.4%, and the median duration of response was 12.5 months. The median duration of progression-free survival was 3.7 months, and the median duration of overall survival was 12.0 months. Keytruda® (pembrolizumab) was approved by the FDA in October 2015 for the treatment of patients with metastatic squamous or non-squamous NSCLC with progression on or after platinum-based chemotherapy.

Significant activity has been observed with durvalumab in NSCLC. In Study CD-ON-durvalumab-1108, 456 of 694 subjects were treated with durvalumab 10 mg/kg Q2W and 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). Among the 86 patients with PD-L1-positive NSCLC, the ORR was 26.7% and the disease control rate (DCR)-24w was 36.0% (durvalumab Investigator's Brochure [IB Version 8.0], Rizvi-2015). Among the 95 patients with PD-L1-negative NSCLC, the ORR was 6.3% and the DCR-24w was 25.3%.

1.1.2   HDAC Inhibition as a Therapeutic Strategy in Cancer

Histone deacetylases (HDACs) are a family of enzymes that, together with histone acetyltransferases (HATs), exert epigenetic control over the acetylation state of chromatin. In eukaryotic cells, transcriptionally active genes are associated with hyperacetylated chromatin, whereas transcriptionally silent genes are associated with hypoacetylated chromatin (Moradei-2005). HATs, acting as transcription co-activators, catalyze the addition of acetyl groups onto the ε-amino group of lysine residues in the N-terminal tails of core histones, which weakens the histone-DNA interaction, thereby increasing the accessibility of a variety of transcription factors to DNA (Moradei-2005). Conversely, HDACs, acting as transcription corepressors, remove the acetyl groups from the acetylated lysines in histones, which condenses the structure of chromatin and restricts the access of transcription factors (Moradei-2005).

Three HDAC classes (Classes I, II and IV) and 11 NAD+-independent HDAC isotypes have been identified in humans (Moradei-2005, De Ruijter-2003). Class I enzymes (HDACs 1, 2, 3, and 8) are ubiquitously expressed, predominantly nuclear, and mainly function as transcriptional co-repressors. Class II enzymes (HDACs 4, 5, 6, 7, 9 and 10) are tissue specific, and have been theorized to have distinct functions in cellular differentiation and developmental processes (Bertos-2001). HDAC 11 comprises Class IV HDACs (Gao-2002).

As HDACs are involved in many cellular processes, such as cell cycle progression and differentiation, deregulation of HDAC activity is associated cancer progression resulting in the silencing of tumor suppressor genes and uncontrolled tumor growth in certain malignancies including lymphomas, bladder, and lung cancers. Numerous studies using tumor cell lines and tumor cell extracts have observed increased HDAC activity in malignancy, beginning with the observations that histone acetylation and deacetylation rates were increased in hepatoma cells compared with normal cells (Horiuchi-1981), and continuing with observations associating HDAC activity with cell transformation (Brehm-1999) and linking HDAC with other nuclear proteins that are important in regulating gene expression in multiple cancer cell lines including leukemia cell lines (Brehm-1999), prostate cancer lines, (Patra-2001) and breast cancer lines (Babic-2004). HDAC inhibition has been implicated in the inhibition of angiogenesis, induction of cellular differentiation, growth arrest, and apoptosis in a broad spectrum of tumor cells, all effects contributing to tumor regression without affecting normal cells (Moradei-2005). Inhibition of HDAC activity results in accumulation of acetylated proteins including histones, transcription factors, and heat shock proteins, leading to global cellular changes in transcription, mitosis, and protein stability. These changes interfere with tumor cell proliferation, survival, and cellular homeostasis, contributing to an anti-tumor effect. As cancer cells adapt to this insult, several mechanism of resistance may develop, including increased drug efflux, HDAC over-expression or desensitization, alterations of stress response mechanisms and increased anti-apoptotic signaling (Fantin-2007).

HDACs have been implicated in the epigenetic regulation of innate and adaptive immunity. Accumulating evidence indicates that tumors evade immune responses by down regulation of MHC molecules and tumor antigens or active suppression of anti-tumor immune responses at the site of the tumor by creating an immune suppressive tumor microenvironment. In addition to a clearly defined anticancer mechanism of action of HDACi in inhibiting cell cycle progression and inducing apoptosis of a wide variety of tumor types, increasing evidence supports the proposal that spectrum-selective inhibitors of class I HDACs can reverse immune evasion and elicit antitumor efficacy through an immunostimulatory mechanism of action (Kroesen-2014, Leggatt-2012, West-2012). The cellular effects of HDACis are mediated by accumulation of acetylated histone proteins and subsequent altered gene transcription. Both the direct antitumor effects and the immunomodulatory activity of HDACis are reported to be mediated through both the modification of gene expression through histone lysine acetylation as well as and the post-translational modification of selected proteins and subsequent

protein function (Kroesen-2014, West-2012). The immunomodulatory properties of class I HDACis are reported to be mediated through several distinct routes including: 1) induction of PD-L1 expression, 2) enhancement of tumor antigenicity via induction of tumor associated antigens (TAAs) and MHC Class I and Class II molecules by tumor cells, 3) induction of immunogenic cell death via activation and cross-presentation of tumor antigens by antigen presenting cells (APCs), 4) enhanced function of T effector cells, and 5) decreased function of immunosuppressive cell subsets including T regulatory (Treg) cells and myeloid-derived suppressor cells (MDSCs) (Kroesen-2014; Leggatt-2012; West-2014). Additional support for the combination of HDAC inhibitors and immunomodulators is provided by nonclinical combination studies in immunocompetent models. Because of the ability of HDAC inhibitors to modify disease biology and induce tumor antigens, induce PD-L1 ligand expression, or modulate tumor infiltrating lymphocyte effector and regulatory populations, the combination with immunotherapy has the potential to enhance activity over that observed with either agent alone (Christiansen-2011, Kim-2014, Shen-2012, West-2012).

It should be noted that distinct and sometimes contrasting immunomodulatory properties of HDAC inhibitors have been reported for different structural classes and HDAC target spectra. Multiple HDAC inhibitors were demonstrated to increase PD-L1 expression and select MHC molecules and TAAs. However, contrasting effects on T effector cell populations and immunosuppressive cell subsets have been observed with different iHDACi classes. The Class I HDAC inhibitor entinostat demonstrated the ability to deplete Tregs and MDSCs and enhance CD8 positive T cells in the tumor microenvironment whereas structurally distinct and broader spectrum HDACs including SAHA, vorinostat, and romidepsin enhanced Treg immunosuppressive activity and reduced T effector cell activity. The class II HDACs including HDACs 6, 7, and 9 have been implicated in the inhibition of Treg immunosuppressive function.

Consistent with this class I HDAC target profile, nonclinical studies with mocetinostat have demonstrated increased PD-L1 and MHC class I molecules, enhanced T effector populations, and reduced Treg and MDSC populations in both systemic and tumor compartments in syngeneic mouse tumor models. In contrast, the dual immunosuppressive and immunostimulatory effects associated with Class II HDACs (HDAC 4-7/HDAC8-10) and pan-HDAC inhibition indicate that the target profile of HDAC inhibitors is of a critical consideration in defining immunomodulatory properties of this class of molecules. In this regard, it should be noted that pan-HDAC inhibitors have been used to limit cytokine production and immune damage in autoimmune diseases including rheumatoid arthritis and following allogenic transplant. The seemingly contrasting role for HDAC_is in distinct disease settings should be evaluated in the context of both disease indications and the difference in HDACi target profiles.

HDAC inhibition induces large scale epigenetic changes affecting multiple cancer signaling networks (Dokmanovic-2007, Marks-2000, Thiagalingam-2003). The anticancer properties of HDAC inhibitors may be due to the accumulation of acetylated histones that leads to the activation (and/or repression) of specific genes, and thereby inhibits tumor cell growth (Moradei-2005). Small molecule HDAC inhibitors identified to date include vorinostat (suberoylanilide hydroxamic acid, SAHA) (Richon-1998), romidepsin (FR901228) (Nakjima-1998), sodium butyrate (Hassig-1997), trichostatin A (TSA) (Yoshida-1995) and oxamflatin (Kim-1999). Although structurally diverse, each of these HDAC inhibitors, particularly the hydroxamic acids (which include vorinostat, TSA and oxamflatin) are pan-inhibitors of all Class I and II HDAC enzymes. Mocetinostat (MGCD0103) is an oral second generation benzamide HDAC inhibitor that selectively inhibits Class I (HDAC 1, 2, 3) and IV (HDAC 11) enzymes (Fournel-2008, Zhou-2008).

1.1.3 *Programmed Cell Death Ligand 1*

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung (Mu-2011), renal (Thompson-2005; Thompson-2006; Krambeck-2007), pancreatic (Nomi-2007; Loos-2008; Wang-2010), ovarian cancer (Hamanishi-2007), and hematologic malignancies (Andorsky-2011; Brusa-2013) tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. For example, in ovarian cancer, the 5-year survival rate in patients with low expression of PD-L1 was 80.2% compared to 52.6% in patients with high expression levels of PD-L1 (Hamanishi-2007). In lung cancer, only 20% of patients with tumors expressing PD-L1 survived more than 3 years compared to 49% of patients with tumors lacking PD-L1 expression (Mu-2011). These data suggest that an antibody targeting PD-L1 has the potential to affect multiple solid tumor types.

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to programmed cell death 1 (PD-1) or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir-2008; Park-2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zhou-2008).

1.2 Mocetinostat

Mocetinostat (MGCD0103) is an oral, second generation benzamide inhibitor of HDAC 1, 2, 3 and 11 with broad spectrum antitumor activity in vitro and in vivo (Fournel-2008, Zhou-2008).

1.2.1 Mocetinostat Drug Substance

Generic Name: Mocetinostat (free base)

Other Name: MGCD0103

Chemical Name: N-(2-amino-phenyl)-4-[(4-pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide

Empiric Formula: $C_{23}H_{20}N_6O$

Molecular Weight: 396.45

1.2.2 Mocetinostat Non-Clinical Data

Mocetinostat has been investigated in non-clinical pharmacokinetic, metabolism and toxicology studies. Detail on these studies can be found in the Investigator's Brochure.

Pharmacodynamics

Mocetinostat was shown to be a selective, potent, and dose-dependent inhibitor of human Class I (isoforms 1, 2, and 3) and Class IV (isoform 11) HDACs (Table 3). There was weak or no activity against Class II HDACs or HDAC 8. A kinetic analysis using HDAC 1 demonstrated that mocetinostat is a potent competitive inhibitor, with a Ki of 64 nM. Binding was reversible, with high affinity and slow kinetics. In addition, mocetinostat induced acetylation of core histones H4 and H3 in human bladder carcinoma (T24) cells, with an EC50 of 0.4 μM and 0.2 μM, respectively. Acetylation of histones was also observed in A549 human non-small cell lung carcinoma cells and A2780-S human ovarian carcinoma cells. Core histone acetylation was dose-dependent and was correlated with HDAC inhibition.

Mocetinostat induced cell cycle arrest of HCT116 human colon carcinoma cells in a dose-dependent manner. G2/M and sub-G1 accumulation was also observed in HeLa human cervical cancer cells and A549 human non-small cell lung carcinoma cells. These effects were shown to occur via a mechanism independent of tubulin polymerization. Exposure of HCT116 cells to mocetinostat at concentrations of 1 to 25 μM resulted in the dose-dependent induction of apoptosis. Dose-dependent apoptosis also was observed in both A549 human lung carcinoma cells and HeLa human cervical carcinoma cells at concentrations of 1 μM (the lowest concentration tested). Mocetinostat also induced significant apoptosis in several hematologic cancer cell lines, including Jurkat T-cell

leukemia cells, MV-4-11 acute myeloid leukemia cells, U266B1 multiple myeloma cells, and HL60 promyelocytic leukemia cells. Induction of apoptosis in all four hematologic cancer cell lines was dose-dependent. Expression of the cyclin-dependent kinase inhibitor p21waf1/Cip1 was upregulated both at the level of transcription and at the level of translation. A concentration of 1 µM mocetinostat induced p21waf1/Cip1 expression at least 2-fold in HCT116 colon carcinoma cells. This effect was independent of p53 status: p21waf1/Cip1 induction was observed both in HeLa cervical cancer cells, which are p53-null, and in A549 lung carcinoma cells, which express wild type p53.

Table 3:   Biochemical Inhibition of HDAC Activity by Mocetinostat

Parameter	Class I HDAC Isoforms				Class II HDAC Isoform				Class IV HDAC Isoforms
	1	**2**	**3**	**8**	**4**	**5**	**6**	**7**	**11**
Inhibition (+/-)	+	+	+	-	-	-	-	-	+
IC$_{50}$ (µM)	0.15	0.29	1.66	>20	15	>20	>20	>20	0.59

Mocetinostat had anti-proliferative activity against A549 lung cancer cells and Du145 prostate cancer cells (IC50 1.0 µM), but not against normal human mammary epithelial cells (IC50 > 20 µM). Inhibition was independent of p53 status as A549 cells express p53, whereas Du145 cells are p53-null. The anti-proliferative activity of mocetinostat was assessed against a variety of other human cancer cells with IC50 results in Table 4.

Table 4:   In Vitro Anti-proliferative Activity Against Various Human Lymphoma Cancer Cell Lines

Cell Lines	Subtype	IC50 (µM)
HMEC	Normal mammary epithelium	21.0
T24	Bladder Cancer	0.71
SKBR3	Breast Cancer	0.32
HCT116	Colon Cancer	0.06
MINO	Mantle cell lymphoma	0.48
HDLM-2	Hodgkin lymphoma	0.25

Nonclinical Studies Supporting Mocetinostat and Durvalumab Combination

A number of nonclinical studies were performed to evaluate the mechanism of action of mocetinostat, its immune stimulatory properties, and the optimal timing for administration in combination with immune checkpoint inhibitors such as PD-L1 antagonists. Initial studies were performed to assess the effect of mocetinostat on PD-L1, on major histocompatibility complex (MHC) class I and II molecules, and on immune co-stimulatory molecule gene and protein expression, across a panel of non-small cell lung cancer (NSCLC) cell lines in vitro. Mocetinostat demonstrated a concentration-dependent increase in PD-L1 gene expression ranging from 2- to 15-fold in all four NSCLC cell lines evaluated (H23, H1437, H1703, H1792) (Figure 1). In addition, mocetinostat increased PD-L1 cell-surface protein expression in 5 NSCLC cell lines, demonstrated by flow-cytometric analysis utilizing a specific PD-L1 antibody (BL-MGCD0103-032). The increased expression of PD-L1 on tumor cells by mocetinostat may signal a shift in dependence of tumor cells on evading tumor-immune response via a PD-1-dependent mechanism. In addition, mocetinostat demonstrated a concentration-dependent increase in gene expression of several members of the human leukocyte antigen (HLA) gene complex, in all four NSCLC lines evaluated (Figure 1). HLA genes comprise the human MHC Class I and II molecules that regulate the presentation of tumor-associated antigens (TAAs) at the cell surface to enable recognition by cytotoxic T cells (CD8+) (BL-MGCD0103-032). The induction of gene expression of MHC-class-I-related molecules, MIC-A and MIC-B, were also observed in all four NSCLC cell lines evaluated. The effector cytolytic responses of T cells and NK cells against tumor cells are mediated by NKG2D receptor-dependent engagement of MIC-A and MIC-B on target tumor cells, indicating that immune stimulatory properties of mocetinostat involve both innate and adaptive immune responses. Finally, mocetinostat induced the expression of the immune co-stimulatory molecule CD86, which is required for T-cell activation and antigen-dependent immune response against tumor cells expressing and presenting TAAs (BL-MGCD0103-032).

Figure 1:   Mocetinostat Modulates Expression of PD-L1 and Antigen Presentation Regulatory Genes in NCSLC Cell Lines
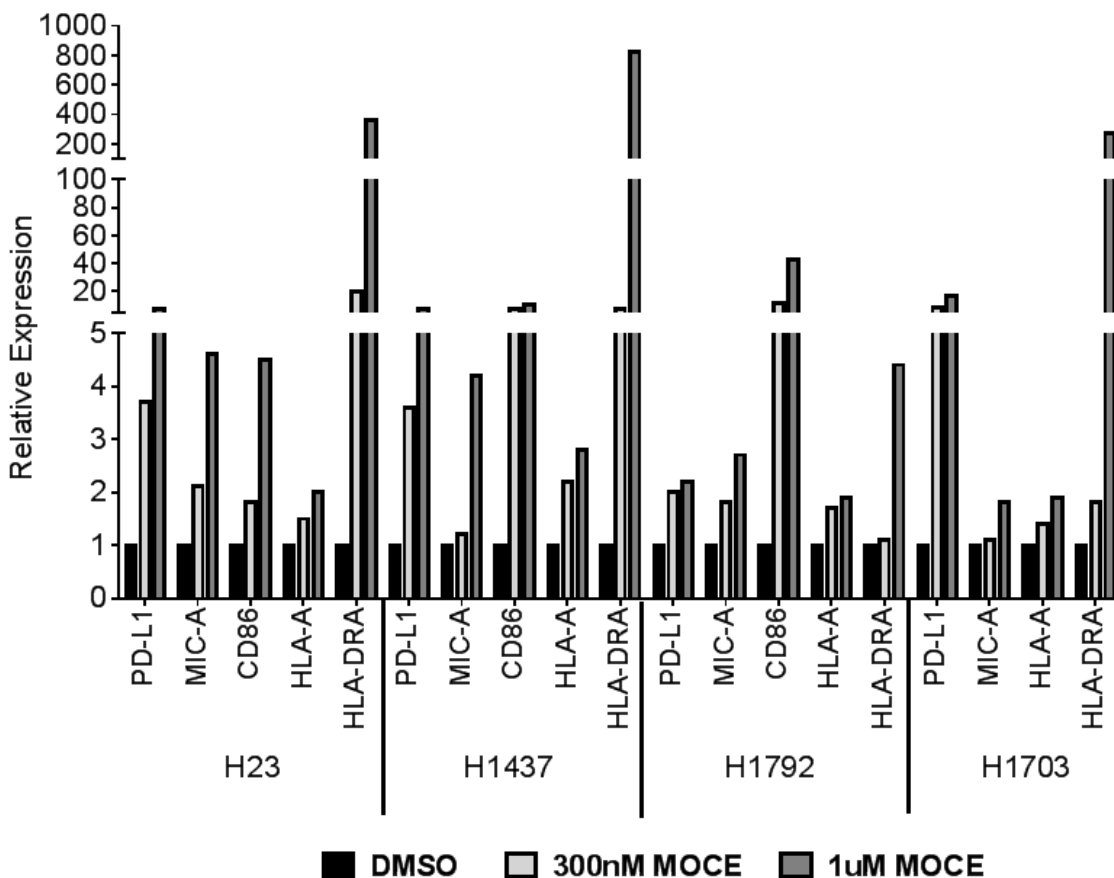
Gene modulation in NSCLC post mocetinostat treatment. Cells were seeded in 10 cm dishes and incubated with various doses of mocetinostat or DMSO for 48 hours. RNA was extracted with Qiagen RNEasy plus kit. Relative gene expression, by quantitative polymerase chain reaction (PCR), was normalized to DMSO treatment.

