A Study of Safety, Tolerability, and Clinical Activity of Durvalumab and Tremelimumab Administered as Monotherapy, or Durvalumab in Combination with Tremelimumab or Bevacizumab in Subjects with Advanced Hepatocellular Carcinoma

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PROTOCOL SYNOPSIS

TITLE

A Study of Safety, Tolerability, and Clinical Activity of Durvalumab and Tremelimumab Administered as Monotherapy, or Durvalumab in combination with Tremelimumab or Bevacizumab in Subjects with Advanced Hepatocellular Carcinoma.

HYPOTHESIS

Durvalumab and tremelimumab as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab can be administered to subjects with advanced hepatocellular carcinoma (HCC) with adequate safety, tolerability, and efficacy.

OBJECTIVES

Primary Objectives

1. To assess the safety and tolerability of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab to subjects with advanced HCC.

Secondary Objectives

1. To evaluate the efficacy of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with bevacizumab or tremelimumab in subjects with advanced HCC.
2. To evaluate the relationship between candidate biomarkers (eg, programmed cell death ligand 1 [PD-L1] expression in the tumor microenvironment) and measures of clinical outcome of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced HCC.

Exploratory Objectives

CCI

STUDY ENDPOINTS

Primary Endpoints

1. Adverse events (AEs), serious adverse events (SAEs), discontinuation of investigational product(s) due to toxicity, and changes from baseline in laboratory parameters (including liver and viral laboratory tests), electrocardiograms (ECG), and vital signs.

Secondary Endpoints

1. Objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DoR), time to progression (TTP), and progression-free survival (PFS) based on investigator

assessments and Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and overall survival (OS).

2. AEs, SAEs, discontinuation of investigational product(s) due to toxicity, and changes from baseline in laboratory parameters (including liver and viral laboratory tests), ECG, and vital signs in three distinct HCC populations: uninfected, HBV+, and HCV+.
3. PD-L1 expression within the tumor microenvironment.

Exploratory Endpoints

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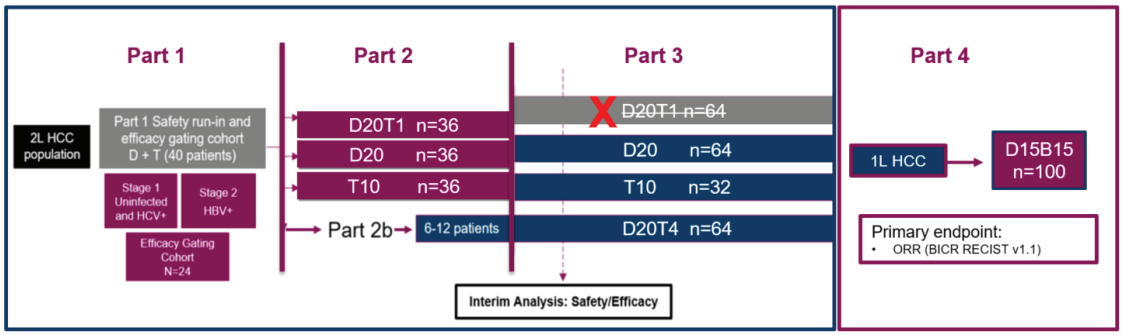
STUDY DESIGN AND TREATMENT REGIMENS

This is a multicenter, open-label, stratified, study designed to evaluate the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab, in subjects with advanced HCC. Approximately 655 subjects will be screened to enroll approximately 456 subjects globally, including approximately 12 subjects in Part 1A, approximately 24 subjects in Part 1B, approximately 108 subjects in Part 2A, approximately 12 subjects in Part 2B, approximately 200 subjects in Part 3, and approximately 100 subjects in Part 4.

The study will comprise 6 parts, as described below. Subjects in Part 1A, Part 1B, and Part 2A will receive weight-based dosing regimens of durvalumab and tremelimumab either as monotherapy or as combination therapy. Subjects in Part 2B and Part 3 will receive fixed dosing regimens of durvalumab and tremelimumab either as monotherapy or as combination therapy. Subjects in Part 4 will receive weight-based dosing regimen of durvalumab and bevacizumab in combination therapy.

Following protocol amendment 5, enrollment of Part 3 Arm A will be closed. Patients who have been randomized to Arm A before this protocol amendment, can continue on assigned study treatment (provided the investigator and patient think it is in the best interests of the patient) until confirmed PD or any other discontinuation criteria as described in section 4.1.6 is met. If a patient has not completed

or started all 4 doses of tremelimumab, the patient may either continue to complete the full schedule or continue with durvalumab monotherapy only.



D15B15=	Durvalumab 15mg/kg (1120mg) + Bevacizumab 15mg/kg Q3W
D20T1=	Durvalumab 1500 mg Q4W + Tremelimumab 75 mg x 4 dose
D20T4=	Durvalumab 1500 mg Q4W + Tremelimumab 300 mg x 1 dose
D20=	Durvalumab monotherapy 1500 mg Q4W
T10=	Tremelimumab monotherapy 750 mg Q4W

2L = second line; 1L = first line; HBV+ = hepatitis B virus positive; HCC = hepatocellular carcinoma; HCV+ = hepatitis C virus positive; D = Durvalumab; T = tremelimumab; B = Bevacizumab

Part 1A: Safety Run-in with Durvalumab and Tremelimumab Combination Therapy.
Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant of, or refused sorafenib-based therapy will be enrolled in Part 1A using a risk-based, staggered approach.

- Stage 1: Approximately 6 subjects with advanced uninfected or HCV+ HCC will be enrolled. Subjects will be administered the durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy every 4 weeks (Q4W) for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. If the frequency of AEs meeting dose-limiting toxicity (DLT) criteria is ≥ 33% for a given viral status/type, then lower dose cohorts in that specific subpopulation may be explored depending on the type and severity of the toxicities seen at this combination dose.
- Stage 2:
  - *HBV+ Cohort:* Enrollment of 6 additional subjects with advanced HBV+ HCC may start after the first 3 subjects in Stage 1 have been observed on study for at least 4 weeks. Subjects will be administered durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. If the frequency of AEs meeting DLT criteria is ≥ 33%, then Dose Level -1 (ie, durvalumab 15 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W followed by durvalumab 15 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met) may be explored depending on the type and severity of the toxicities seen at this combination dose.
  - *Dose for HBV+ HCC Subjects Administered the durvalumab and Tremelimumab Combination:* durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W will be the dose evaluated for HBV+ subjects in Part 1B and Part 2A if the following criteria are met: (1) all 6 subjects have been observed for at least 4 weeks and the DLT frequency is < 33% (ie, < 2 of 6 subjects); AND (2) at least 3 of the 6 subjects have been observed for 6 weeks. If the DLT frequency for the Stage 2 cohort is ≥33% (ie, ≥ 2 of 6 subjects), then Dose Level -1 (ie, durvalumab 15 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 15 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met) will be the dose evaluated for HBV+ subjects in Part 1B and Part 2A assuming the DLT frequency at Dose Level -1 is < 33%.