To determine effect on CD4- and CD8-positive effector T cells and immunosuppressive cellular subsets including T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs), mice bearing syngeneic subcutaneous CT26 colon tumors were treated with 100 mg/kg mocetinostat by daily oral gavage. In these studies, mocetinostat demonstrated an increase in splenic CD4-positive T effector cells and mature cytolytic CD8-positive T cells in tumors compared to vehicle controls by day six of administration (PH-MGCD0103-009) (Figure 2). In addition, mocetinostat treatment decreased tumor FoxP3-positive immunosuppressive Tregs and CD11b/Gr1-positive MDSCs in tumors compared to vehicle controls by day nine of administration (PH-MGCD0103-009).

Figure 2:   Mocetinostat Modulates Key Immune Cell Populations In Vivo
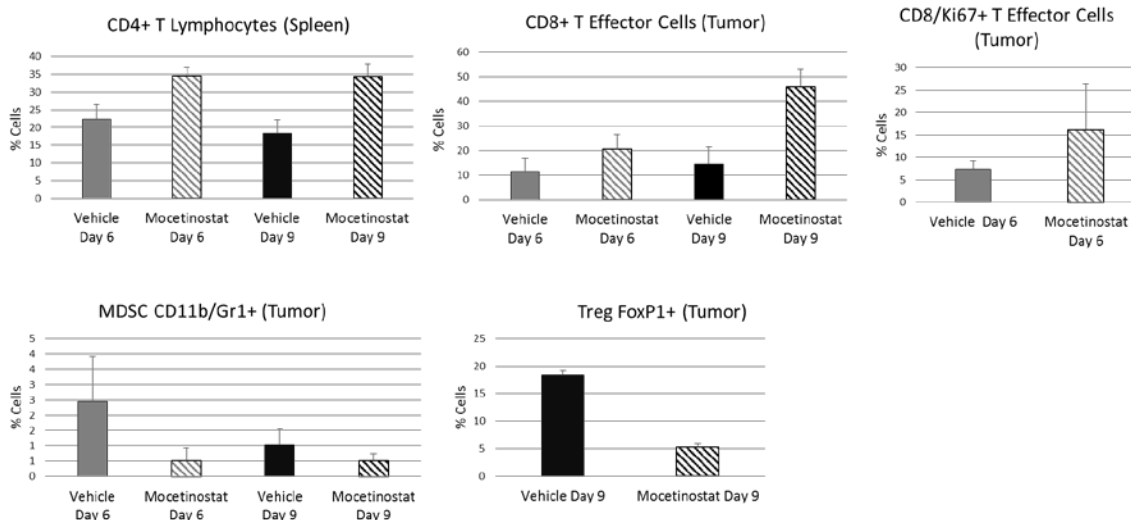
Mocetinostat modulates immune cell populations. Fresh tumor and spleen samples in cold PBS were delivered within 45 minutes. Stained samples were loaded into Attune Autosampler for FACS analysis. Flow cytometry markers included percentages of: T-Cells (CD4+ and CD8+), Regulatory T-Cells (Tregs) Proliferation marker CD8+ cells that are Ki67+, MDSC (CD11b/Gr1+). Error bars represent standard deviation.

To determine the effects of mocetinostat and PD-L1 antibody combination therapy on tumor growth, CT26 tumor-bearing mice were treated with either agent alone or in combination over selected administration schedules. On Day 23, a statistically significant decrease in relative tumor volume was observed in the mocetinostat plus PD-L1 antibody combination group with a three day mocetinostat lead-in period compared with either single agent alone (PH-MGCD0103-010).

1.2.3   *Mocetinostat Clinical Data*

Mocetinostat monotherapy and mocetinostat in combination with other anticancer agents have been evaluated as part of the clinical development program. As of November 2016 Mocetinostat has been investigated in more than 489 clinical trial patients with the following malignancies: Hodgkin's Lymphoma, Non-Hodgkin's Lymphoma (including diffuse large B-cell DLBCL and follicular lymphoma), acute myeloid leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, urothelial carcinoma, non-small cell lung cancer, and advanced solid tumors including adenocarcinoma of the pancreas. Detail on these studies can be found in the Investigator's Brochure, as well as Siu-2008, and Garcia-Manero-2004. When given daily as a single oral dose for 14 days followed by a 7-day rest period, the Maximum Tolerated Dose (MTD) was 12.5 mg/m^2. The dose limiting toxicity at the next higher dose of 17 mg/m^2 (20-30 mg) was fatigue. The 3 times weekly schedule appears to have improved tolerability compared with daily dosing as higher MTDs have been observed. Studies with this schedule identified

60 mg/m^2 (85-125 mg) as the MTD; however with additional testing, the recommended dose for Phase 2 studies is 70 mg or 90 mg, depending on the indication, as a fixed dose administered three times per week. Dose-limiting toxicity at higher doses included fatigue, nausea, vomiting and diarrhea.

In addition to Phase I studies, the safety profile of mocetinostat has been evaluated as a single agent in Phase 2 studies (Investigator's Brochure, Younes-2011, Blum-2009). Four previous Phase 2 studies have evaluated mocetinostat as a monotherapy in the following populations: 1) Elderly, previously untreated patients with AML or MDS or adults with relapsed/refractory AML or high-risk MDS; 2) Patients with relapsed or refractory NHL; 3) Patients with refractory CLL; and 4) Patients with relapsed or refractory HL. The safety profile of mocetinostat has also been investigated in combination with other anticancer agents in Phase 1/2 and Phase 2 studies. Mocetinostat has been evaluated with Vidaza® (azacitidine) in patients with MDS, AML, HL, or NHL, with Gemzar® (gemcitabine) in patients with refractory solid tumors or pancreatic cancer, and with docetaxel in patients with solid malignancies. The overall experience of patients receiving mocetinostat as a single agent or in combination with chemotherapy is summarized in the Investigator's Brochure.

Among 306 patients participating in clinical trials of mocetinostat single agent, treatment-related AEs were reported in 90.5% of patients. The most frequent AEs considered related to study drug (occurring in ≥10% of patients in a preferred term category) were reported for nausea (61.4%), fatigue (57.5%), diarrhea (46.7%), vomiting (37.3%), anorexia (26.8%), decreased weight (19.3%), anemia (15.4%), thrombocytopenia (13.1%), dyspepsia (11.8%) and abdominal pain (11.4%). The most frequent Grade 3/4 AEs considered related to study drug were the following fatigue (19.0%), thrombocytopenia (8.8%), neutropenia (6.5%), nausea (5.2%), anemia (5.6%), asthenia (4.6%), and anorexia (4.2%).

Mocetinostat Adverse Events of Interest

Fatigue

Fatigue has been observed consistently throughout the mocetinostat clinical evaluation program and has been deemed a drug-related toxicity. The etiology of fatigue is not yet understood.

Cystitis

Cystitis symptoms (e.g., dysuria, pollakiuria, hematuria, urgency, and bladder spasm) have been reported in some patients, most commonly after multiple cycles of treatment. Hemorrhagic cystitis has been described as a rare event.

Pericardial Events

Pericardial AEs have been reported in clinical trials of mocetinostat. The types of pericardial events included pericarditis, pericardial effusion, and cardiac tamponade. Of the pericardial adverse events, pericardial effusion was the most common. Findings of the analysis include a higher rate of pericardial SAEs among patients with Hodgkin lymphoma (9.5%) as compared to patients with leukemia or NHL (4.5% and 3.8%, respectively). Most of the pericardial AEs occurred during the first cycle of treatment. The majority of pericardial findings, including SAEs, resolved completely without sequelae, and no pericardial event was considered fatal. Screening assessments for pericardial events were not included in the mocetinostat program during most of the prior clinical trial experience. The current study includes screening assessments and exclusion criteria to ensure that baseline status is known.

Gastrointestinal Toxicities

GI toxicities such as anorexia, nausea, vomiting, and diarrhea have been reported as related to mocetinostat. Dehydration, electrolyte abnormalities (such as hypokalemia), hypotension, and syncope also have been observed in connection with GI toxicity.

Cardiac Arrhythmias

Grade 3 AEs of QTc prolongation (> 500 msec) were reported in 4 of 435 patients in clinical trials with mocetinostat; 3 of those 4 events were also reported as part of SAEs. Three of the 4 patients already had a prolonged QTc at baseline. Three of the events of QTc prolongation occurred in a setting of GI disturbances associated with dehydration and/or hypotension. In 2 cases, there was definite hypokalemia, with concomitant low magnesium in one patient, and in both cases, the QTc values decreased quickly to baseline levels after IV administration of potassium and magnesium. Concomitant treatment with drugs identified as having the potential to cause QTc prolongation may have been a factor in 2 patients.

Although therapy with mocetinostat does not appear to be an obvious risk factor for development of QTc prolongation, ECG monitoring may be warranted in the settings of GI disturbances associated with dehydration and/or electrolyte abnormalities.

1.2.4   Mocetinostat Human Pharmacokinetics and Product Metabolism

The pharmacokinetic profile of mocetinostat has been evaluated in clinical trials, after single and repeated dose administration. Plasma samples for pharmacokinetic analyses were collected over a 24-hour period following single and multiple doses. Plasma drug concentrations were determined using a validated, sensitive, LC-MS/MS assay. In general, mocetinostat was rapidly absorbed following administration with 200 mL of a low pH beverage, with maximum concentration (C_{max}) occurring 0.5 to 1.5 hours after dosing. The elimination half-life ranged from approximately 7 to 12 hours. As determined from the C_{max} and AUC values, exposure to mocetinostat following oral

dosing appears to increase with doses up to 110 mg. Mocetinostat did not appear to accumulate following multiple dosing, and its elimination half-life was approximately 10 hours.

Mocetinostat is metabolized by CYP enzymes that include CYP 2E1 and CYP 3A4, and possibly also CYP 2C8 and CYP 2C19. Caution should be used when mocetinostat is administered with concomitant medications that are inhibitors or inducers of CYP 2E1, or strong inhibitors or inducers of CYP 3A4.

Mocetinostat does not appear to be a strong inducer of CYP enzymes but may be an inhibitor of CYP 2C9. Caution should be used when mocetinostat is administered with concomitant medications that are substrates for CYP 2C9.

In vitro studies indicate that mocetinostat has a low potential for P-gp inhibition at the levels observed in patients.

1.3   Durvalumab

Durvalumab (also known as MEDI4736) is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of PD-L1 (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to PD-1 (CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

1.3.1   Durvalumab Drug Substance

Generic Name: Durvalumab

Other Name: MEDI4736

Molecular Weight: 149 kDa

1.3.2   Durvalumab Non-Clinical Data

The non-clinical experience is fully described in the current version of the durvalumab Investigator's Brochure (Investigator's Brochure V10.0-Durvalumab).

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity

(ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that durvalumab inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the PK/pharmacodynamics and potential toxicity of durvalumab. Following intravenous (IV) administration, the PK of durvalumab in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life (t1/2) increased with increasing doses, suggesting saturable target binding-mediated clearance of durvalumab. No apparent gender differences in PK profiles were observed for durvalumab.

In general, treatment of cynomolgus monkeys with durvalumab was not associated with any durvalumab-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA: durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to durvalumab. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab.

Finally, data from the pivotal 3-month GLP toxicity study with durvalumab in cynomolgus monkeys showed that subchronic dosing of durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the *in vivo* toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

1.3.3 *Durvalumab Clinical Data*

Clinical experience with durvalumab is fully described in the current version of the durvalumab Investigator's Brochure (Investigator's Brochure V10.0-Durvalumab). As of 12 Jul, 2016 across the entire clinical development program, an estimated 5225 patients have been exposed to 1 or more doses of durvalumab in clinical studies, either as monotherapy or in combination, including 2878 patients in open label trials, and 2347 patients as an estimate based on the random scheme in studies where the treatment arm is blinded. Of the 2878 patients in open label studies, 1,744 received durvalumab monotherapy, 808 received durvalumab in combination with tremelimumab, 140 patients received durvalumab in combination with other investigational products and 186 patients received durvalumab in combination with approved products. 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 the study protocols. AEs reported with durvalumab monotherapy in key clinical studies are described below.

Adverse Event Profile of Durvalumab Monotherapy

The safety profile of durvalumab monotherapy in the 970 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1744 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 12Jul2016, among the 970 patients treated with 10 mg/kg Q2W in Study CD-IN-durvalumab-1108, 947 patients (97.6%) had at least 1 AE (regardless of causality). AEs (all grades) reported in decreasing order of frequency in ≥10% of patients were fatigue (37.6%), nausea (23.7%), decreased appetite (23.2%), dyspnoea (21.9%), constipation (20.2%), diarrhoea and cough (17.9% each), back pain (16.5%), vomiting (15.9%), anaemia (15.6%), abdominal pain (14.4%), pyrexia (13.9%), arthralgia (13.1%), oedemaperipheral (12.1%), pruritus (11.6%) and headache (11.2%). Across the tumor types, the overall incidence of AEs was generally similar. A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity. Grade 3 or higher events were reported in 295 subjects (30.4%) and were manageable by general treatment guidelines contained in each of the study protocols. Events occurring in >2% of patients

were anaemia (6.2%), dyspnoea (6.0%), hyponatremia (5.4%), fatigue (3.9%), GGT increased (3.6%), abdominal pain (3.1%), AST increased (2.9%), back pain (2.9%) and dehydration (2.6%). A total of 554 patients (57.1%) reported AEs that were considered by the investigator to be related to investigational product. Treatment-related AEs (all grades) reported in >5% of patients were fatigue (18.7%); nausea (7.9%); diarrhoea (7.6%); pruritus (6.8%), decreased appetite (6.7%); hypothyroidism (6.3%) and rash (6.0%). The majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with ≥Grade 3 events occurring in 88 patients (9.1%). Treatment-related ≥Grade 3 or 4 events reported in ≥2 patients were fatigue (1.6%); AST increased (1.0%); ALT increased (0.8%); GGT increased (0.7%); hyponatremia, diarrhea (0.5% each); colitis (0.4%); decreased appetite and vomiting (0.3% each); and ALP increased, anaemia, arthralgia, autoimmune hepatitis, blood bilirubin increased, dyspnoea, hyperglycaemia, infusion related reaction, leukopenia, nausea, neutropenia, nervous system disorder, rash maculo-papular, thrombocytopenia, transaminases increased and weight decreased and (0.2% each). Four patients had a treatment-related Grade 5 event Treatment related SAEs that occurred in >1 patient each were colitis and pneumonitis (4 patients each); nervous system disorder (3 patients); and acute kidney injury, AST increased, and diarrhoea (2 patients each). The majority of the treatment-related SAEs were Grade 3 or higher in severity and recovered with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 24 subjects (2.5%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were Grade 1 or 2 in severity and resolved with or without sequelae.

The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 12Jul2016, 425 of 444 subjects (95.7%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were fatigue (23.6%), decreased appetite (22.1%), cough (20.3%), pyrexia (17.3%),nausea (16.7%), asthenia (16.0%), dyspnoea (15.8%), constipation (15.1%), diarrhoea (13.3%), anaemia (13.1%), vomiting (11.0%), and pruritus (10.6%). The majority of these AEs were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. The TEAEs of Grade 3 or higher reported in more than 2% of patients in decreasing order of frequency were anaemia (4.7%), dyspnoea (4.3%), and GGT increased (2.7%); none of these events were Grade 5. A total of 40 patients (9.0%) experienced a treatment-related TEAE of Grade 3 or higher. The events experienced by more than 1 patient were pneumonitis and GGT increased (4 patients each), diarrhoea and infusion-related reaction (3 patients each), AST increased, transaminases increased, vomiting and fatigue (2 patients each). All patients with treatment-related Grade 3 or higher pneumonitis, diarrhoea, infusion related reaction, transaminases increased and vomiting, recovered. Overall, the treatment-related Grade 3 or higher events were manageable by appropriate medical management, including in some cases the use of steroids or endocrine therapy, withholding durvalumab

dosing until the event resolved, or permanent discontinuation of durvalumab. SAEs were reported in 116 patients (26.1%); treatment-related SAEs were reported in 27 patients (6.1%). The SAEs with an incidence of ≥1.0% were dyspnoea (2.3%), pneumonia (2.0%), pleural effusion (1.6%), anaemia (1.1%), pneumonitis (1.1%) and pulmonary embolism (1.1%). Of these SAEs, only pneumonitis and anaemia were assessed by the Investigator as being treatment related (5 patients and 1 patient, respectively). All treatment-related SAEs of pneumonitis and anaemia resolved, except 1 pneumonitis event (ongoing at the time of death). A total of 11 patients (2.5%) have died due to an AE. The only TEAE with an outcome of death that was experienced by more than 1 patient was pneumonia (2 patients). Other TEAEs with an outcome of death occurring in 1 patient each were, acute myocardial infarction, cardiac failure, cardio-respiratory arrest, gastric haemorrhage, gastrointestinal haemorrhage, pneumonitis, pulmonary embolism, pulmonary sepsis and sudden death. Four of the 11 deaths were due to both the TEAE and the underlying NSCLC. Ten of the 11 deaths were assessed as not treatment-related. One patient experienced a treatment-related fatal TEAE of pneumonitis after discontinuing durvalumab and starting a subsequent anticancer therapy (erlotinib). Twenty-nine of 444 subjects (6.5%) permanently discontinued durvalumab treatment due to AEs. A total of 10 patients (2.3%) had a treatment-related event that led to discontinuation.

Durvalumab Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event 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 Study Physician.

AESIs based on observed safety events using durvalumab monotherapy and/or class effects for inhibitors of PD-L1 or PD-1 include:

- Colitis

- Pneumonitis

- ALT/AST increases / hepatitis / hepatotoxicity

- Neuropathy / neuromuscular toxicity (i.e., events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)

- Endocrinopathy (i.e., events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)

- Type 1 diabetes mellitus

- Rash/ dermatitis

- Nephritis

- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)

Further information on these risks (e.g., presenting symptoms) can be found in the current version of the Investigator's Brochure V10.0-Durvalumab.

1.3.4   *Durvalumab Human Pharmacokinetics*

As of 09 Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at $\geq$ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses $\geq$ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab $\geq$ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure $\geq$ 40 μg/mL throughout the dosing interval.

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 (WT) on PK of durvalumab (coefficient of $\leq$ 0.5). The impact of body WT-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 WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based

and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

As of 09 Feb2015, a total of 388 subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

1.3.5 *Durvalumab Monotherapy Clinical Activity in Solid Tumor Diseases*

In Study CD-ON-durvalumab-1108, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having $\geq$ 24 weeks follow-up, measurable disease at baseline, and $\geq$ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (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 (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; 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, DCR-24w 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%).

1.4 Expectations for Combination of Mocetinostat and Durvalumab

Potential for Drug-Drug Interactions

Treatment with mocetinostat in combination with durvalumab is unlikely to result in clinically relevant metabolism or elimination-based drug-drug interactions (DDI). Durvalumab is a mAb and is intravenously administered, whereas mocetinostat is a small molecule therapeutic administered orally; no absorption interaction is expected.

The fractional binding of MGCD0103 to human plasma was measured via equilibrium dialysis. At concentrations of 0.5, 1 and 10 μM, MGCD0103 showed binding of 95.1%, 97.5%, and 95.2%, respectively. MEDI4736 is a mAb and only binds specifically to IgG1κ, therefore, no risk of distribution interaction is expected.

Reaction phenotyping results indicated that MGCD0103 was metabolized by CYP2E1 and CYP3A and possibly CYP2C8 and 2C19. No studies on the metabolism of MEDI4736 have been performed *in vitro* or in humans. Like most therapeutic proteins, MEDI4736 is not expected to be metabolized by liver cytochrome P450 (CYP) or other drug metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction.

Evaluation of Potential for Increased Toxicities with Combination Use of Mocetinostat and Durvalumab

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune tolerance and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. Durvalumab (MEDI4736) is a mAb that inhibits binding of PD-L1 to PD-1 and CD80.

Mocetinostat (MGCD0103) is a small molecule inhibitor of Class I and IV HDACs. HDACs are involved in cellular processes such as cell cycle progression and differentiation and have been implicated in the epigenetic regulation of innate and adaptive immunity. Evidence supports the proposal that spectrum-selective inhibitors of Class I HDACs can reverse immune evasion and elicit antitumor efficacy through induction of PD-L1 expression; enhanced tumor antigenicity via induction of TAAs and MHC Class I and Class II molecules; activation and cross-presentation of tumor antigens by APCs; enhanced function of T effector cells; and decreased function of immunosuppressive cell subsets including Treg cells and MDSCs.

When viewed together, the safety profiles of mocetinostat and durvalumab are largely non-overlapping. Frequently observed AEs common to treatment with single agent durvalumab and mocetinostat are non-specific and typical of cancer treatment regimens, including fatigue, anorexia, nausea, vomiting, and diarrhea. Potential exists for these AEs to be observed with increased severity or frequency during use of the combined agents. Management of these effects in patients receiving cancer therapy is well precedented.

More importantly, immune-related AEs of Special Interest based on observed safety events using durvalumab monotherapy and/or class effects for inhibitors of PD-L1 or PD-1 include colitis, pneumonitis, ALT/AST increases / hepatitis / hepatotoxicity, neuropathy / neuromuscular toxicity, endocrinopathy, dermatitis, nephritis and pancreatitis. While Class I HDAC inhibitors may have immunostimulatory effects, autoimmune adverse effects have not been reported in mocetinostat clinical trials or as a class effect. The potential for mocetinostat to exacerbate or promote these adverse events when administered in combination with durvalumab should be borne in mind.

One clinically relevant overlap in toxicity may arise between the immune-related colitis attributed to durvalumab and the non-specific, most often mild to moderate diarrhea observed with both durvalumab and mocetinostat. Immune-related colitis has been reported in approximately 0.8% of patients treated with durvalumab, with a time to onset ranging from 43 to 138 days after the first dose. Diarrhea of uncertain etiology has been reported in approximately half of patients treated with mocetinostat, most often with a time to onset within 30 days of first mocetinostat dose. Low grade diarrhea is less common with durvalumab, occurring in fewer than 8% of patients treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108. The time to onset may be helpful in distinguishing diarrhea that may be attributed to autoimmune effects versus non-specific toxicity.

Two AEs observed in previous clinical trials of mocetinostat for which causality and mechanism are unclear are cystitis and pericardial effusion. The potential for an immune-based mechanism exists, therefore increased risk may be associated with the combination of mocetinostat with durvalumab.

1.5   Study Rationale

Advanced tumors evade host immune responses by down regulation of major histocompatibility complex (MHC) molecules and tumor antigens and by creating an immune suppressive microenvironment around the tumor. Histone deacetylases (HDACs) have been implicated in the epigenetic regulation of innate and adaptive immunity. Increasing evidence supports the proposal that spectrum-selective inhibitors of class I HDACs can reverse immune evasion and elicit antitumor host response through immunostimulatory mechanisms. The immunomodulatory properties of class I HDAC inhibitors are reported to be mediated through multiple mechanisms including:
1) induction of programmed cell death ligand 1 (PD-L1) expression on the tumor cell surface, 2) induction of tumor associated antigens (TAAs) and MHC Class I and Class II molecules on tumor cells, 3) induction of immunogenic cell death via activation and cross-presentation of tumor antigens by antigen presenting cells (APCs), 4) enhanced function of T effector cells, and 5) decreased function of immunosuppressive cell subsets including T regulatory (Treg) cells and myeloid-derived suppressor cells (MDSCs). In addition, HDAC inhibitors are associated with anticancer effects through inhibiting cell cycle progression and inducing apoptosis in tumor. The combination of a class I HDAC inhibitor with an anticancer immunotherapy has the potential to enhance activity over that observed with either agent alone.

Mocetinostat is a spectrum-selective Class I/IV HDAC inhibitor specifically targeting HDACs 1, 2, 3 and 11. Class I and IV HDACs are of particular interest from an immunostimulatory and immune priming perspective.

Durvalumab is a human monoclonal antibody (MAb) that inhibits binding of PD-L1 to programmed cell death 1 (PD-1) and CD80 expressed on host immune effector cells, preventing immune suppression signaling. Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors or hematological malignancies.

The percent of tumor cells expressing PD-L1 is predictive for responsiveness to treatment with durvalumab (Rebelatto-2015). The recommended threshold for positivity is ≥25% of tumor cells demonstrating membrane staining for PD-L1 at any intensity. Among patients with NSCLC, the ORR for cases positive for PD-L1 was 27% (23 of 84; 95% Confidence Interval [CI] 18.2-38.2%) as compared to 5% (5 of 92; 95% CI 1.8-12.2%) for cases negative for PD-L1 expression (Rizvi-2015). Subset analysis by histological classification shows the following disease response rates:

Histology	All Patients	PD-L1 +	PD-L1 -
Squamous	18/88 (21%)	14/43 (33%)	3/37 (8%)
Non-squamous	14/122 (13%)	9/41 (22%)	2/55 (4%)

In this study, the treatment regimen will begin with a 7-Day Lead-In Period of mocetinostat followed by start of the combination regimen of mocetinostat and durvalumab. The Recommended Phase 2 Dose (RP2D) of mocetinostat will be established in the Phase 1 dose escalation segment, followed by evaluation of the clinical activity of the combination regimen in patients having NSCLC.

2   STUDY OBJECTIVES

2.1   Objectives

2.1.1   Primary Objectives

- To determine the RP2D of mocetinostat administered in combination with full dose durvalumab.

- To evaluate the clinical activity of mocetinostat in combination with durvalumab in cohorts of patients with NSCLC having differing tumor expression of PD-L1 or prior tumor responsiveness to treatment with checkpoint inhibitors.

2.1.2   Secondary Objectives

- To evaluate the safety and tolerability of mocetinostat in combination with durvalumab in the selected population.

- To evaluate secondary efficacy endpoints with mocetinostat in combination with durvalumab treatment in the selected population.

- To evaluate mocetinostat and durvalumab PK.

- To evaluate the incidence of ADA to durvalumab.

- To evaluate the effect of mocetinostat during the Lead-In Period on tumor cell PD-L1 expression.

2.2   Endpoints

2.2.1   Primary Endpoints

- Incidence of DLTs occurring during the first 28-day cycle of combination treatment.

- ORR as defined by RECIST 1.1.

2.2.2   Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events and laboratory abnormalities.

- Secondary efficacy endpoints:

  o   DR;

  o   CBR;

  o   PFS;

  o   1-Year Survival Rate; and

  o   OS.

- Blood plasma MGCD0103 and MEDI4736 concentrations.

- ADA detected in blood.

- Tumor PD-L1 expression.

3   STUDY DESIGN

Study 0103-020 is an open-label Phase 1/2 evaluation of mocetinostat in combination with durvalumab. The Phase 1 segment will define the RP2D of mocetinostat to be used in combination with the full dose regimen of durvalumab; eligible patients will have an advanced solid tumor disease that is not amendable to curative treatment. The Phase 2 segment will evaluate the clinical activity of mocetinostat in combination with durvalumab, as assessed by ORR in accordance with RECIST 1.1., in patients with locally advanced, unresectable or metastatic NSCLC who have previously received at least one platinum-containing doublet chemotherapy regimen for advanced disease. Patients who have previously received treatment with checkpoint inhibitors may be enrolled in the Phase 1 assessment and will be enrolled into dedicated cohorts in the Phase 2 assessment. Secondary objectives include secondary efficacy endpoints, PK, incidence of ADA and change in tumor PD-L1 expression. ▮▮ he Schedule of Assessments to be performed in the study is presented in Table 1. Triplicate ECG assessments, PK, and ADA collection time points are presented in Table 2.

The treatment regimen to be evaluated in this study includes a 7-Day Lead-in Period of mocetinostat single agent administered TIW (e.g., Monday, Wednesday and Friday) followed by administration of the combination regimen with durvalumab. The RP2D dose of mocetinostat will be established in successive dose escalation cohorts in the Phase 1 study and utilized in the Phase 2 study. The dose and regimen of durvalumab to be used throughout the study is 1500 mg on Day 1 of each 28-day cycle (i.e., Q4W). Guidelines for adverse event management and associated treatment modifications of each agent are provided in Section 5.

3.1   Phase 1 Study

The dose escalation phase of the study will employ the mTPI method will be employed in decision making concerning mocetinostat dose escalation (Appendix 2).

The mocetinostat dose levels planned for evaluation include 50, 70, and 90 mg TIW, depending on safety observations. In addition, if necessary, dose de-escalation of mocetinostat to 40 mg TIW may be undertaken.

3.1.1   Definition of Dose Limiting Toxicity

The National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03 will be used throughout this study. The definition of DLT includes any of the following events considered to be causally related to treatment with mocetinostat in combination with durvalumab:

- Any Grade 4 immune-related Adverse Event (irAE is defined in Section 8.3.1)

- Grade 3 or greater colitis

- Grade 3 or greater noninfectious pneumonitis irrespective of duration

- Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care

- Grade 3 irAE (excluding colitis or pneumonitis) that:

  o does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids, or

  o does not downgrade to ≤ Grade 1 or baseline within 14 days

- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN

- Grade 3 or greater non-irAE, except for the exclusions listed below:

  o Nausea, vomiting, anorexia, dehydration, or diarrhea that can be managed with typical medical interventions

The definition of DLT excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days

- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic

- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc)

- Concurrent vitiligo or alopecia of any grade

- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management

- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility

- Grade 3 or 4 lymphopenia

- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 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

3.1.2   Dose Escalation Plan

The first cohort of patients to be enrolled will begin with the mocetinostat 7-Day Lead-in Period, receiving 50 mg on 3 days (e.g., Monday, Wednesday and Friday) and will continue into the combination regimen, with 50 mg mocetinostat administered TIW and 1500 mg durvalumab administered Q4W.

For a patient within a dose cohort to be considered evaluable for the dose-escalation decision, the patient must have either been on study for one full cycle and have received treatment with durvalumab and at least 9 of 12 scheduled mocetinostat doses (75%) in Cycle 1 or have experienced a DLT in Cycle 1.

Decision making rules for cohort expansion and dose escalation or de-escalation based on the experience of patients treated at a dose level are presented in Appendix 2.

To ensure sufficient patient experience at the dose selected as the RP2D, enrollment at any dose level under consideration may be expanded to include at least 6 patients.

3.1.3   Definition of Maximum Tolerated Dose

The Maximum Tolerated Dose (MTD) is defined as the highest mocetinostat dose administered in the combination regimen associated with the decision to "stay with the current dose" as determined from the Dose-Finding Spreadsheet (Appendix 2) using the experience of at least 6 patients during the first 28-day treatment cycle.

3.1.4   Definition of Recommended Phase 2 Dose

The RP2D will be the highest dose of mocetinostat evaluated that is associated with:

- sufficient safety/tolerability to anticipate that patients will typically be able to receive treatment with at least 75% of the intended dose intensity of mocetinostat and 100% dose intensity of durvalumab; and

- no observed ≥Grade 3 or serious irAEs causally related to the combination regimen.

A dose level below the MTD may be selected as the RP2D.

3.2   Phase 2

The Phase 2 study will enroll patients with NSCLC into one of the following
4 population cohorts:

Cohort 1 – Patients naïve to treatment with immunotherapy, having tumor with
no/low PD-L1 expression.

Cohort 2 – Patients naïve to treatment with immunotherapy, having tumor with high
PD-L1 expression.

Cohort 3 – Patients previously treated with an anti-PD-L1 or anti-PD-1 agent with
clinical benefit response followed by progression of disease.

Cohort 4 – Patients previously treated with an anti-PD-L1 or anti-PD-1 agent with
progression or disease ≤ 16 weeks after initiation of treatment.

Tumor PD-L1 expression will be determined by the PD-L1 (SP263) CDx assay. No/low
PD-L1 expression is defined as positivity < 25% of tumor cells; high PD-L1 expression is
defined as positivity ≥25% of tumor cells. Tumor samples used to establish PD-L1
expression for eligibility must have been collected after the most recent systemic therapy.

The sample sizes for the populations to be enrolled in the Phase 2 portion of the study are
based on Predictive Probability Design, which allows for flexibility in the number of
patients to be included at each stage in order to ensure that sufficient number of evaluable
patients are available for decision to continue or to stop enrollment of additional patients.

- Cohorts 1, 3 and 4: Stage 1 of enrollment will include a minimum of 9 evaluable
  patients. With exactly 9 evaluable patients at Stage 1, if at least 1 patient has an
  Objective Response, 8 additional evaluable patients will be enrolled, for a total
  sample size of 17 evaluable patients. If at least 3 objective responses are observed,
  further investigation may be warranted.

- Cohort 2: Stage 1 of enrollment will include approximately 17 evaluable patients.
  With exactly 17 evaluable patients at Stage 1, if at least 5 patients have Objective
  Responses, 27 additional evaluable patients will be enrolled, for a total sample size of
  44 evaluable patients. If at least 18 Objective Responses are observed, further
  investigation may be warranted.

The exact stopping rules for all cohorts will be calculated based on the Predictive
Probability Design, once the exact number of patients evaluable at Stage 1 is known. The
aim is to get a minimum of 9 evaluable patients at Stage 1 for cohorts 1, 3 and 4 and
about 17 evaluable patients at Stage 1 for cohort 2.