Part 1B: Efficacy Gating Cohort for Durvalumab and Tremelimumab Combination Therapy. Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant of, or refused sorafenib-based therapy will be enrolled in Part 1B.

Approximately 24 subjects (uninfected, HBV infected, or HCV infected) will be enrolled in an efficacy gating cohort to determine if there is sufficient evidence of clinical activity to warrant opening enrollment to Part 2. Refer to Section 4.8.7 for details regarding the definition of sufficient evidence. Subjects will be administered the durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. After approximately 12 of the 24 subjects have been enrolled, enrollment of subjects who have progressed on or are intolerant to sorafenib may be paused in favor of subjects who have refused sorafenib to ensure a minimum enrollment of 12 subjects who have refused sorafenib in Part 1 (A and B). The total number of subjects with a specific viral status may be restricted in this cohort to ensure that all types of patients have an opportunity to enroll. For example, as enrollment proceeds if emerging data indicate that the majority of patients enrolling are all HBV infected, enrollment of this specific viral type of HCC may be paused to allow other types of subjects (uninfected and HCV infected) to enroll.

If during Part 1B of the study, ≥ 33% of subjects with a specific viral status type discontinue therapy for treatment-related toxicity, enrollment for that specific viral status type may be paused and study data will be reviewed to determine whether additional monitoring, alternate dose levels, or treatment schedules should be evaluated prior to further enrollment of subjects with that specific viral status type.

Part 2A: Randomized Arms Evaluating Durvalumab and Tremelimumab Combination Therapy, Durvalumab Monotherapy, and Tremelimumab Monotherapy. Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant of, or refused sorafenib-based therapy, will be stratified based on viral status (uninfected, HCV infected, or HBV infected) and PD-L1 expression (positive, negative, or non-evaluable).

- Subjects may not enroll into any arm of Part 2A until sufficient evidence, as specified in Section 4.8.7 (in Part 1A and Part 1B), is observed.
- Subjects will be randomized 1:1:1 within each stratum to 1 of the 3 treatment arms with approximately 36 subjects (approximately 12 subjects/viral status type) per treatment arm:
  - Arm A: durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met
  - Arm B: durvalumab 20mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met
  - Arm C: Tremelimumab 10 mg/kg monotherapy Q4W for 7 doses followed by every 12 weeks (Q12W) until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

If during Part 2A of the study, ≥ 33% of subjects with a specific viral status type within a given arm discontinue therapy for treatment-related toxicity, enrollment for that specific viral status type may be paused and study data will be reviewed to determine whether additional monitoring, alternate dose levels, or treatment schedules should be evaluated prior to further enrollment of subjects with that specific viral status type. Enrollment into any arm of Part 2A may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial to a given arm.

All subjects in Part 1A, Part 1B, and Part 2A will be evaluated for efficacy as specified in the protocol, and their disease status primarily analyzed according to RECIST v1.1. All subjects will be followed for survival until the end of study as defined in section 6.3. For biomarker analysis, subjects will be required to have a fresh tumor tissue biopsy at screening, an optional post-dose biopsy, and an optional biopsy at disease progression. Collection of noncancerous liver tissue at screening should also be attempted if it can be done safely (as judged by the investigator) during the same procedure in which the fresh tumor tissue biopsy is obtained. Evaluation of PD-L1 expression status will be done in real-time while the study is ongoing.

Part 2B: Safety Run-in for Additional Treatment Regimen of Durvalumab and Tremelimumab Combination Therapy. Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant to, or have refused sorafenib-based therapy will be enrolled in Part 2B.

Approximately 6 to 12 subjects will be enrolled into Arm D evaluating a single higher dose of tremelimumab in combination with durvalumab:

- Arm D: durvalumab 1500 mg and tremelimumab 300 mg combination therapy for 1 dose followed by durvalumab 1500 mg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

A safety evaluation will be performed once 6 safety evaluable subjects have completed 4 weeks of follow-up. A safety evaluable subject is defined as a subject who has received at least 1 dose of study drug and completed at least 4 weeks of follow-up or discontinued treatment prior to the completion of 4 weeks of follow-up due to an adverse event.

Enrollment into Part 2B may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial.

For biomarker analysis, all subjects in Part 2B will be required to have a newly acquired (fresh or acquired within 3 months, preferred) or archival (< 3 years) tissue sample at screening, an optional post-dose biopsy, and an optional biopsy at disease progression.

Part 3: **Randomized Arms Evaluating Durvalumab and Tremelimumab Combination Therapy, Durvalumab Monotherapy, and Tremelimumab Monotherapy.** Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant to, or have refused sorafenib or another approved VEGFR TKI-based therapy will be stratified based on viral status (uninfected, HCV infected, or HBV infected) and sorafenib/VEGFR TKI treatment (refusers or all others).

- Subjects may not enroll into any arm of Part 3 until enrollment in Part 2A and Part 2B has been completed and the safety evaluation of the first 6 subjects in Part 2B has been completed.
- Subjects will be randomized at a ratio of 2:1:2 into 1 of up to 3 treatment arms with approximately 64 subjects in each of the durvalumab monotherapy or combination treatment arm (B and D) and approximately 32 subjects in the tremelimumab monotherapy treatment arm (Arm C). No prerequisite number of subjects for viral status is set for any arms in Part 3:
  - Arm A (recruitment closed following protocol amendment 5): durvalumab 1500 mg and tremelimumab 75 mg combination therapy Q4W for 4 doses followed by durvalumab 1500 mg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. Following protocol amendment 5, enrollment into Arm A of Part 3 will close. Patients randomized to this arm before protocol amendment 5 can continue on assigned study treatment (provided the investigator and patient think it is in the best interests of the patient) until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. If a patient has not completed or started all 4 doses of tremelimumab, the patient may either continue to complete the full schedule or continue with durvalumab monotherapy only.
  - Arm B: durvalumab 1500 mg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met
  - Arm C: Tremelimumab 750 mg monotherapy Q4W for 7 doses followed by Q12W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met
  - Arm D: durvalumab 1500 mg and tremelimumab 300 mg combination therapy for 1 dose followed by durvalumab 1500 mg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

All subjects in Part 3 will be evaluated for safety and efficacy as specified in the protocol, and their disease status will be primarily analyzed according to RECIST v1.1. An interim analysis will occur after approximately 10 subjects per treatment arm in Part 3 have completed 4 weeks of follow-up as described in Section 4.8.7. All subjects will be followed for survival until the end of study.

For biomarker analysis, subjects will be required to have a newly acquired (fresh or acquired within 3 months, preferred) or archival (≤ 3 years) tissue sample at screening, an optional post-dose biopsy, and an optional biopsy at disease progression.

Enrollment into any arm of Part 3 may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial in a given arm.