The populations included in Cohorts 3 and 4, who have had progression of disease during treatment with a checkpoint inhibitor, represent a potential unmet medical need. For this reason, if results in Stage 2 of enrollment are of high interest, enrollment may be expanded to as many as 100 patients total in each cohort to narrow the 95% Confidence Interval (CI) around the ORR point estimate and more fully characterize the secondary endpoints in the population of interest.

In order to be part of the clinical activity evaluable population, the patient must have at least one on-study disease assessment or discontinue from treatment for PD prior to this assessment. Patients who discontinue treatment prior to the first on-study disease assessment for an AE, toxicity, or withdraw consent are considered non-evaluable for disease assessment. These patients will not be part of the clinical activity evaluable population.

Disease response and progression as documented by the investigator in the CRF will be the basis for patient management and study expansion decision making. Unconfirmed objective responses recorded in the CRF may be used as the initial basis for expansion of study enrollment; however, follow-up evaluations on patients with unconfirmed responses must continue to support the decision to continue to the full number of patients to be included in the next stage. Central radiology review for disease response and progression may be added to the study during Stage 2. If this occurs, central review of all radiologic assessments performed in the study will be expected (including retrospective review of patients enrolled in Stage 1), and central radiology review for disease response will be the basis for the primary statistical analyses to estimate the objective response rate and its confidence interval, as well as the duration of response and PFS.

Study treatment will continue until disease progression, unacceptable adverse events, patient refusal or death.

4   SUBJECT SELECTION AND ENROLLMENT

Patient eligibility must be reviewed and documented by an appropriately qualified member of the investigator's study team before patients are included in the study. No exceptions to the patient eligibility requirements will be granted by the Sponsor.

4.1   Inclusion Criteria

Patients must meet all of the following inclusion criteria as applicable for phase of the study to be eligible for enrollment into the study:

1. Diagnosis and disease status:

    a. Phase 1 – Histologically or cytologically confirmed solid tumor malignancy with metastatic or unresectable, locally advanced disease

    b. Phase 2 – Histologically confirmed NSCLC (any histology) with metastatic or unresectable, locally advanced disease

2. Prior treatments:

    a. Phase 1

        i. Not amenable to treatment with curative intent

        ii. May have received treatment with checkpoint inhibitors (e.g., anti-PD-1 or anti-PD-L1)

    b. Phase 2

        i. Receipt of at least one prior treatment in the advanced disease setting that included a platinum-based doublet or immunotherapy regimen. If prior platinum-based therapy was received in the neoadjuvant or adjuvant setting, relapse must have occurred within 1 year of end of treatment.

        ii. Cohorts 3 and 4 – Most recent treatment regimen must have included a checkpoint inhibitor, e.g., anti-PD-1 or anti-PD-L1 treatment.

3. Molecular analysis for PD-L1 expression on tumor cells:

   a. Phase 1 – PD-L1 tumor expression testing is not required but is encouraged; any expression status is eligible

   b. Phase 2

      i. Cohorts 1 and 2 – Molecular analysis of tumor sample collected following most recent therapy, assessed using the PD-L1 (SP263) CDx assay. Inclusion in the treatment arms will be based on documented no/low PD-L1 expression (positivity < 25% of tumor cells) or high PD-L1 expression (positivity ≥25% of tumor cells).

      ii. Cohorts 3 and 4 – PD-L1 tumor expression testing is not required but is encouraged; any expression status is eligible.

4. Response to previous treatment with checkpoint inhibitor:

   a. Phase 1 – Any response is eligible, as applicable.

   b. Phase 2

      i. Cohort 3 – clinical benefit (i.e., RECIST defined partial or complete response or stable disease for at least 16 weeks [+2 week window permitted for radiograph scheduling]) followed by radiographic progression of disease

      ii. Cohort 4 – radiographic progression of disease ≤ 16 weeks after initiation of treatment (+2 week window permitted for radiograph scheduling)

5. Measurable disease

   a. For Phase 1 – Measurable or evaluable, as per RECIST version 1.1

   b. For Phase 2 – Measurable disease, as per RECIST version 1.1. Indicator lesions intended for repeat biopsy during the study should be excluded from selection as target lesions at baseline

6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

7. Adequate bone marrow and organ function demonstrated by:

   a. Hemoglobin ≥ 9.0 g/dL

   b. Absolute neutrophil count ≥ 1,500/mm^3 (≥ 1. 5 × 10^9/L)

    c. Platelet count $\geq 100 \times 10^9$/L ($\geq$ 100,000 per mm^3)

    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ Upper Limit of Normal (ULN), or $\leq 5.0 \times$ ULN for patients with documented liver metastases

    e. Serum bilirubin $\leq 1.5 \times$ ULN or $\leq 3.0 \times$ ULN for patients with Gilbert Syndrome or documented liver metastases

    f. Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance

8. $\geq$ 18 years of age

9. Women of child-bearing potential (WOCBP) or men whose partner is a WOCBP agrees to use contraception while participating in this study, and for a period of 6 months following termination of study treatment

10. Completed informed consent process, including signing IRB/EC-approved informed consent form

11. Willing to comply with clinical trial instructions and requirements

4.2 Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Prior therapies:

    a. All Cohorts

        i. HDAC inhibitor for the treatment of the malignancy under study

        ii. Immunotherapies not previously specified, including anti-CTLA-4, anti-OX40 and anti–CD137

    b. Phase 2 Cohorts 1 and 2 – prior treatment with anti-PD-1 or anti-PD-L1

    c. Phase 2 Cohorts 3 and 4 – receipt of systemic cancer treatments since progression of disease during or following administered checkpoint inhibitor

2. Patients with any history of tumors that test positive for *EGFR, ROS1, ALK* mutations or *ALK* fusions or any other mutations for which there are tyrosine kinase inhibitors available or under development.

3. Most recent prior therapeutic regimen discontinued $\leq$ 3 weeks before first study treatment dose date (i.e., mocetinostat Lead-in Period).

4. Lack of recovery from the adverse effects of prior therapy at the time of enrollment to ≤ Grade 1 (excluding alopecia or neuropathy).

5. Previous treatment-related, severe (≥ Grade 3) AE or any neurologic or ocular AE of any grade while receiving checkpoint inhibitors. **NOTE:** Patients with a prior endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

6. Active or prior documented autoimmune disease within the past 2 years.
   NOTE: Patients with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

7. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

8. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

9. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.

10. History of primary immunodeficiency.

11. Known history of previous clinical diagnosis of tuberculosis.

12. Known history of acute or chronic hepatitis B, human immunodeficiency virus (HIV), or acute hepatitis C.

13. History of allogeneic organ transplant.

14. History of hypersensitivity to durvalumab, mocetinostat or any drug product excipient.

15. History of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.

16. History of stroke or transient ischemic attack within the previous 6 months.

17. Any of the following cardiac abnormalities:

    a. Unstable angina pectoris,

    b. Congestive heart failure ≥ NYHA Class 3,

    c. QTc ≥470 milliseconds on electrocardiogram (ECG) calculated using Frediricia's Correction, or

    d. Current or history of a small, moderate or large pericardial effusion, and/or hemodynamic compromise due to pericardial effusion of any size. Minimal or trivial pericardial effusion is not excluded.

18. Concomitant medication known to cause prolonged QT which cannot be discontinued or changed to a different medication prior to enrollment.

19. Active brain metastases. Subjects are eligible if brain metastases are adequately treated and subjects are neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment without the use of corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).

20. Known or suspected presence of another malignancy that could be mistaken for the malignancy under study during disease assessments.

21. Pregnancy. WOCBP must have a negative serum or urine pregnancy test documented within the screening period prior start of study drug.

22. Breast-feeding or planning to breast feed during the study or within 6 months after study treatment.

23. Any psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the patient to give written informed consent.

24. Any serious illness, uncontrolled inter-current illness, active or uncontrolled infection, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results.

4.3   Life Style Guidelines

Patients who are biologically capable of having children and sexually active must agree to use an acceptable method of contraception for the duration of the treatment period and for at least 6 months after the last dose of study treatment. The investigator will counsel the patient on selection of contraception method and instruct the patient in its consistent and correct use. Examples of acceptable forms of contraception include:

1. Oral, inserted, injected or implanted hormonal methods of contraception, provided it has been used for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide.

4. Male sterilization with confirmed absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation or bilateral salpingectomy.

The investigator will instruct the patient to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Note: Women are considered post-menopausal and/or not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 months ago. In case of any ambiguity, the reproductive status of the woman should be confirmed by hormone level assessment.

4.4   Enrollment into Study

Evaluation of tumor PD-L1 expression for Phase 2 patients naïve to treatment with immunotherapy may have been performed historically or more recently for the purpose of determining enrollment into Cohort 1 or 2 of this study. A 14-day turn-around time should be expected from the time of receipt of adequate samples at the central lab to test results returned to the study site. Questions concerning adequacy of samples will cause delay beyond this timeframe.

Following completion of the study-specific informed consent process and review of all screening procedures, patient eligibility will be confirmed by appropriately qualified staff at the investigational site. Patients will be enrolled by entry into a patient registration log provided by the Sponsor and maintained by the study site, and completion of the patient registration procedure detailed in the Study Manual. Each patient will be assigned a sequential number by the study site. The patient number must be used on all documentation and correspondence with the Sponsor, Contract Research Organization (CRO) and laboratory vendors.

5   STUDY TREATMENT

5.1   Mocetinostat Study Drug Management

5.1.1   Formulation and Packaging

Mocetinostat study drug contains the free-base form of mocetinostat (MGCD0103) and inert excipients: microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, non-bovine magnesium stearate.

Mocetinostat hard gelatin capsules will be supplied by the Sponsor. Capsule strengths to be used in this study are 10 mg (white opaque capsule), 20 mg (white opaque capsule), 25 mg (Swedish orange capsule), and 50 mg (Swedish orange capsule). Refer to the Pharmacy Manual for details on number of capsules per bottle, and clinical trial material supply, distribution and control.

Medication labels comply with the legal requirements of the United States and will be printed in the languages required in the countries in which the study is conducted.

5.1.2   Drug Storage and Accountability

Mocetinostat capsules should be stored protected from light, at room temperature (suggested range is 15-30°C, 59-86°F) according to instructions on the label. The storage area should be secure with limited access and monitored for temperature using a calibrated thermostat. Shelf-life evaluation of the intact bottles is ongoing. Available stability data support $\geq$ 12-months shelf-life when stored under the above conditions, depending on capsule strength.

All study treatment supplies will be accounted for in the drug accountability inventory forms supplied by the Sponsor or using locally approved forms that include all required information. The drug accountability inventory forms must identify the study drug, including batch or lot numbers and account for its disposition on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug.

5.1.3   Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Study site personnel should dispense to patients the appropriate number of capsules required to support one 28-day cycle (12 doses) plus one dose. Mocetinostat capsules are to be dispensed in the Sponsor provided High-Density Polyethylene (HDPE) bottles along with a provided desiccant packet.

5.1.4 Medication Compliance

Study site personnel should provide each patient with written dosing information for mocetinostat capsules and review it with the patient during clinic visits. Patients will be asked to record their daily mocetinostat dosing on Sponsor provided diary cards and report any missed doses or lost capsules at the next clinic visit. Patients will also be told to bring study treatment capsule bottle(s) (empty or not) with them to the clinic visit for a compliance check and capsule count. Study site personnel will record compliance information in the source document and on the CRF and retain the bottle(s) until a monitor has completed reconciliation.

See the Study Manual for additional details regarding compliance and reconciliation.

5.1.5 Destruction

At the end of the study, all unused mocetinostat drug supplies will be destroyed in accordance with local Standard Operating Procedure provided to the Sponsor for the Trial Master File, or returned to the Sponsor or its appointed agent, as directed by the Sponsor.

5.1.6 Administration

Mocetinostat capsules will be administered orally on a three times per week dosing schedule, in 28 day cycles. The starting dose for mocetinostat in the Phase 1 dose escalation study is 50 mg orally TIW with potential to escalate to 70, and 90 mg TIW. The dose may be deescalated to 40 mg TIW depending on observed safety. The RP2D will be established based on the Phase 1 results.

The following guidelines should be followed for mocetinostat administration:

- Patients should be instructed to take the dose of mocetinostat three days per week (e.g., Monday/Wednesday/Friday), in the morning, at approximately the same time each day.

- Mocetinostat should be taken on an empty stomach (e,g,. after an overnight fast or at least 3 hours since the previous meal) and wait at least 2 hours before eating the next meal.

- Capsules should be taken with at least 200 mL (7 oz.) of water.

- Patients should swallow the capsules whole and not chew them.

- If vomiting occurs after dosing, mocetinostat doses should not be replaced. If vomiting occurs on a day when PK collection is required, PK samples should continue to be collected.

- Mocetinostat doses should not be taken 2 days in a row and gaps longer than 3 days (~72 hours) should be avoided when possible.

On days mocetinostat and durvalumab are both administered and scheduled for PK assessment, mocetinostat dosing and sampling should precede durvalumab. Mocetinostat dosing should occur in the clinic at each visit where Mocetinostat PK collection is scheduled, but there are no dosing time restrictions on non-PK days (e.g. C2D15, C4D1, C5D1). Cycle 1 Day 15 Mocetinostat dosing must occur at the clinic but all other Day 15 Mocetinostat dosing can be done at home or at the clinic.

5.1.7 Dose Modification and Discontinuation

Mocetinostat dose reductions will be performed as outlined in Table 5. Once a dose has been reduced, re-escalation will not be permitted. If the administration of mocetinostat is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose.

If treatment with the study drug is withheld for ≥ 28 consecutive days, then study drug should be considered for permanent discontinuation.

Table 5:   Dose Modifications for Mocetinostat

Mocetinostat Dose Levels to be Investigated and Sequential Dose Reductions*
90 mg three times per week
70 mg three times per week
50 mg three times per week
40 mg three times per week**

*   Dose reduction should be based on the worst preceding toxicity
**   Dose reduction below 40 mg 3×/week is not allowed. If a dose reduction below 40 mg 3×/week is required, the patient should be permanently discontinued from mocetinostat.

5.1.8 Mocetinostat Adverse Event Management Guidelines

5.1.8.1 Management of Mocetinostat in Response to Immune-Related Adverse Event

Administration of mocetinostat as a single agent or in combination with chemotherapy has not been associated with irAEs. However, the potential exists for mocetinostat to contribute to irAEs associated with durvalumab treatment, which may include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. In the event of an irAE, administration of mocetinostat should be interrupted until the event stabilizes to Grade ≤1 and after completion of any steroid taper (similar to the guidance for resumption of durvalumab treatment as presented in Table 9, and Appendix 4). At the time of resumption of mocetinostat dosing, a dose reduction may be implemented at the discretion of the Investigator.

5.1.8.2   *Management of Mocetinostat in Event of Non-Hematological Toxicities*

Non-hematological toxicities ≥ Grade 3 and considered to be treatment-related should be managed with mocetinostat treatment interruption until resolution of toxicity to ≤ Grade 1 or to baseline value. If the toxicity is adequately managed by routine supportive care (such as anti-emetics, anti-diarrheals, or electrolyte supplementation), treatment may be resumed at the same dose; if not, treatment may be resumed at a reduced dose (Table 6). Recurrence of the toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

Table 6:   Mocetinostat Dose Modifications – Non-Hematological Drug-Related Toxicities[1]

Toxicity	Treatment Delay	Dose Modification
< Grade 3	May be implemented based on Investigator and patient discretion	
Grade 3 or 4, manageable with routine supportive care	Hold until ≤ Grade 1 or return to baseline	Not required
Grade 3 or 4, not manageable with routine supportive care	Hold until ≤ Grade 1 or return to baseline	Resume at next lower dose level

1   For pericardial toxicity, see Section 5.1.8.5.

5.1.8.3   *Management of Mocetinostat in Event of Hematological Toxicities*

Hematological toxicities ≥ Grade 3 and considered to be treatment-related should be managed with treatment interruption until resolution as described in Table 7. Recurrence of the toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

Table 7:   Mocetinostat Dose Modifications – Hematological Drug-Related Toxicities

Neutropenia	
Grade 1 (ANC < LLN – 1.5×10^9/L)	Maintain dose level
Grade 2 (ANC < 1.5-1.0×10^9/L)	
Grade 3 (ANC < 1.0 - 0.5×10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ by 1 dose level
Grade 4 (ANC < 0.5×10^9/L) Febrile neutropenia (ANC < 1.0×10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then ↓ by 1 dose level

Table 7:   Mocetinostat Dose Modifications – Hematological Drug-Related Toxicities (Continued)

Thrombocytopenia	
Grade 1 (PLT < LLN – 75 × 10^9/L)	Maintain dose level
Grade 2 (PLT < 75 – 50 × 10^9/L)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ by 1 dose level
Grade 3 (PLT < 50-25 × 10^9/L)	Omit dose until resolved to ≤ Grade 1, then ↓ by 1 dose level
Grade 4 (PLT < 25 × 10^9/L)	
Treatment Delay ≥ 4 weeks	
Any hematologic or non-hematologic toxicity requiring interruption for ≥ 28 days	Discontinue mocetinostat

5.1.8.4   Management of Mocetinostat Associated Cystitis

In the event of symptoms of cystitis (e.g., dysuria, pollakiuria, hematuria, urgency, or bladder spasm) suspected to be attributable to mocetinostat treatment:

- Perform diagnostic evaluation and manage per institutional standards;

- If clinically significant symptoms persist despite a negative diagnostic assessments or treatment of an associated condition, interrupt study treatment until resolution of clinically significant symptoms; and

- Resume dosing of mocetinostat when medically appropriate, at the same or a reduced dose level as per the Investigator's judgment.

5.1.8.5   Management of Mocetinostat in Event of Pericardial Toxicity

Patients will be assessed for evidence of pericardial toxicity during scheduled visits according to the Schedule of Assessments (Table 1).

The following findings would heighten suspicion of pericardial effusion or pericarditis and prompt immediate evaluation by ECHO:

- Symptoms: shortness of breath, orthopnea, chest pain, dizziness, rapid pulse

- Clinical exam: hypotension, jugular venous distension, pulsus paradoxus, faint heart sounds, friction rub, and/or arrhythmia

- ECG: sinus tachycardia, atrial fibrillation, atrial flutter, low voltage with nonspecific ST-T wave changes and ST elevation or PR depressions, arrhythmia

ECHOs will be used to assess and categorize pericardial fluid as minimal (or trivial), small, moderate or large and will assess for hemodynamic compromise.

Pericardial effusions will be assessed and managed as follows (Table 8):

Table 8: Pericardial Effusion and Patient Management Guidelines

Category	Definitions	Patient Management
Minimal (or trivial)	A small echo-free space in the posterior atrioventricular groove that is visible only in systole when the heart has pulled away from the pericardium. Typically represents a normal amount of pericardial fluid in a disease-free state.	De novo (i.e., not present at baseline) pericardial effusion: • Study treatment may be continued at the discretion of the investigator. • Increased ECHO and ECG monitoring weekly until effusion is no longer present or has not progressed over a period of 2 weeks. • Regular assessment schedule afterwards.
Small	< 1 cm of posterior echo-free space, with or without fluid accumulation elsewhere, present throughout the cardiac cycle, including diastole (and not only systole).	• Study drug will not be discontinued in these Patients, at the discretion of the investigator, unless the effusion progresses. • Increased ECHO and ECG monitoring weekly for the first month after the new effusion first noted or until the effusion has regressed (if sooner). • Treatment for the effusion may be administered at the discretion of the Investigator.
Moderate	1 to 2 cm of echo-free space. Moderate effusions tend to be seen along the length of the posterior wall but not anteriorly.	• Remove immediately from study treatment. • Manage according to the standard of care at the discretion of the investigator. • Refer to cardiologist for follow-up as clinically indicated, until resolution of stabilization.
Large	> 2 cm of maximal separation. Large effusions tend to be seen circumferentially.	
Hemodynamic Compromise	RV compression, IVC dilation without respiratory variation, abnormal flow variation across the AV valves without respiratory variation, enlarged or collapsed ventricles. RA diastolic collapse in isolation is too non-specific to signal hemodynamic compromise, but should be considered consistent with this diagnosis when accompanied by other findings	• Remove immediately from study treatment. • Refer to cardiologist for follow up as clinically indicated, until resolution or stabilization. • Collect blood and test for anti-nuclear antibody (ANA) and anti-histone antibody.

In exceptional circumstances where ECHO is not considered a technically optimal assessment of pericardial space (e.g., overweight patient), other methods (e.g., MRI) should be used for pericardial assessments. In such cases, the guidelines provided in Table 8 would not apply, and the evaluation should be performed in consultation with the Sponsor. In the event that a pericardial effusion is first identified by a method other than ECHO, efforts should be made to obtain an ECHO for assessment of effusion size.

5.2 Durvalumab Study Drug Management

5.2.1 Formulation and Packaging

Durvalumab study drug will be supplied as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Refer to the Pharmacy Manual for details on durvalumab clinical trial material supply, distribution and control. Medication labels comply with the legal requirements of the United States and will be printed in the languages required in the countries in which the study is conducted.

5.2.2 Drug Storage and Accountability

Durvalumab investigational product vials should be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label. The storage area should be secure with limited access and monitored for temperature using a calibrated thermostat.

All study treatment supplies will be accounted for in the drug accountability inventory forms supplied by the Sponsor or using locally approved forms that include all required information. The drug accountability inventory forms must identify the study drug, including batch or lot numbers and account for its disposition on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug.

5.2.3 Preparation and Dispensing

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Each dose of 1500 mg durvalumab will be administered using an intravenous (IV) bag containing 100 to 1000 mL 0.9% saline. Remove a volume of solution from the IV bag equal to the calculated volume of durvalumab to be added (ie, 30.0 mL for 1500 mg of durvalumab). The final concentration should range from 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F), or

- 4 hours at room temperature.

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

5.2.4   Medication Compliance

Study site personnel should document durvalumab intravenous administration in the patient's source document and CRF along with administration start/stop times.

5.2.5   Destruction

At the end of the study, all unused durvalumab drug supplies will be destroyed in accordance with local Standard Operating Procedure provided to the Sponsor for the Trial Master File, or returned to the Sponsor or its appointed agent, as directed by the Sponsor.

5.2.6   Administration

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. The entire contents of the IV bag should be administered over approximately 60 minutes (± 5 minutes), using a 0.2-, or 0.22-μm in-line filter. Less than 55 minutes is considered a deviation. After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV solution (0.9% saline) equal to the priming volume of the infusion set used, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Standard infusion time is 1 hour. 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 outlined above and in Section 5.2.3, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

On days mocetinostat and durvalumab are both administered and scheduled for PK assessment, mocetinostat dosing and sampling should precede durvalumab.

5.2.7   Infusion Modification and Discontinuation

Patients will be monitored before, during and after the infusion with assessment of vital signs, pulse rate and blood pressure every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, 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. The standard infusion time is 1 hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature. The maximum total time from needle puncture to start of administration should not exceed 4 hours at room temperature (otherwise a new infusion preparation is required).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

5.2.8   Durvalumab Adverse Event Management Guidelines

For adverse events (AEs) that are considered at least partially due to administration of durvalumab, the following dose adjustment guidance may be applied:

- Treat each AE with maximum supportive care (including holding the agent suspected of causing the toxicity where required).

- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab (see below).

- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued.

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed. Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Table 9, Appendix 4, Table 10 and Table 11, respectively.

Based on the mechanism of action of durvalumab, leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or progressive disease) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related. Overall guidelines for management of durvalumab treatment in response to an irAE are detailed in Table 9 and in more detail by type of AE in Appendix 4.

Table 9: Immune-Related Adverse Events, Overall Management

<table>
<tr>
<td colspan="2"><u>**Durvalumab Treatment Modification**</u>
Drug administration modifications made to manage potential immune-related AEs are based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.

In addition criteria for permanent discontinuation based on severity (Appendix 4), permanently discontinue for the following conditions:

•   Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug
•   Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.</td>
</tr>
<tr>
<td>Grade 1</td>
<td>No dose modification</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hold study drug dose until Grade 2 resolution to ≤ Grade 1

• If toxicity worsens then treat as Grade 3 or Grade 4

Study drug/study treatment can be resumed once event stabilizes to Grade ≤1 and after completion of steroid taper.

Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated on the following conditions:

1) the event stabilizes and is controlled,

2) the patient is clinically stable as per Investigator or treating physician's clinical judgment, and

3) doses of prednisone are at less than or equal to 10mg/day or equivalent.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Depending on the individual toxicity, may permanently discontinue. Refer to guidelines below.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Permanently discontinue

Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen.</td>
</tr>
</table>

Table 9: Immune-Related Adverse Events, Overall Management (Continued)

Toxicity Management

- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.)

- In the absence of a clear alternative etiology, all events should be considered potentially immune related

- Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events

- For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent

- If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2-4mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper)

- More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) – should be considered for events not responding to systemic steroids (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive)

- Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based on a benefit/risk analysis for that patient

Table 10:   Durvalumab Infusion-Related Reactions

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

Table 11:   Non-immune Mediated Reactions

Severity Grade	Dose Modification	Toxicity Management
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline. For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

Abbreviations:

AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

5.3 Medication Error

Medication errors may involve patient exposure to a wrong study drug, at a wrong dosing frequency, or at a wrong dose level (e.g., a dose that is not planned in the study). Medication errors occurring during the conduct of this study will be documented as AEs (regardless of whether clinical signs or symptoms are observed) and if serious consequences are observed, will be reported on Serious Adverse Event (SAE) forms. In all cases of medication error, the sponsor should be notified immediately.

There is currently no specific treatment in the event of an overdose of mocetinostat or durvalumab. The investigator will use clinical judgment to treat any overdose.

5.4 Concomitant Therapies

5.4.1 Concomitant Medication(s)

Concomitant medications must be locally-approved and used at doses and regimens that are considered standard-of-care for the treated indication.

Treatment for co-morbidities, disease signs and symptoms and treatment emergent adverse events should be provided as necessary in the judgment of the investigator. Antibiotics and analgesics should be used as needed. Patients with neutropenic fever or infection should be treated promptly. Therapeutic colony-stimulating factors should be used in accordance with ASCO guidelines. Packed red blood cell and platelet transfusions may be administered as clinically indicated.

5.4.1.1 Permitted Concomitant Medications

Supportive Care/Palliative Care: Supportive and palliative care for disease related symptoms may be administered at the investigator's discretion, including the use of analgesics.

Anti-emetics: Patients may be premedicated for nausea and vomiting. Recommended anti-emetic agents include granisetron 1 mg as premedication, and then granisetron and/or prochlorperazine as needed.

Transfusions: Patients may receive transfusions as necessary.

5.4.1.2 Cautioned Concomitant Medications and Substances

P450 Considerations: Caution should be used when mocetinostat is administered to patients taking medications metabolized by CYP2C9, or that inhibit or induce metabolism by CYP2E1 or CYA3A4. See Appendix 3 for examples of medications of interest. If a patient is taking a drug on one these lists, it is encouraged to substitute a different medication if possible.

Anti-Coagulation: At the discretion of the investigator and under medical supervision, patients may continue to receive prophylactic or therapeutic low molecular weight heparin (but not therapeutic treatment with warfarin, other coumarin derivatives) as clinically indicated.

5.4.1.3   *Concomitant Medications and Substances to be Avoided On-Study*

Warfarin or Coumarin Derivatives: Therapeutic doses of warfarin or other coumarin derivative anticoagulants are not permitted. Warfarin has a narrow therapeutic range and mocetinostat can have inhibitory effects on CYP2C9, the main metabolizing enzyme of warfarin.

Drugs with QTc Prolonging Activity: As listed in Appendix 3. This list is not exhaustive. Any questions should be discussed with the Sponsor.

Herbal Medications/Preparations: Herbal medications and preparations are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe (yohimbine), saw palmetto, and ginseng. Patients should stop using these herbal medications at least 7 days prior to first dose of study treatment.

Gastric Acid Neutralizers: Medications that directly increase gastric pH such as short-acting antacids should be avoided 4 hours before and 2 hours after administration of mocetinostat. Medications that affect gastric acid secretion, such as H_2 antagonists or proton pump inhibitors should be avoided.

Contraceptives: Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study, since induction of CYP3A4 may not be excluded in patients receiving mocetinostat.

Immunosuppressive Medications: Including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).

Vaccines: Live attenuated vaccines within 30 days of durvalumab dosing are to be avoided (i.e., 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab). Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

5.4.2   *Concomitant Surgery or Radiation Therapy*

The use of surgery to manage cancer lesions during study treatment is discouraged. The impact of treatment with mocetinostat on wound healing has not yet been characterized. For patients with bone involvement, any foreseeable need for palliative radiotherapy should be addressed before study entry, if possible and clinically appropriate (e.g., bone lesions at risk for spontaneous micro-fractures or painful lesions). However, these treatments may be used in cases where it is medically necessary.

5.4.3   *Other Anticancer or Experimental Therapy*

Use of approved or investigational anticancer treatment will not be permitted during the study treatment period, including chemotherapy, biological response modifiers, hormone therapies or immunotherapy. No other investigational drug may be used during treatment on this protocol. Concurrent participation in another therapeutic clinical trial is not allowed.

6   STUDY ASSESSMENTS

6.1   Screening

Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed. Patients who completed the informed consent process but did not enroll on the study will be considered as screen failures. Limited information will be recorded in the CRF for these patients.

6.2   Study Period

For details on procedures during the study period, see Schedule of Assessments as shown in Table 1 and Table 2.

6.3   End of Treatment Assessment

All patients will be followed for AEs for at least 28 days and for SAEs for at least 90 days following the last dose of Study Treatment. See the Schedule of Assessments (Table 1) for evaluations to be performed at the End of Treatment visit.

6.4   Long-Term Follow-up and End of Study Assessment

Blood samples for MEDI4736 PK and ADA will be collected approximately 90 days after the last infusion of durvalumab. Survival status and subsequent therapies will be collected during long term follow-up as outlined in the Schedule of Assessments (Table 1) until death or lost to follow-up. Beyond 90 days after last treatment, follow-up

may be performed by telephone contact. Treatments received following participation in the study will be collected in the CRF.

6.5   Patient Discontinuation/Withdrawal

Patients may discontinue from study treatment or from the study at any time at their own request, or they may be discontinued at any time at the discretion of the investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Criteria that may be used to discontinue patients from receipt of study medication will include, but will not be limited to:

- Objective disease progression according to RECIST 1.1 as determined by the investigator (patients who may derive clinical benefit may continue on treatment at the discretion of the investigator);

- Global deterioration of health status requiring discontinuation;

- Adverse event;

- Significant protocol violation;

- Lost to follow-up;

- Refusal for further treatment;

- Study termination by Sponsor;

- Death.

Reasons for discontinuation from study follow-up may include:

- Study terminated by Sponsor;

- Lost to follow-up;

- Refusal for further follow-up for survival;

- Death.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. At least 2 attempts should be made to contact the patient, and each attempt should be recorded in the source documents. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the

reason for withdrawal, request that the patient returns for a final visit, and if applicable, follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study treatment and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such refusal for further follow-up.

7 PROCEDURES

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that there may be circumstances outside of the control of the investigator that may make it unfeasible to perform a protocol-specified assessment. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol required test cannot be performed, the investigator will document in the source document and CRF the reason and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1 Sample Collection for PD-L1 Expression

Tumor tissue testing for PD-L1 expression is required for patients enrolling in Phase 2 Cohorts 1 and 2 and encouraged for patients enrolling in the Phase 1 study or Phase 2 Cohorts 3 and 4. In Cohorts 1 and 2, the sample tested must have been collected following completion of the most recent systemic treatment regimen. In other patient cohorts, when the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than 3 years of age.

Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e., > 100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.

Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Further guidance on sample preparation and submission can be found in the Study Laboratory Manual.

7.2   Efficacy

All patients enrolled in the study are to be evaluated for disease activity as outlined in the Schedule of Assessments (Table 1). Screening/baseline tumor assessments should include CT or MRI of the chest, abdomen, and pelvis, whole body bone scan, MRI of the brain and evaluation of any superficial lesions. On-study assessments will include all known and suspected sites of disease and will be performed at 8 week intervals until approximately 1-year and then every 12 weeks. The allowable windows for assessments are 4 weeks prior to first study treatment for screening/baseline assessments and ±10 days for on-study disease assessments.

CT scans should be performed with contrast agents unless contraindicated for medical reasons. If intravenous contrast is medically contraindicated, the imaging modality to be used (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. Depending on the adequacy for evaluation of disease, a combination of CT without contrast and MRI should most often be used. CT without contrast is preferred for evaluation of lesions in lung parenchyma. MRI is not adequate for evaluation of lung parenchyma but should also be performed to evaluate all other aspects of the chest. MRI of the abdomen and pelvis should substitute for CT with contrast unless the method does not adequately depict the individual's disease, in which case CT without contrast is preferred. For those sites that routinely use PET scans for assessment of bone lesions in lieu of skeletal scintigraphy, PET scans may be used on-study, with the same modality planned throughout the study for any given patient.

For patients having effusions or ascites, cytological proof of malignancy should be obtained prior to selection of the effusion as a non-target lesion. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be considered to be cancer lesions.

Disease response will be assessed in accordance with RECIST 1.1 (Eisenhauer-2009). Appendix 5 provides guidance in using the response criteria and include a modification to RECIST 1.1 to address potential temporary treatment effects such as tumor lesion cavitation or flare response. Assessments will be performed until objective disease progression is documented by the investigator, or subsequent anti-cancer therapy is begun.

Patients experiencing tumor response (Partial Response [PR] or Complete Response [CR]) should undergo confirmatory assessment at least 4 weeks after initial documentation of response. It is acceptable to perform confirmatory assessments at the next appointed evaluation per protocol. Bone scan is required as an element of the confirmation of PR or CR if bone lesions were identified at the baseline assessment.

The investigator's assessment of disease response and progression will be the basis for patient management and study expansion decision making. Potential exists for individual tumor lesions to cavitate or become otherwise difficult to evaluate for a period of time as the result of beneficial study treatment impact. For example, tumor necrosis and cavitation may result in minor increase in overall individual lesion size or unclear tumor margins prior to recovery to a smaller lesion, development of scar tissue, or complete resolution. For this reason, investigators may delay reaching the conclusion of disease progression until subsequent on-study disease assessments are performed.

Central radiology review to assess RECIST outcome may be undertaken after Stage 1 of the study. Materials to be forwarded for independent review will be all imaging studies performed at screening and on study, preferably in digital format, using an electronic transfer through a portal to the review vendor or transfer on compact disc or optical disc. All digital media must be in DICOM format. Films may be forwarded for review if necessary; all films should be originals (second original films acceptable) rather than copies of films.

7.3   Safety Assessments

7.3.1   *Adverse Events*

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.03]), timing, seriousness, and relatedness to study treatment.

Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present at baseline will be recorded in the CRF as AEs beginning on Day 1 of study treatment and onward throughout the study. The actual date of onset should be recorded in all cases. Ongoing AEs that change in attribution or severity should have the date of change entered as the "end date" and a new AE record should be opened with the changed details.

7.3.2   *Documentation and Reporting of Pericardial Events*

Since pericardial abnormalities (e.g., pericarditis, pericardial effusion, and hemodynamic compromise) exist along a continuum with overlap between the clinical symptomatology and diagnoses, each pericardial AE (including grading of severity for each individual event) along the continuum should be captured separately (Table 12).

Table 12:   Definitions of Pericardial Events

Event Term	Definition	Characteristics/Diagnosis
Pericarditis	Inflammation of the pericardium	The major clinical manifestations of acute pericarditis include: 1) chest pain, 2) pericardial friction rub, 3) ECG changes (with new, widespread ST elevation or PR depressions), and 4) pericardial effusion. At least 2 of these features are usually considered necessary to make the diagnosis.
Pericardial effusion	Excess exudate, or fluid, in the pericardium	Once a pericardial effusion is suspected, the diagnostic approach consists of 3 steps: 1) establish the presence of effusion, 2) assess the hemodynamic impact, and 3) establish the cause. Clinical evaluation and ECG findings may suggest the presence of a pericardial effusion, but imaging, usually ECHO, is required to establish a diagnosis.
Hemodynamic Compromise	Mechanical compression of the heart by large amounts of fluid or blood within the pericardial space that limits the normal range of motion and function of the heart	The diagnosis of hemodynamic compromise is based upon clinical and imaging evidence. The following physical findings 1) sinus tachycardia, 2) elevated jugular venous pressure, and 3) pulsus paradoxus are suggestive of frank tamponade. Echocardiogram or other imaging of the pericardium is essential to the diagnosis of hemodynamic compromise.

All pericardial findings, regardless of seriousness and relationship to study medication, should be reported to the Sponsor with the use of the "Pericardial Event Report Form" provided by the Sponsor, according to the procedures for SAE expedited reporting (see Section 8.4.2). When reporting pericardial events, available ECHO results/reports (or other means of diagnosis if available) should also be provided, for review by the Medical Monitor.

7.3.3   *Physical Examination and Vital Signs*

A physical examination including all major body systems is mandated at Screening and End of Treatment Visits only. During study treatment, symptom directed physical examinations will be performed.

Vital signs to be assessed include weight, body temperature, blood pressure, and pulse rate. Height will be recorded at screening only. In addition, blood pressure and pulse rate will be assessed every 30 minutes (± 5 minutes) between the start and end of durvalumab infusions (periods of infusion interruption included) and, for the first infusion, for 1 hour post infusion.

Clinically significant findings noted during screening will be reflected on the medical history CRF, while those noted during study treatment will be collected on the AE CRFs.

7.3.4   *Laboratory Safety Assessments*

Laboratory safety assessments for which data will be collected in this study will include hematology, coagulation, thyroid tests, urinalysis and chemistry parameters presented in Table 13.

Laboratory tests will be drawn at the time points described in the Schedule of Assessment (Table 1) and analyzed at local laboratories. Additional laboratory tests may be performed per standard of care, at the investigator's discretion for the purpose of planning treatment administration, dose modification, following adverse events, or as clinically indicated.

Table 13:   Laboratory Safety Parameters

Hematology Panel	Blood Chemistry Panel
Hemoglobin	Aspartate aminotransferase (ALT)
Platelet count	Alanine aminotransferase (AST)
White blood cell count (WBC)	Alkaline phosphatase
Neutrophil count	Lactate dehydrogenase (LDH)
Lymphocyte count	Total bilirubin (if Total bilirubin is ≥2×ULN and no evidence of Gilbert's syndrome, then fractionate into direct and indirect bilirubin)
Basophil count	Gamma glutamyltransferase Screening, C1D1, and as clinically indicated
Monocyte count	Lipase
Eosinophil count	Amylase
Coagulation	Creatinine
International normalized ratio (INR)	Blood urea nitrogen (BUN) or urea, depending on local practice
Prothrombin time (PT)	Uric acid
Partial thromboplastin time (PTT)	Total protein
	Glucose (non-fasted)
Urinalysis (dip stick)	Albumin
Blood	Calcium
Glucose	Sodium
Protein	Potassium
	Chloride
Thyroid Function Test	Magnesium
Thyroid-stimulating hormone (TSH)	Bicarbonate [CO_2]
Free-T3 (if TSH abnormal)	
Free-T4 (if TSH abnormal)	

Pregnancy Testing: For patients of childbearing potential, a serum or urine pregnancy test will be performed at screening. Pregnancy tests will also be done whenever pregnancy is suspected during the study. Additional pregnancy testing may be necessary if required by local practices or regulations.

7.3.5   *Electrocardiogram (ECG)*

Single and triplicate ECGs are to be performed as outlined in the Schedule of Assessments (Table 1). It is preferable that the machine used has a capacity to calculate the standard intervals automatically. In addition, QTc will be manually calculated using the Fridericia's formula. Assessments reported by automated read as prolongation of QTc should be over-read by a cardiologist to ensure accuracy of interpretation.

7.3.6   *Echocardiogram (ECHO)*

Echocardiograms will be performed at screening, and thereafter as in the Schedule of Assessments (Table 1). Additional assessments of LVEF and evaluation of pericardial effusions may be performed as clinically indicated at the investigator's discretion if there are signs or symptoms of cardiotoxicity. Where abnormalities indicating pericardial effusion exist, weekly assessments should be performed until normalization as described in Section 5.1.8.5. In exceptional circumstances where ECHO is not considered a technically optimal assessment of pericardial space (e.g., overweight patient), other methods (e.g., MRI) should be used for pericardial assessments.

7.4   Laboratory Studies

Laboratory studies for which blood will be collected include evaluation of PK, ADA, and PD. The schedules for sample collection are outlined in Table 2. Blood samples will be collected using an in-dwelling catheter or venipuncture into specified vacutainer tubes. Full details on sample collection, processing, storage and shipment are presented in the Study Laboratory Manual.

7.4.1   *Pharmacokinetic Evaluation*

The PK of mocetinostat and durvalumab will be determined using plasma samples collected at specified time points prior to and following study treatment dosing. Every effort will be made to collect these PK samples at the exact nominal times relative to dosing. A variation window is allowed for each time point as outlined in Table 2. The actual time of each sample collection will be recorded on the source document and CRF.

All plasma samples will be stored frozen and shipped on dry ice according to instructions provided. Analysis of plasma samples will be performed using specific validated bioanalytical methods. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.4.2   *Anti-Drug Antibody Evaluation*

Blood samples for measurement of durvalumab ADA concentrations in serum will be collected in samples taken according to the schedules of study procedures presented in Table 2. Details for collection, aliquoting, storage, and shipment of serum samples for ADA evaluations are presented in a separate Laboratory Manual. Validated electrochemiluminescence assays using a Meso Scale Discovery platform will be used for the determination of ADAs to durvalumab in human serum.

7.4.3   *Pharmacodynamic Evaluation in Tumor Tissue*

Pharmacodynamic parameters in tumor tissue that may be investigated in this study include but are not limited to PD-L1 expression, CD8+ TILs, NK-cells, Tregs, and MDSCs, prior to and during treatment. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.5   Post-treatment Follow-up

Blood samples for MEDI4736 PK and ADA will be collected approximately 90 days after the last infusion of durvalumab. Survival status and subsequent therapies will be collected during long term follow-up as outlined in the Schedule of Assessments (Table 1) until death or lost to follow-up. Beyond 90 days after last treatment, follow-up may be performed by telephone contact. Treatments received following participation in the study will be collected in the CRF.

8   ADVERSE EVENT REPORTING

8.1   Sponsor Medical Monitor Personnel

The contact information for the sponsor's Medical Monitor personnel for this trial is available in the study contact list located in the Study Manual.

8.2   Adverse Events

An adverse event (AE) is any reaction, side effect or other undesirable medical event that occurs during participation in a clinical trial, regardless of treatment group or suspected causal relationship to study treatment. A treatment emergent AE (TEAE) is an AE that occurs after the first dose of any study treatment or any preexisting condition that increases in severity after the first dose of study treatment.

All observed or volunteered AEs will be recorded in source documents and reported in the CRF. The best available medical terminology should be used to describe AEs in source documents and CRFs. Terms describing the diagnosis are preferred over individual signs and symptoms of the diagnosis. If determination of the diagnosis is delayed, record signs and symptoms and add the diagnosis as an AE when available; follow all recorded AEs to resolution. Examples of AEs include but are not limited to:

- Signs or symptoms of co-morbidity, illness, or toxicity of study treatment;

- Signs or symptoms of worsening malignancy under study (disease progression assessed by measurement of malignant lesions should not be reported as an AE).

- Laboratory abnormalities (see Section 8.2.1 for guidance for reporting in CRF);

- Hypersensitivity;

- Drug abuse, dependency, overdose, withdrawal or misuse;

- Signs or symptoms of drug interactions;

- Extravasation;

- Exposure during pregnancy or via breastfeeding;

- Medication error; or

- Occupational exposure.

8.2.1   Laboratory Abnormalities

An abnormal laboratory test results should be reported as an AE in the CRF only if it is associated with one or more of the following:

- Clinical symptoms;

- Requires additional tests (beyond repeats), treatment or intervention;

- Results in change in study treatment dosing;

- Requires discontinuation from study treatment; and/or

- Considered by the investigator or Sponsor to be an AE.

Hy's Law

Hepatic function abnormality is defined as any increase in ALT or AST to greater than $3 \times \text{ULN}$ and concurrent increase in total bilirubin to be greater than $2 \times \text{ULN}$. 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 disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Cases where a patient shows an AST or ALT $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$ may need to be reported as SAEs. These cases should be reported as SAEs if 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. Additionally, study drug should be permanently discontinued for a Hy's Law case.

8.2.2   Severity Assessment

AEs occurring during this study will be graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03). Documentation of AE grading in the source documents and CRF should be consistent with provided definitions.

8.2.3   Causality

For each AE, the investigator should determine and document whether there exists a reasonable possibility that the study treatment caused or contributed to the AE. The investigator's assessment should be recorded in the source document. The CRF will provide the options for attribution to study treatment as "related" and "not related." If the investigator's causality assessment is "unknown but not related to investigational

product," this should be recorded in the CRF as "not related." If the investigator does not know whether or not the study treatment is causally-related to the event, reporting for study purposes will be as "related" to study treatment.

Collection of causal relationship for AEs associated with study procedures (e.g., tumor biopsy) is provided for separately in the CRF.

8.3   Serious Adverse Events

8.3.1   Definition of a Serious Adverse Events

An SAE is any event that meets any of the following criteria:

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/permanent damage (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

  o Intensive treatment in an emergency room or at home for allergic bronchospasm

  o Blood dyscrasias or convulsions that do not result in inpatient hospitalization

  o Development of drug dependency or drug abuse

Progression of the malignancy under study, including any signs or symptoms of progression that may require hospitalization, should <u>not</u> be reported as an SAE unless the outcome is fatal within the safety reporting period.

Definition of Terms

Life threatening: An AE is life threatening if the patient was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Hospitalization: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

Disability/permanent damage: An AE is disabling or caused permanent damage if it resulted in a substantial disruption of a person's ability to conduct normal life functions, e.g., a significant, persistent or permanent change, impairment, damage or disruption in body function/structure, physical activities and/or quality of life.

Adverse Event of Special Interest (AESI): AESIs are of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Immune-related Adverse Events (irAE): An irAE is defined as an adverse event 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.

8.3.2   *Exposure During Pregnancy*

Exposure during pregnancy (i.e., exposure in-utero [EIU]) may occur in a female study participant, the female partner of a male study participant or study site personnel working with the investigational product (e.g., occupational exposure) if:

- A female becomes or is found to be pregnant during treatment or within 6 months after discontinuing treatment or having been directly exposed to the investigational product;

- A male is exposed to the investigational product prior to or around the time of conception or during the pregnancy of his partner.

If exposure in-utero occurs, the investigator must submit an SAE form and an EIU Supplemental Form within 24 hours of awareness of the exposure, regardless of whether an AE or SAE has occurred.

In the event of pregnancy in a female study participant, if the pregnancy is continued, study treatment will be immediately discontinued.

In the event of exposure of the pregnant partner of a male study participant, the study participant should be asked to deliver an EIU Pregnant Partner Release of Information Form to his partner. The Investigator must document on the EIU Form that the patient was given this letter to provide to his partner.

Follow-up to obtain pregnancy outcome information is to be conducted for all EIU reports. In the case of a live birth, the health of the neonate should be assessed at the time of birth and for up to 3 months after birth. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the event the pregnancy is terminated, the reason(s) for termination should be reported and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection.

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), an SAE report should be submitted to the Sponsor.

8.3.3   *Adverse Events of Special Interest*

8.3.3.1   *Durvalumab Adverse Events of Special Interest*

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Sponsor.

AESIs observed with durvalumab include:

- Colitis

- Pneumonitis

- ALT/AST increases / hepatitis / hepatotoxicity

- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)

- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)

- Dermatitis

- Nephritis

- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

8.3.3.2   *Mocetinostat Adverse Event of Special Interest*

All pericardial findings, regardless of seriousness and relationship to study medication, should be reported to the Sponsor with the use of the "Pericardial Event Report Form" provided by the Sponsor, according to the procedures for SAE expedited reporting (see Section 8.4.2). When reporting pericardial events, available ECHO results/reports (or other means of diagnosis if available) should also be provided, for review by the Medical Monitor.

8.4   Reporting of SAEs and AEs

8.4.1   *Reporting Period*

The active reporting period for SAEs begins from the time that the patient provides informed consent (i.e., prior to undergoing any study-specific procedure or assessment) and continues until 90 days post last administration of either therapy. All SAEs will be followed until the event has resolved or stabilized to a chronic condition, whichever is later. Death must be reported if it occurs during the active reporting period for SAEs regardless of whether a subsequent anticancer therapy is administered. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them and if the investigator assesses at least a reasonable possibility of being related to study drug.

The reporting period for non-serious AEs begins from the day of first dose of study treatment and continues until at least 28 days after last administration of study treatment and/or until recovery from all acute toxicities associated with the drug administration to a chronic condition, whichever is later. If a patient begins a subsequent anticancer therapy, the AE reporting period ends at the time the new treatment is started.

8.4.2   Reporting Requirements

All SAEs must be reported within 24 hours of Investigator/site knowledge of the event, irrespective of the extent of available AE information, by faxing the SAE report to the Sponsor's pharmacovigilance representative designated in the Study Manual. The 24-hour timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports and to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding. The need for an expedited report to regulatory authorities will be determined by the Sponsor and necessary reporting will be performed by the Sponsor. The Sponsor will notify study investigators of all Suspected, Unexpected (as judged against the Investigator Brochure) Serious Adverse Reaction (SUSAR) reports. The investigator is responsible for reporting all SUSARs to the IRB/EC.

All AE (including SAEs) must be documented in source documents and reported in the CRF. Please note that the CRF and SAE report forms may collect information in somewhat different formats. Where the requested data overlap in different formats, the information should be consistent between the two forms.

9   STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1   Hypothesis and Sample Size

9.1.1   Phase 1

Approximately 24 patients may be enrolled into the Phase 1 portion of the study and up to 261 patients will be enrolled into the Phase 2 portion. Precise sample size cannot be defined, as it is dependent on the number of dose escalations based on the mTPI method, and the number of patients enrolled in the expansion cohorts.

The mTPI method (Ji-2013) will be employed in decision making concerning dose escalation within each regimen investigated. The assumptions to be applied in establishing the mTPI methodology are:

- each specific regimen exploration will include up to 30 patients;

- the MTD is defined to have 0.25 probability of toxicity; and

- the acceptable variance around the MTD is ± 0.05 (i.e., the region of the MTD is 20% to 30% incidence of dose limiting toxicity).

9.1.2   Phase 2

The 4-cohort Phase 2 portion uses sample sizes based on Predictive Probability Design (Lee-2008). ORR in accordance with RECIST 1.1 is the primary clinical benefit endpoint. In creating the statistical designs, the Type 1 error (α) is constrained to <0.05 and Power (1-β) is constrained to ≥0.90.

Statistical Design Applied to Phase 2 Cohorts 1, 3 and 4

The ORR using a PD-L1 inhibitor in the population with advanced NSCLC having no or low PD-L1 expression, or prior disease progression on a checkpoint inhibitor, is assumed to be 5% (p_0); thus this rate is considered uninteresting. The target ORR using mocetinostat in combination with durvalumab in this study is 30% (p_1). Stage 1 of enrollment will include a minimum of 9 evaluable patients. With exactly 9 evaluable patients at Stage 1, if at least 1 patient has an Objective Response, 8 additional evaluable patients will be enrolled, for a total sample size of 17 evaluable patients. If at least 3 Objective Responses are observed, further investigation may be warranted. If the true ORR is 5% (null hypothesis), the probability of early termination during the study is 0.63; the Type 1 error is equal to 0.0466 and the power is equal to 0.9045.