Part 4: **Single Arm Evaluating Durvalumab with Bevacizumab in Combination.** Subjects with advanced HCC who have not received any prior systemic therapy can be enrolled into Part 4. Approximately 100 subjects will be enrolled into a single arm in Part 4 to evaluate the safety and efficacy of durvalumab in combination with bevacizumab:

- durvalumab 15 mg/kg (1120 mg) and bevacizumab 15 mg/kg combination therapy Q3W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

An interim analysis will occur after approximately 100 subjects in Part 4 have had the opportunity for 18 weeks of follow-up. Another interim analysis will occur after approximately 100 subjects in Part 4 have had the opportunity for 36 weeks of follow-up.

All subjects will be followed for survival until the end of study as per section 6.3.

TARGET SUBJECT POPULATION

Subjects will be male or female, ≥ 18 years of age (all countries except Japan) or ≥ 20 years of age (Japan only), with a diagnosis of advanced HCC confirmed pathologically or by noninvasive imaging methods and, have preserved liver function (Child-Pugh Score class A).

Subjects in Part 1 to Part 3 must be immunotherapy-naive and have either progressed on, are intolerant to, or have refused treatment with sorafenib/other VEGFR TKI. Subjects in Part 4 must not have received any prior systemic therapy for HCC.

STATISTICAL METHODS

Sample Size and Power Calculations

The sample sizes for Part 1A were determined empirically and are consistent with those used in clinical studies to evaluate the safety of a proposed administered dose in a new patient population. There is a 47% to 91% probability of observing an AE from 6 subjects if the true incidence rate is 10% to 33%.

For Part 1B, approximately 24 subjects will be enrolled. For the combined sample size of approximately 36 subjects for Part 1A and Part 1B, there is an 84% to 98% probability of observing at least one AE if the true incidence rate is 5% to 10%. The sample size of 36 subjects is chosen to obtain a preliminary assessment of antitumor activity. Table 1 provides the estimated ORR and the 95% confidence interval (CI) based on the exact probability method for a range of possible responses out of 36 subjects. The preliminary assessment of antitumor activity will help determine if there is sufficient evidence of clinical efficacy to warrant continued enrollment of subjects in Part 2.

Table 1. Estimated ORR and 95 Percent CI Out of 36 Subjects

Number (%) of Responses	2 (5.6)	4 (11.1)	6 (16.7)	8 (22.2)	10 (27.8)	12 (33.3)	14 (38.9)
Lower limit of 95% CI	0.7%	3.1%	6.4%	10.1%	14.2%	18.6%	23.1%
Upper limit of 95% CI	18.7%	26.1%	32.8%	39.2%	45.2%	50.9%	56.5%

Part 2A dose expansion analysis cohort will include the approximately 108 subjects who are enrolled as a part of the global recruitment. The subjects will be stratified in a 1:1:1 ratio based on viral status (HBV vs HCV vs uninfected) and PD-L1 status and assigned randomly within each stratum in a 1:1:1 ratio to 1 of the 3 treatment arms (Arms A, B, and C). With 12 subjects (per viral status cohort) treated with durvalumab or tremelimumab monotherapy respectively, there is a 72% to 86% probability of observing at least 1 AE from 12 subjects if the true incidence rate is 10% to 15%.

Part 2B is a safety cohort for the evaluation of durvalumab in combination with a higher single-dose of tremelimumab (Arm D) in which approximately 6 to 12 subjects will be enrolled.

Part 3 is a dose-expansion cohort in which approximately 200 subjects. Following protocol amendment 5, subjects in Part 3 will be assigned randomly at a ratio of 2:1:2 to 1 of 3 treatment arms (Arms B, C, or D). There is a 96% probability of observing at least 1 AE from 64 subjects if the true incidence rate is 5%.

To evaluate the efficacy in terms of ORR of durvalumab and tremelimumab administered as monotherapy and in combination to subjects with advanced HCC, data from Part 2 and Part 3 will be analyzed for each part separately and for both parts combined. If the true ORR is 20% in the combination therapy of

durvalumab 1500 mg and tremelimumab 75 mg Q4W for 4 doses (or durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses), a sample size of 100 subjects will provide at least 95% power to test the hypothesis that ORR is greater than 7% at a 0.05 significance level.

Part 4 is a single arm cohort to evaluate the safety and efficacy of durvalumab in combination with bevacizumab in which approximately 100 subjects will be enrolled. The primary efficacy endpoint is ORR assessed by BICR according to RECIST 1.1. If the true ORR is 32%, a sample size of 100 subjects will provide at least 83% power to test the hypothesis that ORR is greater than 18.8% (Kudo et al 2018) at a 0.05 (2-sided) significance level.

During the course of the study, subjects' tumor samples will be analyzed for PD-L1 expression and the prevalence of PD-L1-positive expression for this population will be evaluated.

Analysis Timing

An interim analysis will occur after approximately 10 subjects per treatment arm in Part 3 have completed 4 weeks of follow-up. The objective of this interim analysis is to assess futility and safety of the monotherapy arms (Arms B and C) and safety of the additional durvalumab and tremelimumab combination therapy arm (Arm D).

For Part 4, an interim analysis will occur after approximately 100 subjects have had the opportunity for 18 weeks of follow-up. Another interim analysis will occur after approximately 100 subjects in Part 4 have had the opportunity for 36 weeks of follow-up. The main objective of this interim analysis is to assess the safety and efficacy of durvalumab in combination with bevacizumab. The primary efficacy endpoint is ORR assessed by BICR according to RECIST 1.1.
Additional interim analyses with the same aims may be performed to support the ongoing PIII development for Parts 1-3. No formal adjustments will be made to the significance level used for testing.

The final analysis for this study, which will include all study endpoints, will be performed 12 months after the first dose to the last patient in the study.

Post final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive study durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab toxicity management guidelines.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab (in Parts 1-3) may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits assessment per its protocol. Any patient that would be proposed to move to such study would be given a new Informed Consent.

Efficacy

Efficacy data will be analyzed on the Response Evaluable Population, which will include all treated subjects who have a baseline tumor assessment and measurable disease at baseline. Summaries and analyses will be performed for each part separately and for Part 2 and Part 3 combined. Efficacy data will be presented by treatment arm.

The efficacy endpoints of ORR and DCR will be estimated based on their 2-sided 95% CIs using an exact probability method. DCR at 24 weeks will be estimated along with its 2-sided 95% exact CI.

Time-to-event endpoints, including TTR, DoR, TTP, PFS, and OS, will be analyzed using the Kaplan-Meier method. The median of each time-to-event endpoint and its 95% CI will be estimated based on the Kaplan-Meier curves. Only subjects with an objective response (best overall response of complete or partial response) will be included in the analysis of DoR. The landmark 6-month PFS rate, 6-month TTP, and 1-year OS rate will be estimated based on the Kaplan-Meier curves along with their 95% CIs. Primary analysis of all tumor assessment-related endpoints will be based on BICR assessments according to RECIST v1.1. Sensitivity analysis of these endpoints will be performed using investigator assessments according to RECIST v1.1.