Statistical Design Applied to Phase 2 Cohort 2

The ORR using a PD-L1 inhibitor in the population with advanced NSCLC having high PD-L1 expression is assumed to be 27% (p_0); thus this rate is considered uninteresting. The target ORR using mocetinostat in combination with durvalumab in this study is 50% (p_1). Stage 1 of enrollment will include approximately 17 evaluable patients. With exactly 17 evaluable patients at Stage 1, if at least 5 patients have Objective Responses, 27 additional evaluable patients will be enrolled, for a total sample size of 44 evaluable patients. If at least 18 Objective Responses are observed, further investigation may be warranted. If the true ORR is 27% (null hypothesis), the probability of early termination during the study is 0.50; the Type 1 error is equal to 0.0303 and the power is equal to 0.9018.

The exact stopping rules for all cohorts will be calculated based on the Predictive Probability Design, once the exact number of patients evaluable at Stage 1 is known. The aim is to get about 9 evaluable patients at Stage 1 for cohorts 1, 3 and 4 and about 17 evaluable patients at Stage 1 for cohort 2.

If Stage 2 results in Cohorts 3 and 4 are of high interest for efficacy, enrollment may be expanded to as many as 100 patients total in each cohort to narrow the 95% Confidence Interval (CI) around the ORR point estimate. Table 14 presents estimates of the 95% CI around the observed ORR for several potential outcomes using the sample size of 100 patients, and the Clopper-Pearson method.

Table 14:   Estimates of 95% CI Using Clopper-Pearson in After Enrollment of 100 Patients

Number of Observed Responses Among 100 Patients	ORR	95% CI
25	25%	16.9-34.7%
30	30%	21.2-40.0%
35	35%	25.7-45.2%
40	40%	30.3-50.3%
50	50%	39.8-60.2%

9.2   Data Handling

Listings of all patient data will be prepared. Data summaries will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Details of planned analyses will be described in the SAP.

For all variables, only the observed data from patients will be used in the statistical analyses; there is no plan to estimate missing data. Patients without a valid clinical response assessment will be assigned a best overall response of not evaluable (NE). Data from patients who are lost to follow-up or have missing observations before reaching an endpoint in any of the time-to-event analyses will be treated as censored with specific rules defined in the SAP.

9.3   Analysis Populations

9.3.1   Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population is defined as all patients who receive treatment with both mocetinostat and durvalumab on this study.

The primary efficacy analyses of the primary and secondary efficacy endpoints will be performed in the mITT population. In addition, the mITT population will be used in making decisions to expand the study to the next stage of enrollment (to up to 100 patients).

9.3.2   Clinical Activity Evaluable Population

In order to be considered eligible for the clinical activity evaluable population, the patient must have at least one on-study disease assessment or discontinue from treatment for PD. Patients who discontinue treatment prior to the first on-study disease assessment for an AE, toxicity, or withdraw consent are considered non-evaluable for disease assessment and will not be part of the clinical activity evaluable population.

This population will be used to present tumor responses as well as to make decision on the Predictive Probability design.

9.3.3   Safety Population

The Safety population is defined as all patients who received at least 1 dose of either mocetinostat or durvalumab. The Safety population will be used for all safety analyses.

9.3.4   DLT Evaluable Population

For a patient to be considered evaluable for dose-escalation decisions, or "DLT-evaluable," the patient must have either been on study for one full cycle and have received treatment with durvalumab and at least 9 of 12 scheduled mocetinostat doses (75%) in Cycle 1 or have experienced a DLT in Cycle 1.

9.3.5   Molecular Marker Evaluable Population

The molecular marker evaluable population will consist of all patients who receive at least one dose of either mocetinostat or durvalumab for whom PD-L1 expression results are available.

9.3.6   Pharmacokinetic Evaluable Population

The Pharmacokinetic evaluable population will consist of all patients who had sufficient concentration-time data to permit calculation of PK parameters for mocetinostat or durvalumab. For patients who were noncompliant with respect to administration of mocetinostat, or for patients with incomplete data, a decision as to their inclusion in the analysis will be made on a case-by-case basis.

9.3.7   Pharmacodynamic Evaluable Population

The Pharmacodynamic evaluable population will consist of all patients who receive at least one dose of either mocetinostat or durvalumab for whom PD results are available.

9.3.8   Anti-Drug Antibody Evaluable Population

The ADA evaluable population will consist of all patients who receive at least one dose of durvalumab for whom ADA results are available.

9.4   Efficacy Endpoint Definitions and Analyses

9.4.1   Objective Response Rate

Objective disease response will be categorized in accordance with RECIST v1.1 (Appendix 5). Objective Response Rate (ORR) is defined as the percent of patients documented to have a <u>confirmed</u> Complete Response (CR) or Partial Response (PR). If central review of disease response is undertaken, ORR as reported by the central

radiology review laboratory will be used to calculate ORR and the exact 95% confidence intervals (CI). ORR as reported by the investigator will be used in study expansion decision making (Predictive Probability design) and supportive analyses.

Descriptive statistics (frequency and percentage) for ORR, CR, and PR will be presented. The exact 95% CI of these response rates will be calculated. An exact test for single proportion (two-sided α=5%) will be performed to test H_0: ORR $\leq$ 5% against H_1: ORR > 5% in cohorts 1, 3 and 4 and to test H_0: ORR $\leq$ 27% against H_1: ORR > 27% in cohorts 2. Other details will be described in the SAP.

9.4.2   Clinical Benefit Rate

Clinical Benefit Rate (CBR) is defined as the percent of patients documented to have a confirmed Complete Response (CR), Partial Response (PR), or Stable Disease (SD) documented during at least 2 on-study assessments and including at least 14 weeks on study (e.g., allowance for 2-week window around Week 17 assessment).

9.4.3   Duration of Response

Duration of Response (DR) is defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of Objective Progression of Disease (PD) or to death due to any cause in the absence of documented PD. Censoring for the DR endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified and the patient does not die while on study. DR will only be calculated for the subgroup of patients with an objective response. The Kaplan-Meier method will be used to obtain the estimate of median DR.

9.4.4   Progression Free Survival

Progression-free survival (PFS) is defined as the time from date of first study treatment to first PD or death due to any cause in the absence of documented PD. Censoring for the PFS endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified and the patient does not die while on study. For patients in whom two or more sequential assessments are missed, followed by the finding of tumor progression, the PFS endpoint will be censored on the date of the last tumor assessment before the gap. Patients lacking an evaluation of disease after first study treatment will have their PFS time censored on the date of first dose with duration of 1 day. Patients who start a new anti-cancer therapy prior to documented PD will have the endpoint censored at the date of the last tumor assessment prior to the start of the new therapy. The Kaplan-Meier method will be used to obtain the estimate of median progression-free survival time.

9.4.5   *Overall Survival*

Time to death is defined as the time from date of first study treatment to death due to any cause. Censoring for the survival endpoint will be assigned on the date of the last on-study follow-up that the patient is reported to be alive. The Kaplan-Meier method will be used to estimate the median OS and 1-year Survival Rate; the 95% confidence interval of the 1-year survival rate will also be reported.

9.5   Safety Data Presentations and Summaries

9.5.1   *Adverse Events*

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. Listings will include the verbatim term, preferred term, and system organ class (SOC). The number of patients with treatment emergent AEs and the incidence of TEAEs by SOC and preferred term will be summarized. TEAEs will be summarized by maximum intensity and relationship to study therapy. Separate summaries will be provided for TEAEs, TESAEs, treatment-related AEs, treatment-related SAEs, and other significant AEs (e.g., AEs leading to study discontinuation).

9.5.2   *Prior and Concomitant Medications*

Collected prior and concomitant medications will be coded by WHO medical dictionary; patients who received these medications will be listed and summarized.

9.5.3   *Clinical and Laboratory Assessments*

Clinical and laboratory assessments include clinical laboratory tests (hematology, coagulation, urinalysis, thyroid function tests and chemistry), vital signs, ECHO and 12-lead ECGs.

Clinical laboratory results will be listed by patient and, as appropriate, summarized descriptively, which will include a display of change from baseline. Selected parameters will be presented in shift tables of baseline against worst grade test result. Laboratory values outside of the normal ranges will be identified. Laboratory values that meet Grade 3 or 4 criteria according to NCI CTCAE v.4.03 will be listed and summarized.

ECG assessments will be evaluated for change of QTc from baseline as an exposure: response analysis. The investigator's interpretation of QTc will be used in the clinical management of patients. The study analysis will use the Fridericia formula applied programmatically to the ECG data collected in CRFs.

Vital signs, ECHO and ECG measurements will be listed for each patient at each visit. Descriptive statistics of observed values and changes from baseline will be summarized by treatment group.

9.5.4   Patient Demographics, Baseline Characteristics and Disposition

Presentations of patient characteristics will include a summary of the following for all patients enrolling in the study:

- Demographics

- Baseline disease characteristics

- Pre-existing conditions/concurrent illness

- Prior therapies/surgeries

A summary of patient enrollment and disposition will include reasons for study discontinuation.

9.5.5   Analysis of Study Treatment Dosing

Study treatment administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered for each agent separately and for the combination, dose intensity, and reasons for the deviations from planned therapy.

9.6   Other Study Endpoints

9.6.1   Pharmacokinetic Analysis

The PK exposure data from this study may be used in the development of population PK and PK/PD models for mocetinostat and durvalumab. Additional PK parameters may be defined and described in the Pharmacokinetic Analysis Plan. Plasma concentrations will be listed by patient for the PK Population. Summary statistics of MGCD0103 and MEDI4736 concentrations will be reported by dose level, Day and Cycle. Only samples with acceptable PK (as defined in the Pharmacokinetic Analysis Plan) will be included in the summary statistics and a listing of individual data points or patients excluded from the analysis will be presented.

9.6.2   Pharmacodynamic Analysis

No formal statistical analysis of PD endpoints will be performed. PD data from each assay will be listed by dose level and Phase 2 cohort. Possible relationships between PD variables, PK parameters, safety, and clinical activity may be examined if appropriate.

9.6.3　*Anti-Drug Antibodies*

The immunogenic potential of durvalumab following combination therapy with mocetinostat will be assessed by summarizing the number and percentage of patients who develop detectable ADAs. The titer for the confirmed positive ADA samples will be reported. Additionally, the impact of ADAs on PK, clinical response and safety will be assessed if data allow.

9.7　Interim Analysis

No interim statistical analysis is planned during this study.

9.8　Data Monitoring Committee

No Data Monitoring Committee is planned during this study.

10　ETHICS AND RESPONSIBILITIES

10.1　Ethical Conduct of the Study

This study will be conducted in accordance with International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonization [ICH] 1996), ICH E6 (R2), and concepts that have their origin in the Declaration of Helsinki (World Medical Association 1996, 2008 & 2013). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

10.2　Obligations of Investigators

The Investigator is responsible for complying with the protocol and all applicable regulations and guidelines governing clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

All Investigators must provide the sponsor with a current *curriculum vitae*. Only Investigators and designated Sub-Investigators are permitted to sign CRFs and examination findings (e.g., laboratory results or ECGs).

The Investigator or designee is responsible for informing the patient of all available information relevant to his/her safety and obtaining signed, written consent from all participating patients. Additionally, the Investigator is responsible for monitoring patient safety and providing periodic and requested reports to the IRB/EC.

The Investigator is responsible for the accuracy and completeness of all study records including CRFs, source documents, and the Site Trial Master File. The Investigator will allow the study monitor, Sponsor, auditor, regulatory agencies, and IRB/EC full access to the study and source documents.

10.3   Institutional Review Board/Ethics Committee/Research Ethics Board (IRB/EC)

Prior to the shipment of clinical supplies or initiation of the study, the clinical trial protocol along with the informed consent form (ICF), Investigator's Brochure, and any other written information or instructions for the patient must be submitted to the IRB/EC for written approval. The Investigator will provide the Sponsor with a copy of the IRB/EC's written approval, as well as the membership list or a compliance statement from the IRB/EC. The Investigator is responsible for notifying the IRB/EC of any Sponsor-approved amendments to the protocol or ICF, SAEs occurring in patients treated at the study site in accordance with local IRB/EC practice, and all expedited safety reports from SAEs occurring at other study sites participating in the drug development program.

10.4   Informed Consent Form

The ICF must contain all elements required by the Food and Drug Administration (FDA) under 21 Code of Federal Regulations (CFR) Part 50 and the ICH GCP guidelines (ICH E6) in addition to any other elements required by applicable national, state, provincial, and local regulations, or institutional policies.

All patients who choose to participate in the study must provide written consent after having had adequate time to consider whether they will participate in the study. The written consent must be obtained prior to any protocol-related procedures that are not part of the patient's normal medical care. The patient must be advised of his/her right to withdraw from the study at any time.

Written documentation of consent must be recorded in the patient's source documents, study records and CRF indicating the date the consent was signed. The patient should receive a signed copy of the consent form according to GCP guidelines.

10.5   CONFIDENTIALITY

All information generated in this study is considered confidential, is subject to applicable privacy rules and regulations, and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor and otherwise except in accordance with applicable law or regulations. However, authorized regulatory officials, IRB/EC personnel, the Sponsor and its authorized representatives (as and to the extent authorized in the patient's ICF) are allowed access to the records.

Identification of patients in CRFs shall be by study assigned patient numbers only. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

10.6   Reporting of Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction (i.e., clinical hold) imposed by an applicable Regulatory Authority, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor must be informed immediately. In addition, the investigator will inform the Sponsor immediately of any serious breaches of this protocol or of ICH GCP of which the investigator becomes aware.

11 RECORDS MANAGEMENT

11.1   Source Documentation

Source documents include hospital or clinical patient charts, pertinent historical medical records, laboratory test reports, ECG tracings and reports, pathology reports, radiographs, etc. All source documents must be legible. Data reported in CRFs and evidence of patient's informed consent must be documented in source documents.

11.2   Study Files and Records Retention

A CRF must be completed for each patient for whom informed consent for the study is obtained. The CRFs must be maintained by properly trained and delegated site representatives. The Principal Investigator has responsibility for ensuring the authenticity, accuracy, completeness and timeliness of all data collected in the CRF. CRFs must be signed by the Principal Investigator or by an authorized Sub-Investigator to attest that the information included is true.

The study site will maintain a Site Trial Master File in accordance with GCPs.

The Investigator shall retain all records for the longest of the following periods:
(i) 15 years; (ii) the period of time that conforms to ICH GCP guidelines; (iii) the period of time required by applicable law or regulations, or (iv) the period of time specified in the Clinical Research Agreement.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring Procedures

Sponsor appointed Site Monitor(s) must be allowed access to all study records, original source documents, and investigational products throughout the duration of the study. These personnel are responsible to assess compliance with the protocol, appropriate health authority regulations, ICH GCP guidelines, and Sponsor requirements.

The study monitor is responsible for complying with the monitoring guidelines established by the Sponsor for the study, assessing the site's needs, and liaising with the assigned Sponsor staff.

Source documents are defined as all medical records, medical notes, pathology or radiology reports, laboratory results, ECG tracings, and any additional documents that have original patient information contained within it.

If the Investigator withdraws from the study and relinquishes his/her responsibility for the maintenance and retention of records, he/she must notify the Sponsor in writing so arrangements can be made to properly store the study materials.

12.2 Auditing and Inspection Procedures

The Sponsor's Quality Assurance representatives, IRB/EC reviewers, or inspectors from regulatory agencies may perform an audit or inspection at any time during or after completion of the clinical study. All study-related documentation must be made available to the designated auditor. In addition, representatives of applicable regulatory health authorities may choose to inspect a study. A Sponsor representative will be available to assist in the preparation for such an inspection.

13 CHANGES IN STUDY CONDUCT

13.1 Protocol Amendments

Changes to the study protocol, except those intended to reduce immediate risk to study patients, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/EC is notified within 5 days. Any urgent safety measures taken by the investigator to protect the study patients against any immediately life threatening hazard must be reported immediately to the Sponsor.

Any permanent change to the protocol must be handled as a protocol amendment. The change and the justification will be documented in writing by the Sponsor, as an Administrative Letter or amended protocol. Protocol amendments will be provided with a separate document describing each change and rationale. The written Administrative Letter or amendment must be submitted to the IRB/EC and the investigator must await approval before implementing the changes. The Sponsor will be responsible for submitting protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/EC, the investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consents (revised as appropriate to address protocol amendments) will be obtained for patients enrolled in the study before continued participation.

13.2 Protocol Deviations

Prospective permission to deviate from the eligibility criteria for this protocol will not be provided by the Sponsor. Study specified assessments should not be omitted and the study treatment regimen should not deviate from protocol specifications. Minor, occasional adjustments in the clinic visit schedule may be necessary for logistical reasons (e.g., due to weather conditions) but must not become routine or systematically alter the study schedule. The IRB/EC should be informed of any deviations that may affect a patient's treatment or informed consent, especially those increasing potential risks, which must receive prior written approval by the IRB/EC.

14 END OF TRIAL

14.1 End of Trial in a European Union Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (i.e., Clinical Trial Application (CTA)) and ethics application in the Member State.

14.2 End of Trial in all other Participating Countries

End of Trial in all other participating countries is defined as the time at which all patients enrolled in the study have completed the last study visit and data from those visits have been reviewed by the investigator or designee.

14.3 Premature Termination

Premature termination of this study may occur at any time because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety concerns, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of mocetinostat and durvalumab at any time. If termination becomes necessary, the Sponsor will inform the appropriate regulatory authorities of the termination and the reason. The Principal Investigator will inform the IRB/EC of the same. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the patients' interests.

15 STUDY REPORT AND PUBLICATION POLICY

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication of study results will be governed by the applicable Clinical Research Agreement between the Sponsor and the Study Site and Investigator (as applicable).

16 REFERENCES

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Appendix 1. ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

Appendix 2. Dose-Finding Spreadsheet of the Modified Toxicity Probability Interval (MTPI) Method

Number of Patients Treated at Current Dose (columns 1–30); Number of Dose Limiting Toxicities (rows 0–30)

DLTs \ n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		U	D	D	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			U	U	U	D	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E
4				U	U	U	U	U	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E
5					U	U	U	U	U	U	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
6						U	U	U	U	U	U	U	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
7							U	U	U	U	U	U	U	U	U	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
8								U	U	U	U	U	U	U	U	U	U	S	S	S	S	S	S	S	S	S	S	S	S	S
9									U	U	U	U	U	U	U	U	U	U	U	S	S	S	S	S	S	S	S	S	S	S
10										U	U	U	U	U	U	U	U	U	U	U	U	U	S	S	S	S	S	S	S	S
11											U	U	U	U	U	U	U	U	U	U	U	U	U	U	S	S	S	S	S	S
12												U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	S	S	S	S
13													U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	S	S
14														U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
15															U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
16																U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
17																	U	U	U	U	U	U	U	U	U	U	U	U	U	U
18																		U	U	U	U	U	U	U	U	U	U	U	U	U
19																			U	U	U	U	U	U	U	U	U	U	U	U
20																				U	U	U	U	U	U	U	U	U	U	U
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22																						U	U	U	U	U	U	U	U	U
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27																											U	U	U	U
28																												U	U	U
29																													U	U
30																														U

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 0.25
Sample Size = 30
$\varepsilon_1 = 0.05$
$\varepsilon_2 = 0.05$

Appendix 3. Medications or Substances Prohibited or to be used with Caution During Study Treatment with Mocetinostat

Bold font indicates medications or substances that might be relatively commonly used.

Italic font indicates medications for indications that are exclusionary for the current study or would likely result in discontinuation from study treatment with mocetinostat for management of a concurrent illness.

DRUGS THAT MAY PROLONG QT INTERVAL

Drugs Prohibited During Treatment with Mocetinostat

Drugs with a Known Risk of Torsades de Pointes	Amiodarone, anagrelide, *arsenic trioxide*, astemizole (off US market), **azithromycin**, bepridil (off US market), chloroquine, **chlorpromazine**, cisapride (off US market), **citalopram**, **clarithromycin**, cocaine, disopyramide, dofetilide, domperidone (not on US market), dronedarone, **droperidol**, **erythromycin**, **escitalopram**, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl (off US market), mesoridazine (off US market), **methadone**, moxifloxacin, **ondansetron**, *pentamidine*, pimozide, probucol (off US market), procainamide, quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), terfenadine (off US market), thioridazine, *vandetanib*.

Drugs To Be Used with Caution During Treatment with Mocetinostat

Drugs with a Conditional Risk of Torsades de Pointes	**Amantadine**, amisulpride, amitriptyline, amoxapine, chloral hydrate, **ciprofloxacin**, clomipramine, desipramine, **diphenhydramine**, doxepin, **fluconazole**, **fluoxetine**, **furosemide**, galantamine, **hydrochlorothiazide**, imipramine (melipramine), indapamide, **itraconazole**, ivabradine, **ketoconazole**, metronidazole, *nelfinavir*, nortriptyline, **paroxetine**, posaconazole, protriptyline, quinine sulfate, *ritonavir*, **sertraline**, solifenacin, *telaprevir*, trazodone, **trimethoprim-sulfa**, trimipramine, voriconazole.

CAUTION WHEN TAKING THE FOLLOWING MEDICATIONS AND SUBSTANCES

Enzyme	
Inhibitor of CYP 2E1	Disulfiram
Inducers of CYP 2E1	**Ethanol**, isoniazid, **tobacco**
Strong Inhibitors of CYP 3A4	*Boceprevir*, **clarithromycin**, *conivaptan*, grapefruit juice, *indinavir*, **itraconazole**, **ketoconazole**, *lopinavir/ritonavir*, *mibefradil (withdrawn from US market)*, nefazodone, *nelfinavir*, **posaconazole**, *ritonavir*, *saquinavir*, *telaprevir*, **telithromycin**, **voriconazole**
Strong Inducers of CYP 3A4	Carbamazepine, phenytoin, rifampin
Substrates of CYP 2C9	Celecoxib, diclofenac, fluvastatin, **glipizide**, **ibuprofen**, **irbesartan**, **losartan**, **naproxen**, phenytoin, piroxicam, **rosiglitazone**, **sulfamethoxazole**, *tamoxifen*, tolbutamide, torsemide

Appendix 4. Management of Specific Immune-Related Adverse Events

Pneumonitis/ILD

Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below.

Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.

Grade of AE	Dose Modifications	Toxicity Management
Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	• None required. • Consider holding as clinically appropriate and during diagnostic work-up for other etiologies	• Monitor, follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated • Consider pulmonary and infectious disease consult
Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	• Hold until ≤ Grade 1 • If worsens, treat as Grade 3 or Grade 4 • If improves to ≤ Grade 1, decision to reinitiate study drug/regimen based on clinical judgment and after completion of steroid taper.	• Monitor daily and consider hospitalization • Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day or IV equivalent) • Reimage as clinically indicated • If no improvement within 3-5 days, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started • If still no improvement within 3-5 days despite IV methylprednisone, promptly start immunosuppressive therapy such as TNF inhibitor (e.g. infliximab at 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation, ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects") • Consider pulmonary and infectious disease consult • Consider as necessary discussing with study physician
Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	• Permanently discontinue	• Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Obtain pulmonary and infectious disease consult • Hospitalize the patient • Supportive Care (oxygen, etc.) • If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Diarrhea/ Enterocolitis
- Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus)
- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.)
- Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event
- Use analgesics carefully; they can mask symptoms of perforation and peritonitis

Grade of AE	Dose Modifications	Toxicity Management
Grade 1 diarrhea (stool frequency of < 4 over baseline per day)	• None required	• Monitor for worsening symptoms • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics per clinical judgment.
Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	• Hold until resolution to ≤ Grade 1 • If worsens treat as Grade 3 or Grade 4 • If improves to ≤ Grade 1, study drug/study regimen can be resumed after completion of steroid taper.	• Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide • Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent • If not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. • If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks). Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab • Consult study physician if no resolution to ≤ Grade 1 in 3-4 days • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥ 7 over baseline per day; Grade 4: life threatening consequences)	• Permanently discontinue	• Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent • Monitor stool frequency and volume and maintain hydration • Urgent GI consult and imaging and/or colonoscopy as appropriate • If still no improvement within 3-5 days of IV methylprednisolone 2-4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5 mg/kg once every 2 weeks). • Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Hepatitis (Elevated LFTs)

- **Infliximab should not be used for management of Immune Related Hepatitis**
- Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin
- Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)

Grade of AE	Dose Modifications	Toxicity Management
Grade 1 (AST or ALT > ULN to 3 times ULN and/or TB > 1.5 times ULN)	• None required • If it worsens, treat as Grade 2 event	• For Grade 1 AST or ALT and/or TB elevation • Continue LFT monitoring per protocol
Grade 2 (AST or ALT > 3-5 times ULN and/or TB > 1.5-3.0 times ULN)	• Hold dose until Grade 2 resolution to ≤ Grade 1 • If worsens then treat as Grade 3 or Grade 4 • If improves to ≤ Grade 1 or baseline resume study drug/study regimen after completion of steroid taper.	• For Grade 2 AST or ALT and or TB elevation - Frequent checking of LFTs (e.g. every 1-2 days) until elevations improving or resolved. • If no resolution in 1-2 days, discuss with study physician. • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day PO or IV equivalent. • If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil). Discuss with study physician if mycophenolate mofetil is not available. Infliximab should NOT be used. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Grade 3 (AST or ALT > 5-20 times ULN and/or TB > 3.0-10 times ULN	• For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN • Hold dose until resolution to ≤ Grade 1 or baseline • Resume if elevations downgrade ≤ Grade 1 or baseline within 14 days, and after completion of steroid taper	• For Grade 3 or 4 AST or ALT and/or TB elevation: • Promptly initiate empiric IV methylprednisolone at 1-4 mg/kg/day or equivalent • If still no improvement within 3-5 days despite 1-4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. • Hepatology consult, abdominal workup, and imaging as appropriate. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Hepatitis (Elevated LFTs)
• **Infliximab should not be used for management of Immune Related Hepatitis**
• Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin
• Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)

Grade of AE	Dose Modifications	Toxicity Management
Grade 3 (AST or ALT > 5-20 times ULN and/or TB > 3.0-10 times ULN (cont'd)	• Permanently discontinue if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days • For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue • Permanently discontinue for any case meeting Hy's law criteria (AST and/or ALT > 3 × ULN + bilirubin > 2 × ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause • (FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation NCI CTCAE version 4.03)	See above.
Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	• Permanently discontinue	

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Nephritis or Renal Dysfunction (Elevated Serum Creatinine)
Consult with Nephrologist
Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.)
Patients 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

Grade of AE	Dose Modifications	Toxicity Management
Grade 1 (Serum Creatinine > 1-1.5 × baseline; > ULN to 1.5 × ULN)	• No dose modification	• Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4 • Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
Grade 2 (Serum Creatinine>1.5-3.0 × baseline; >1.5 ×-3.0 × ULN)	• Hold until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline resume study drug/study regimen after completion of steroid taper.	• Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. • Carefully monitor serum creatinine every 2-3 days and as clinically warranted • Consult Nephrologist and consider renal biopsy if clinically indicated • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day PO or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. • Once improving gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). • When event returns to baseline, resume and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 × baseline; > 3.0-6.0 × ULN Grade 4: Serum Creatinine > 6.0 × ULN)	• Permanently discontinue	• Carefully monitor serum creatinine on daily basis • Consult Nephrologist and consider renal biopsy if clinically indicated • Promptly start prednisone 1-2 mg/kg/day PO or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Rash (excluding Bullous skin formations) Refer to NCICTCAE for definition of severity/grade depending on type of skin rash Monitor for signs and symptoms of dermatitis (rash and pruritis) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED AND STUDY DRUG DISCONTINUED**		
Grade of AE	**Dose Modifications**	**Toxicity Management**
Grade 1	• No dose modification	• Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
Grade 2	• For persistent (> 1-2 weeks) Grade 2 events, hold until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves to ≤ Grade 1 or baseline resume study drug/study regimen after completion of steroid taper.	• Obtain dermatology consult • Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) • Consider moderate-strength topical steroid • If no improvement within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent • Consider skin biopsy if persistent for > 1-2 weeks or recurs
Grade 3	• Hold until resolution to ≤ Grade 1 or baseline • If holding does not provide improvement to ≤ Grade 1 or baseline within 30 days, then permanently discontinue	• For Grade 3 or 4: • Consult dermatology • Promptly initiate empiric IV methylprednisolone 1-4 mg/kg/day or equivalent • Consider hospitalization • Monitor extent of rash [Rule of Nines] • Consider skin biopsy (preferably more than 1) as clinically feasible.
Grade 4	• Permanently discontinue	• Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • Discuss with Study Physician

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)
- Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity
- Consult Endocrinologist
- Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness.
- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.)
- Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy.
- If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing

Grade of AE	Dose Modifications	Toxicity Management
Grade 1	• No dose modification	• For Grade 1: (including those with asymptomatic TSH elevation) • Monitor patient with appropriate endocrine function tests • If TSH < 0.5 × LLN, or TSH > 2 × ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
Grade 2	• For Grade 2 endocrinopathy other than hypothyroidism, hold dose until patient is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 • Can resume once event stabilizes and after completion of steroid taper.	• For Grade 2: (including those with symptomatic endocrinopathy) • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Initiate hormone replacement as needed for management • Evaluate endocrine function, and as clinically indicated, consider pituitary scan • For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones). • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated. Note: Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated on the following conditions: 1) the event stabilizes and is controlled ,2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.
Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	• For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold dose until endocrinopathy symptom(s) are controlled • Can be resume at the next scheduled dose once event stabilizes to grade ≤ 1 and 5-7 days have passed after completion of steroid taper	• Consult endocrinologist • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Promptly initiate empiric IV methylprednisolone 1-2 mg/kg/day or equivalent • Administer hormone replacement therapy as necessary. • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity • Once improving, gradually taper immunosuppressive steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • Discuss with study physician

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis, autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)

- Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.)
- Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness)
- Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations)
- Symptomatic treatment with neurological consult as appropriate

Grade of AE	Dose Modifications	Toxicity Management
Grade 1	• None required	• See recommendations above.
Grade 2	• For acute motor neuropathies or neurotoxicity, hold dose until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding dose until resolution to ≤ Grade 1. • If toxicity worsens then treat as Grade 3 or Grade 4 • Can resume once event improves to Grade ≤ 1 and after completion of steroid taper.	• Discuss with the study physician • Obtain Neurology Consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) • Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent • If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
Grade 3	• Hold until resolution to ≤ Grade 1 • Permanently discontinue if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.	• For Grade 3 or 4: • Discuss with study physician • Obtain Neurology Consult • Consider hospitalization • Promptly initiate empiric IV methylprednisolone 1-2 mg/kg/day or equivalent
Grade 4	• Permanently discontinue	• If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) • Once stable, gradually taper steroids over ≥ 28 days

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis

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

Grade of AE	Dose Modifications	Toxicity Management
Grade 1	• None required	• Discuss with the study physician • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above • Obtain a neurology consult unless the symptoms are very minor and stable
Grade 2	• Hold until ≤ Grade 1 • Permanently discontinue if does not resolve within 30 days or if there are signs of respiratory insufficiency or autonomic instability	• Discuss with the study physician • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above • Obtain a Neurology Consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) • *MYASTHENIA GRAVIS* • Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. • Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. • If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. • *GUILLAIN-BARRE:* Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.

Appendix 4 Management of Specific Immune-Related Adverse Events (Continued)

Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis

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- Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult
- Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation
- Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG

Grade of AE	Dose Modifications	Toxicity Management
Grade 3	• Hold dose until resolution to ≤ Grade 1 • Permanently discontinue if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	• For severe or life threatening (Grade 3 or 4) events • Discuss with study physician • Recommend hospitalization • Monitor symptoms and obtain neurological consult • *MYASTHENIA GRAVIS* • Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. • Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. • If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. • *GUILLAIN-BARRE*: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
Grade 4	• Permanently discontinue	

Appendix 5. Abbreviated Presentation of RECIST Version 1.1 Guidelines

A modification to RECIST 1.1 has been made to account for the possibility of temporary changes resulting from the potentially beneficial treatment responses of tumor necrosis, cavitation or flare response.

Categorizing Lesions at Baseline

Measurable Lesions

- Accurately measured in at least one dimension.

- When assessed by CT or MRI, longest diameter at least 10 mm or greater (slice thickness 5-8 mm), measured in the axial plane. If the slice thickness is greater than 5 mm (including any inter-slice gap), the longest diameter must be at least twice the slice thickness.

- Malignant lymph nodes with a short axis (defined as the largest measurement perpendicular to the longest diameter of the lesion) 15 mm or greater when assessed by CT or MRI.

The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other lesions.

Non-Measurable Disease

- Lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) or truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, and abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

- Previously irradiated lesions (or those subjected to other local treatment) are non-measurable unless it they have progressed since completion of treatment.

Normal Lesions

- Non-malignant simple cysts should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above.

- Lymph nodes with short axis <10 mm are considered normal and should not be followed as disease.

Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. All required scans must be done within the window of time specified in the Schedule of Assessments (Table 1) prior to treatment. If the baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

The determination of whether lesions are measurable is performed only at baseline. "Measurable" at baseline means eligible for selection as target lesions, and thus for quantitative assessment throughout the trial. Once selected as a target lesion, a lesion remains target throughout the trial.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to look for partial response at later assessments.

- If 2 target lesions coalesce the longest diameter measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

- When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-Target Lesions

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather qualitative evaluations of status will be recorded. Multiple non-target lesions in one organ may be recorded as a single item on the CRF (e.g., 'multiple liver metastases').

Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast. If not, subsequent objective statuses may be indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Progressive Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy) with a minimum absolute increase of 5 mm.

- Indeterminate: Progression has not been documented, and

  o one or more target lesions have not been assessed,

  o or assessment methods used were inconsistent with those used at baseline and impaired assessment,

  o or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure),

  o or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

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

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Lesion Changes That May Be Transient

Potential exists for individual tumor lesions to develop necrosis, to cavitate, have a flare response to treatment or become otherwise difficult to evaluate for a period of time as the result of beneficial study treatment impact. For example, tumor necrosis, cavitation or flare may result in increase in overall size of individual lesions or unclear tumor margins prior to recovery to smaller lesions, development of scar tissue, or complete resolution. The true tumor measurements of lesions should be recorded but the conclusion of progressive disease may be suspended until continued assessment clarifies the nature of the tumor change. If repeat assessments indicate progression of disease, then PD should be recorded on the date of the first assessment giving the impression of progression. If repeat assessments indicate that the change was a process of transition, then NE (not evaluable) should be recorded during the period of transition, and PR or CR may be recorded for subsequent evaluations. The CRF will collect information on the observations during the period of transition to support the assessment conclusions.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

Best Objective Response

Target Lesions	Non-Target Lesions	New Lesion	Point in Time Response	Best Response
CR	CR	No	CR	CR and PR require confirmation at least 4 weeks after first observation
CR	Non-CR/Non-PD	No	PR	
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	SD requires an on-study assessment after at least 6weeks on treatment. Unconfirmed PR or CR are reported as SD.
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Subjective Progression

Patients requiring discontinuation of treatment due to worsening health status attributable to advancement of the malignancy under study but without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status.