Tumor samples (archival and/or from fresh biopsies) will be analyzed to determine the expression level of selected immune-related pathways (eg, PD-L1 protein expression as determined by immunohistochemistry) that may predict increased frequency of response or longer disease stabilization. CCI [redacted]

Safety

Safety summaries will be performed for each part separately and for Part 2 and Part 3 combined. Safety data will be presented by treatment arm.

Safety data will include AEs, SAEs, discontinuation of investigational product due to toxicity, and changes from baseline in laboratory parameters (including liver and viral labs), ECGs, and vital signs. These data will be summarized by treatment arm for each viral status cohort (HBV vs HCV vs uninfected) in the As-treated Population.

The number and percentage of subjects reporting treatment-emergent AEs will be summarized overall and by the worst National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 grade, system organ class, and preferred term. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs and treatment-emergent AE/SAEs considered related to investigational product(s) will be summarized. Laboratory abnormalities will be graded according to the NCI CTCAE v4.03, if applicable. Frequencies of maximum observed grade will be presented for each laboratory parameter as well as the rates of subjects with Grade 3-4 toxicities. A shift table, presenting the 2-way frequency tabulation for baseline and post-baseline grade at scheduled time of evaluation as well as the maximum post-baseline grade, will be provided for clinical laboratory tests.

Other Analyses

CCI [redacted]

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
CCI	
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
CCI	
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
BICR	Blinded Independent Central Review
BP	blood pressure
CD	cluster of differentiation
CI	confidence interval
C_{max}	Maximum observed plasma drug concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
D5W	5% dextrose in water
DC	disease control
DCR	disease control rate
DCR-12w	disease control rate at 12 weeks
DEHP	bis (2-ethylhexyl) phthalate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FAAN	Food Allergy and Anaphylaxis Network
Fc	fragment crystallizable
FDG	^{18}F-Fluoro-deoxyglucose
FDG-PET	^{18}F-Fluoro-deoxyglucose positron emission tomography
GCP	Good Clinical Practice
HBc	hepatitis B core
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

Abbreviation or Specialized Term	Definition
HCV	hepatitis C virus
HDV	hepatitis D virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irCR	immune-related complete response
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
IXRS	interactive response system
mAb	monoclonal antibody
CCI [redacted]	
[redacted]	
CCI [redacted]	
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCA	non-compartmental analysis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Diseases
NK	natural killer
NSCLC	non-small-cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
CCI [redacted]	
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
CCI [redacted]	
PR	partial response
PT	prothrombin

Abbreviation or Specialized Term	Definition
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QTcB	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
TIL	tumor-infiltrating lymphocyte
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
US/USA	United States
w/v	weight per volume

1 INTRODUCTION

1.1 Disease Background

1.1.1 Cancer and Immune Function

The importance of the immune system in cancer development and progression has been recognized during the past decade (Hanahan and Weinberg, 2000). Failure of immune surveillance of preneoplastic lesions and micrometastases is a key step in cancer development. Chronically immunosuppressed individuals show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immune-competent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggest that this may be an oversimplification. Some sporadic tumors are highly immunogenic, but actively suppress the local immune environment through production of immunosuppressive cytokines (Shields et al, 2010). As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity.

The complexity and redundancy of the immune system offers multiple targets that may be manipulated to maximize the body's inherent immune response to a tumor. Immune response may be augmented by directly stimulating effector cells, indirectly stimulating effectors by augmenting antigen presentation activity or costimulation, or by suppressing immunosuppressive factors, cells, or messages (Monti et al, 2005).

1.1.2 Immune-checkpoint Inhibition

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers (Gooden et al, 2011). Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through expression of inhibitory molecules. Engagement of TIL cell-surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression (Baitsch et al, 2012; Crespo et al 2013). Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types (Wolchok et al, 2009; Hodi et al, 2010; Robert et al, 2011; Brahmer et al, 2010; Topalian et al, 2012). Specifically, blockade of immune-checkpoint inhibitors such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1) have shown clinical activity not only in conventionally immune-responsive tumors such as melanoma and renal cell carcinoma but also in non-small-cell lung cancer (NSCLC; Brahmer et al, 2010; Brahmer et al, 2012; Topalian et al, 2012; Gordon et al, 2013), prostate cancer (Harzstark and Small, 2010;

Slovin et al, 2013), pancreatic cancer (Royal et al, 2010), mesothelioma (Calabrò et al, 2013), and other solid tumors (Brahmer et al, 2010; Brahmer et al, 2012; Gordon et al, 2013).

1.2 Durvalumab and Tremelimumab and VEGF Inhibitors Background

Durvalumab and tremelimumab are briefly described below. Refer to the current Investigator's Brochures (IBs) for details. Background information on bevacizumab is provided in local prescribing information.

1.2.1 Durvalumab Background

Durvalumab is a human immunoglobulin G (IgG)1 kappa mAb directed against human PD-L1. Durvalumab is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and cluster of differentiation (CD)80. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC; Oganesyan et al, 2008).

1.2.2 Tremelimumab Background

Tremelimumab (formerly CP-675,206) is a human IgG2 mAb being investigated as a cancer immunotherapeutic agent. Tremelimumab is expressed in NS0 (murine myeloma) cells and has an overall molecular weight of approximately 149 kDa. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins. Tremelimumab blocks the inhibitory effect of CTLA-4, and therefore enhances T-cell activation. Tremelimumab shows minimal specific binding to Fc receptors, does not induce natural killer (NK) ADCC activity, and does not deliver inhibitory signals following plate-bound aggregation.

1.2.3 VEGF Inhibitors Background

Vascular Endothelial Growth Factor (VEGF) is an important regulator of tumor angiogenesis and promotes the proliferation, survival, and migration of endothelial cells and induces microvascular permeability (Ferrara 2002). VEGF has been shown to play a role in the development and spread of HCC (Kaseb et al 2009). Additional evidence suggests that the combination of PD-L1 inhibition with vascular endothelial growth factor (VEGF) inhibition may result in synergistic activity and improved clinical benefit (Barsoum et al 2014, Voron et al 2015, Yasuda et al 2013). Preliminary data from an ongoing Phase Ib study testing atezolizumab (a PD-L1 inhibitor) and bevacizumab therapy as first-line treatment in patients

with advanced HCC showed promising clinical activity, with an ORR of 65% (Stein et al 2018). This data indicates further evaluation of durvalumab therapy in combination with VEGF inhibitor therapy in patients with advanced HCC is warranted.

There are multiple approved therapies that target VEGF. Two of those drugs include sorafenib and regorafenib, which are oral tyrosine kinase inhibitors that target VEGF among other targets. Both of these drugs have shown clinical benefit in advanced HCC, and both drugs are Food and Drug Administration (FDA) approved for the treatment of metastatic HCC. Bevacizumab, a mAb targeting VEGF, is approved by the FDA for the treatment of several types of cancer, including colorectal cancer, non-small cell lung cancer, glioblastoma, renal cell carcinoma, cervical cancer, ovarian cancer, fallopian tube cancer, and peritoneal cancer.

Bevacizumab has immunomodulatory effects (eg, increased dendritic cell maturation, enhanced T cell infiltration, and reduced myeloid-derived suppressor cells and Tregs into the tumor) that may enhance the efficacy of durvalumab. This may lead to more significant clinical benefits in the investigation of anti-PD-L1 in combination with anti-VEGF (Stein et al 2018). Other studies have a similar rationale for this combination (Campesato and Merghoub et al 2017, Hato et al 2014, Khan and Kerbel 2018).

1.3 Summary of Nonclinical Experience

For nonclinical information on durvalumab and tremelimumab, refer to the current IBs.

1.4 Summary of Clinical Experience

Clinical experience with durvalumab and tremelimumab is briefly described below. Refer to the current IBs for the most recent details. Background information on bevacizumab is provided in local prescribing information.

1.4.1 Durvalumab Clinical Experience

As of 14 Jul 2014, more than 500 subjects have been enrolled and treated with durvalumab in 10 ongoing clinical studies: 5 employing durvalumab as monotherapy and 5 as combination therapy (Table 1.4.1-1). No studies have yet been completed. The majority of the clinical data are from Study CD-ON-durvalumab-1108.

Update: To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Refer to the

current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

Table 1.4.1-1 Overview of Ongoing Clinical Studies of Durvalumab in Which Subjects Have Been Treated

Study Number	Phase	Study Population	Treatment Regimen
Monotherapy Studies			
CD-ON- durvalumab -1108	1/2	Advanced solid tumors including HCC	durvalumab Q2W or Q3W
D4190C00002	1	Advanced solid tumors	durvalumab Q2W or Q3W
D4190C00007	1	MDS	durvalumab Q2W
D4190C00003/ ATLANTIC	2	NSCLC	durvalumab Q2W
D4190C00001/PACIFIC	3	NSCLC	durvalumab Q2W or placebo Q2W
Combination Therapy Studies			
CD-ON- durvalumab -1161	1	Melanoma	durvalumab Q2W + trametinib BID ± dabrafenib QD
D4190C00006	1b	NSCLC	durvalumab Q2W or Q4W + tremelimumab Q4W
D791PC00001	1	NSCLC	durvalumab Q2W + gefitinib daily
D6020C00001	1	Advanced malignancies	durvalumab Q2W + MEDI0680 (AMP-514) Q2W or Q4W
LUD2013-003[a]	1	Advanced solid tumors	durvalumab Q2W + tremelimumab Q4W

BID = twice daily; HCC = hepatocellular carcinoma; MDS = myelodysplastic syndrome; NSCLC = non-small-cell lung cancer; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; QD = once daily.

[a] All studies in this table are sponsored by AstraZeneca/MedImmune, except LUD2013-003.

Data from Study CD-ON-durvalumab-1108 (durvalumab monotherapy) are presented below. Refer to Section 1.4.3 for data from Study D4190C00006 (durvalumab in combination with tremelimumab) and to the durvalumab IB for the most recent detailed description of all studies.

Study CD-ON-durvalumab-1108

Study CD-ON-durvalumab-1108 is a Phase 1, first-time-in-human, multicenter, open-label, dose-escalation, and dose-expansion study to determine the maximum tolerated dose (MTD) or optimal biologic dose, safety, pharmacokinetics (PK), immunogenicity, and antitumor activity of durvalumab in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. As of 21Aug2014, 408 subjects across 8 tumor types (NSCLC, squamous cell carcinoma of the head and neck, pancreatic adenocarcinoma, uveal melanoma, cutaneous melanoma, gastroesophageal cancer,

triple-negative breast cancer, and hepatocellular carcinoma [HCC (n = 21); hepatitis B virus (HBV) or hepatitis C virus (HCV) positive]) have received durvalumab 10 mg/kg every 2 weeks (Q2W) for a median of 6 doses (Segal et al, 2014).

Overall, durvalumab 10 mg/kg Q2W was well tolerated in this subject population (Segal et al, 2014). Adverse events (AEs), regardless of severity or causality, were reported in 372 of 408 subjects (91%). A total of 170 subjects (42%) reported ≥ Grade 3 AEs; these events were considered to be treatment related in 30 subjects (7%). The most common treatment-related AE, regardless of severity, was fatigue (16%); ≥ Grade 3 fatigue occurred in 2% of subjects. Other select treatment-related AEs of interest (all grades) were vomiting, diarrhea, rash (6% each); pruritus dyspnea (4% each); pyrexia, hypothyroidism, increased alanine transaminase (ALT), increased aspartate transaminase (AST; 3% each); abdominal pain, hyperthyroidism (2% each), and hyperglycemia, pneumonitis, peripheral neuropathy (1% each). No treatment-related colitis of any grade, and no ≥ Grade 3 pneumonitis were reported. Five subjects (1%) reported AEs that resulted in discontinuation of investigational product. No treatment-related AEs resulted in death. Overall, AEs were manageable and generally reversible with treatment interruption, discontinuation, and/or steroids. The safety profile of durvalumab 10 mg/kg Q2W was similar across all tumor types.

Partial efficacy data are available as of 21Aug2014 (Segal et al, 2014). In this study, 352 of 408 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response analysis, which included subjects who had at least 12 weeks of follow-up as of the data cutoff date, measurable disease at baseline, and at least 1 follow-up scan (included discontinuations due to progressive disease [PD] or death prior to first follow-up scan). Early (5 weeks) and durable (56+ weeks) activity were observed across multiple tumor types. Disease control rate (DCR) at 12 weeks (DCR-12w) was 33% (115/352 subjects) and objective response rate (ORR) was 10% (36/352 subjects) across the 8 tumor types. Greater DCR-12w (47% vs 28%) and ORR (22% vs 5%) were observed in subjects with PD-L1-positive versus PD-L1-negative tumors. Responses are ongoing in 92% of subjects (33/36) with an objective response (OR).

A total of 21 advanced stage HCC subjects, including 4 HBV+ and 5 HCV+ subjects, received durvalumab monotherapy (10 mg/kg Q2W; Segal et al, 2014). As of the 21Aug2014 data cutoff, the safety profile of the HCC cohort appears similar to all other tumor type cohorts. Thirteen subjects (62%) experienced any treatment-related AE, 2 subjects (10%) experienced a Grade 3 or higher treatment-related AEs, and 1 subject (5%) experienced a treatment-related serious adverse event (SAE). There were no reported AEs leading to

discontinuation of investigational product or death. In addition, of the 19 evaluable subjects, 4 (21%) demonstrated prolonged stable disease (SD; ≥ 3 months) while there were no ORs.

As of 01May2014, PK data were available for 38 subjects in the dose-escalation (n = 26) and dose-expansion (n = 12) phases following dosing with durvalumab 0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks. durvalumab monotherapy exhibited nonlinear (dose-dependent) PK. The area under the concentration-time curve (AUC) from 0 to 14 days increased in a greater than dose-proportional manner over the dose range of 0.1 to 15 mg/kg and approached linearity at ≥ 3 mg/kg, suggesting that the nonlinear PK of durvalumab is likely due to saturable target-mediated clearance. Of the 220 subjects for whom antidrug antibody (ADA) data were available, 5 were detected ADA positive, with an impact on PK/pharmacodynamics reported in 1 subject.

1.4.2 Tremelimumab Clinical Experience

Refer to the current tremelimumab IB for the most recent detailed description of all studies.

As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cut-off date of 04Dec2014), 22 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 9 are ongoing. Tremelimumab has been administered as monotherapy to 973 subjects (not including 497 subjects who have been treated in the blinded Phase 2b study, D4880C00003 [DETERMINE]) participating in 10 of the 22 clinical studies, 2 of which are ongoing. In addition, 208 subjects with a variety of tumor types have received tremelimumab in combination with other anticancer agents in 12 of the 22 sponsored clinical studies, 7 of which are ongoing.

Update: To date tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

Across the clinical development program for tremelimumab a pattern of efficacy has emerged, also observed for the related anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumor types for this class of agents. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting months to years even in subjects with aggressive tumors, such as, refractory metastatic melanoma. Some subjects may have had progression of their disease early during treatment, with delayed tumor response or disease stabilization.

Tremelimumab has been tested in a Phase 3 study for advanced melanoma. Although the study failed to demonstrate improved overall survival (OS; primary endpoint) following a prespecified interim futility analysis, the final analysis showed a median OS of 12.6 months in the tremelimumab arm and 10.7 months in the dacarbazine/temozolomide arm (hazard ratio = 1.1416, p = 0.1272). The ongoing Phase 2b study in recurrent pleural or peritoneal malignant mesothelioma is testing an alternative dosing schedule of tremelimumab with a dose of 10 mg/kg every 4 weeks (Q4W) to maximize exposure to tremelimumab while managing safety according to the established anti-CTLA-4 AE management guidelines. The 10 mg/kg Q4W regimen is also being tested in an ongoing Phase 2 investigator-sponsored study in malignant mesothelioma (NCT01655888).

In clinical subjects, tremelimumab exhibits linear (dose-proportional) PK following intravenous (IV) infusion. The estimate of clearance, volume of distribution at steady state, and terminal-phase half-life is 0.132 mL/hour/kg, 81.2 mL/kg, and 22.1 days, respectively. These values are consistent with those of natural IgG2.

The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that seems to be confined to subjects with melanoma). As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), AEs (all grades, regardless of causality) reported in > 10% of subjects in the completed and rollover tremelimumab monotherapy studies (N = 973, integrated data) were diarrhea (45.3%), fatigue (37.5%), nausea (32.5%), rash (28.8%), pruritus (27.3%), decreased appetite (22.8%), vomiting (22.5%), pyrexia (15.3%), cough (15.0%), constipation (14.4%), abdominal pain (13.9%), headache (13.8%), dyspnea (12.4%), and decreased weight (10.2%). Based on integrated data from completed studies of tremelimumab in combination with other agents (N = 116), AEs (all grades, regardless of causality) reported in > 15% of subjects were diarrhea (54.3%); nausea (40.5%); fatigue (38.8%); rash (35.3%); pruritus, decreased appetite (30.2% each); vomiting (27.6%); pyrexia (26.7%); influenza like illness (20.7%); arthralgia (19.8%); constipation (19.0%); thrombocytopenia, injection site reaction (18.1% each); and increased aspartate aminotransferase (15.5%). Most of these events occurred at a higher rate with tremelimumab plus sunitinib than with other combinations. The events of diarrhea, rash, and pruritus are considered as identified risks. Acute renal failure was reported in subjects who received the combination of tremelimumab and sunitinib; however, acute renal failure has not been an expected AE for single-agent tremelimumab. The incidence and/or severity of many of the AEs observed following administration of

tremelimumab can be reduced by adherence to current immune-related toxicity management guidelines.

Tremelimumab at a dose of 15 mg/kg IV every 90 days has been administered to 20 subjects with HCV+ HCC (43% Child-Pugh class B; Sangro et al, 2013). Overall, tremelimumab was well tolerated; no subjects received systemic steroids and there were no treatment-related deaths. Transient increases in transaminases were observed after the first dose in more than half of the subjects and 45% of the cases had increases to Grade 3 or higher without simultaneous decline in liver function. Seventeen subjects were evaluable for response with confirmed partial responses (PRs) observed in 3 subjects (17.6%).

In another Phase I/II study, 32 advanced HCC (Child-Pugh class A/B7) patients were treated with tremelimumab at 2 dose levels (3.5 and 10 mg/kg IV Q4W) in combination with subtotal ablation (RFA/TACE) during Week 6 of treatment (Duffy et al 2016). Safety evaluation showed no clear trend in AEs across the cohorts utilizing different doses of tremelimumab. No DLT was encountered on the study. The most common Grade 3 or Grade 4 toxicities were AST elevation (21%), ALT elevation (9%), and hyperbilirubinemia (9%). There were no episodes of Grade 3 or Grade 4 diarrhea, colitis, or pneumonitis. Of 19 patients evaluable for response outside of the areas treated directly with TACE/RFA, 5 (26.3%) achieved confirmed partial response (PR).

1.4.3 Clinical Experience with Durvalumab and Tremelimumab Combination

Refer to the current durvalumab and tremelimumab IBs for the most recent detailed descriptions of all studies with durvalumab and tremelimumab combination therapy.

- Update: To date more than 3000 patients have received the combination using a number of doses and dosing schedules.

Study D4190C00006 is a multicenter, open-label, dose-escalation, and dose-expansion study of durvalumab in combination with tremelimumab to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of durvalumab in combination with tremelimumab in adult subjects with advanced NSCLC.

The safety, efficacy and PK/pharmacodynamics of the combination were explored using the modified zone-based design (Huang et al, 2007). The zone based design allowed for the comparison of multiple combinations of doses at the same time.

The schedules used in this study were:

- For durvalumab:
  - Q4W dosing schedule - durvalumab was administered Q4W for 13 doses.
  - Q2W dosing schedule - durvalumab was administered Q2W for 26 doses.
- For tremelimumab combined in both schedules of durvalumab
  - Tremelimumab was administered Q4W for 6 doses and every 12 weeks (Q12W) for 3 doses; Dose 7 is given at 4 weeks from Dose 6 and Dose 8 is given at 12 weeks from Dose 7.

As of 27Jan2015, a total of 74 subjects with advanced NSCLC have been treated in Study D4190C00006 (Table 1.4.3-1) in 10 combination dose cohorts. This included subjects with tumors that were both PD-L1 positive and negative. Subjects have received between 1 and 9 doses of tremelimumab and between 1 and 13 doses of durvalumab. The greater number of durvalumab doses is due to the inclusion of both schedules of durvalumab Q4W dosing schedule and Q2W. Fifty-eight of these subjects were in the durvalumab Q4W dosing schedule and 16 subjects were in the Q2W dosing schedule.

Table 1.4.3-1 Number of Subjects Treated by Cohort (Study D4190C00006)

Cohort	Durvalumab Dose (mg/kg)	Tremelimumab Dose (mg/kg)	Subjects Treated
Dosing Schedule	Q4W (every 4 weeks)	Q4W	
1a	3	1	3
2a	10	1	3
3a	15	1	12
3b	10	3	3
4	20	1	11
4a	15	3	11
5	15	10	9
5a	20	3	6
Q4W Total			58
Dosing Schedule	Q2W (every 2 weeks)	Q4W	
8	10	1	6
9	10	3	10
Q2W Total			16
Overall Total			74

1.4.3.1 Clinical Experience with Durvalumab and Tremelimumab Combination Therapy Regimens (Study D4190C00006)

Safety

Refer to the current durvalumab and tremelimumab IBs for the most recent detailed description of the safety for all studies with durvalumab and tremelimumab combination therapy.

Overall, 62 (83.8%) of the 74 subjects reported an AE regardless of causality. The most frequently (10 or more subjects) reported AEs were fatigue (37.8%; 28 subjects); diarrhea (32.4%; 24 subjects); amylase increased and pruritus (16.2%; 12 subjects); decreased appetite, dyspnea, nausea, and rash (14.9%; 11 subjects each), and headache and pyrexia (13.5%; 10 subjects).

Twenty of the 62 subjects who experienced AEs regardless of causality had events that were Grade 1 or 2 in severity. Forty-two of the 62 subjects reported ≥ Grade 3 events. The most frequently reported ≥ Grade 3 events (in 3 or more subjects) were diarrhea (7 subjects); colitis (6 subjects); increased lipase (4 subjects); and anemia, increased ALT, increased AST, dehydration, and pneumonitis (3 subjects each).

Fifty of the 74 subjects reported a treatment-related AE. The most frequently reported treatment-related AEs were fatigue (24.3%; 18 subjects); diarrhea (21.6%; 16 subjects); increased ALT (13.5%; 10 subjects); pruritus (12.2%; 9 subjects); and rash (10.8%; 8 subjects). Twenty-four of the 50 subjects who experienced treatment-related AEs reported Grade 1 or 2 events only. Twenty-six of the 50 subjects reported ≥ Grade 3 events. The most frequently reported treatment-related ≥ Grade 3 events (in 3 or more subjects) were colitis and diarrhea (6 subjects each), increased lipase (4 subjects), and increased ALT, increased AST, and pneumonitis (3 subjects).

Q4W Cohorts

For the Q4W cohorts, 43 (74.1%) of 58 subjects reported treatment-related AEs (Table 1.4.3-2). The most frequently reported (5 or more subjects) treatment-related AEs were fatigue (16 subjects), diarrhea (14 subjects), increased amylase (10 subjects), increased ALT, increased lipase, pruritus, and rash (7 subjects each), colitis (6 subjects), and increased AST and decreased appetite (5 subjects each).

Table 1.4.3-2 Number of Subjects in the Q4W Cohorts with Treatment-related Adverse Events (All Grades), As-treated Population, Study D4190C00006

System Organ Class/Preferred Term (MedDRA V17.1)	M3/T1 (N = 3) n (%)	M10/T1 (N = 3) n (%)	M10/T3 (N = 3) n (%)	M15/T1 (N = 12) n (%)	M15/T3 (N = 11) n (%)	M15/T10 (N = 9) n (%)	M20/T1 (N = 11) n (%)	M20/T3 (N = 6) n (%)	Total (N = 58) n (%)
Total subjects reporting 1 or more events	1 (33.3)	3 (100)	3 (100)	7 (58.3)	9 (81.8)	8 (88.9)	7 (63.6)	5 (83.3)	43 (74.1)
Endocrine Disorders	0	2 (66.7)	1 (33.3)	0	1 (9.1)	0	0	1 (16.7)	5 (8.6)
Hypothyroidism	0	1 (33.3)	1 (33.3)	0	1 (9.1)	0	0	0	3 (5.2)
Gastrointestinal Disorders	0	2 (66.7)	2 (66.7)	4 (33.3)	5 (45.5)	4 (44.4)	2 (18.2)	3 (50.0)	22 (37.9)
Abdominal pain	0	0	1 (33.3)	1 (8.3)	2 (18.2)	0	0	0	4 (6.9)
Colitis	0	0	1 (33.3)	1 (8.3)	1 (9.1)	1 (11.1)	1 (9.1)	1 (16.7)	6 (10.3)
Diarrhoea	0	0	2 (66.7)	3 (25.0)	4 (36.4)	2 (22.2)	0	3 (50.0)	14 (24.1)
Dyspepsia	0	1 (33.3)	0	0	0	0	1 (9.1)	1 (16.7)	3 (5.2)
Nausea	0	1 (33.3)	0	2 (16.7)	0	0	0	1 (16.7)	4 (6.9)
Vomiting	0	1 (33.3)	0	1 (8.3)	0	0	0	2 (33.3)	4 (6.9)
General Disorders and Administration Site Conditions	0	1 (33.3)	0	5 (41.7)	4 (36.4)	4 (44.4)	1 (9.1)	3 (50.0)	18 (31.0)
Fatigue	0	1 (33.3)	0	5 (41.7)	4 (36.4)	4 (44.4)	0	2 (33.3)	16 (27.6)
Pyrexia	0	0	0	2 (16.7)	0	0	1 (9.1)	0	3 (5.2)
Investigations	1 (33.3)	2 (66.7)	1 (33.3)	4 (33.3)	0	4 (44.4)	3 (27.3)	4 (66.7)	19 (32.8)
Alanine aminotransferase increased	0	1 (33.3)	1 (33.3)	2 (16.7)	0	0	1 (9.1)	2 (33.3)	7 (12.1)
Amylase increased	1 (33.3)	0	1 (33.3)	3 (25.0)	0	2 (22.2)	1 (9.1)	2 (33.3)	10 (17.2)
Aspartate aminotransferase increased	0	1 (33.3)	0	1 (8.3)	0	0	1 (9.1)	2 (33.3)	5 (8.6)
Blood thyroid stimulating hormone decreased	0	0	0	0	0	2 (22.2)	0	2 (33.3)	4 (6.9)
Blood thyroid stimulating hormone increased	0	0	0	0	0	1 (11.1)	1 (9.1)	1 (16.7)	3 (5.2)

Table 1.4.3-2 Number of Subjects in the Q4W Cohorts with Treatment-related Adverse Events (All Grades), As-treated Population, Study D4190C00006

System Organ Class/Preferred Term (MedDRA V17.1)	M3/T1 (N = 3) n (%)	M10/T1 (N = 3) n (%)	M10/T3 (N = 3) n (%)	M15/T1 (N = 12) n (%)	M15/T3 (N = 11) n (%)	M15/T10 (N = 9) n (%)	M20/T1 (N = 11) n (%)	M20/T3 (N = 6) n (%)	Total (N = 58) n (%)
Gamma-glutamyltransferase increased	0	0	0	1 (8.3)	0	0	0	2 (33.3)	3 (5.2)
Lipase increased	0	0	0	3 (25.0)	0	1 (11.1)	1 (9.1)	2 (33.3)	7 (12.1)
Thyroxine free decreased	0	0	0	0	0	0	1 (9.1)	2 (33.3)	3 (5.2)
Metabolism and Nutrition Disorders	0	2 (66.7)	1 (33.3)	2 (16.7)	0	1 (11.1)	1 (9.1)	0	7 (12.1)
Decreased appetite	0	1 (33.3)	0	2 (16.7)	0	1 (11.1)	1 (9.1)	0	5 (8.6)
Musculoskeletal and Connective Tissue Disorders	0	2 (66.7)	1 (33.3)	4 (33.3)	3 (27.3)	1 (11.1)	0	1 (16.7)	12 (20.7)
Arthralgia	0	0	1 (33.3)	2 (16.7)	0	0	0	0	3 (5.2)
Myalgia	0	1 (33.3)	1 (33.3)	0	1 (9.1)	1 (11.1)	0	0	4 (6.9)
Respiratory, Thoracic and Mediastinal Disorders	0	0	0	0	2 (18.2)	2 (22.2)	1 (9.1)	0	5 (8.6)
Pneumonitis	0	0	0	0	2 (18.2)	2 (22.2)	0	0	4 (6.9)
Skin and Subcutaneous Tissue Disorders	0	1 (33.3)	2 (66.7)	1 (8.3)	5 (45.5)	5 (55.6)	1 (9.1)	2 (33.3)	17 (29.3)
Dry skin	0	0	0	0	0	2 (22.2)	0	1 (16.7)	3 (5.2)
Pruritus	0	0	1 (33.3)	0	2 (18.2)	2 (22.2)	1 (9.1)	1 (16.7)	7 (12.1)
Rash	0	0	1 (33.3)	1 (8.3)	3 (27.3)	1 (11.1)	1 (9.1)	0	7 (12.1)

MedDRA = Medical Dictionary for Regulatory Activities; M(x)/T(y) = durvalumab (x) mg/kg and tremelimumab (y) mg/kg; Q4W = every 4 weeks.

Q2W Cohorts

Seven (43.8%) of 16 subjects in the Q2W cohorts experienced treatment-related AEs (Table 1.4.3-3). Colitis, diarrhea, fatigue, and pruritus were each reported in 2 subjects. All other events were reported in a single subject only. For most AEs, the incidence was higher in the durvalumab 10 mg/kg and tremelimumab 3 mg/kg group than the durvalumab 10 mg/kg and tremelimumab 1 mg/kg group.

Table 1.4.3-3 Number of Subjects in the Q2W Cohorts with Treatment-related Adverse Events (All Grades), As-treated Population, Study D4190C00006

System Organ Class/Preferred Term (MedDRA V17.1)	M10/T1 (N = 6) n (%)	M10/T3 (N = 10) n (%)	Total (N = 16) n (%)
Total subjects reporting 1 or more events	1 (16.7)	6 (60.0)	7 (43.8)
Ear and Labyrinth Disorders	0	1 (10.0)	1 (6.3)
Tinnitus	0	1 (10.0)	1 (6.3)
Endocrine Disorders	0	1 (10.0)	1 (6.3)
Hyperthyroidism	0	1 (10.0)	1 (6.3)
Gastrointestinal Disorders	0	3 (30.0)	3 (18.8)
Colitis	0	2 (20.0)	2 (12.5)
Diarrhoea	0	2 (20.0)	2 (12.5)
General Disorders and Administration Site Conditions	1 (16.7)	1 (10.0)	2 (12.5)
Fatigue	1 (16.7)	1 (10.0)	2 (12.5)
Metabolism and Nutrition Disorders	0	1 (10.0)	1 (6.3)
Decreased appetite	0	1 (10.0)	1 (6.3)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (10.0)	1 (6.3)
Pneumonitis	0	1 (10.0)	1 (6.3)
Skin and Subcutaneous Tissue Disorders	1 (16.7)	3 (30.0)	4 (25.0)
Pruritus	1 (16.7)	1 (10.0)	2 (12.5)
Rash	0	1 (10.0)	1 (6.3)
Rash maculo-papular	0	1 (10.0)	1 (6.3)

MedDRA = Medical Dictionary for Regulatory Activities; M(x)/T(y) = durvalumab (x) mg/kg and tremelimumab (y) mg/kg; Q2W = every 2 weeks.

Safety Comparison of Durvalumab 15 mg/kg Q4W, 20 mg/kg Q4W, and 10 mg/kg Q2W Cohorts with Varying Doses of Tremelimumab

Both durvalumab and tremelimumab as monotherapy have a distinct safety profile in comparison to the combination of durvalumab and tremelimumab.

In regards to durvalumab monotherapy as of 21Aug2014, 408 subjects have received durvalumab 10 mg/kg Q2W. AEs (all grades, regardless of causality) were reported in 372 of 408 subjects (91%). A total of 170 subjects (42%) reported ≥ Grade 3 AEs; these events were considered to be treatment related in 30 subjects (7%). The most common treatment-related AE, regardless of severity, was fatigue (16%); ≥ Grade 3 fatigue occurred in 2% of subjects.

In regards to tremelimumab monotherapy as of the data cutoff date of 12Nov2014, AEs were considered to be treatment related in 770 of 973 subjects (79.1%). A total of 485 subjects (49.8%) reported treatment related ≥ Grade 3 AEs. The most frequent treatment-related AEs (in > 5% of subjects) were diarrhea (41.2%), rash (27.2%), pruritus (25.1%), fatigue (23.8%), nausea (21.9%), vomiting (13.5%), decreased appetite (11.3%), headache (7.2%), pyrexia (7.0%), abdominal pain (6.7%), and colitis (5.5%).

In the cohort of durvalumab 15 mg/kg Q4W in combination with varying doses of tremelimumab (1 mg/kg [n = 12], 3 mg/kg [n = 11], and 10 mg/kg [n = 9]), the percentage of subjects who reported at least 1 treatment-related AE or treatment-related AE resulting in discontinuation of investigational product was numerically lower when durvalumab 15 mg/kg Q4W was combined with tremelimumab 1 mg/kg versus higher tremelimumab doses (3 and 10 mg/kg; Table 1.4.3-4). Specifically, the durvalumab 15 mg/kg Q4W and tremelimumab 1 mg/kg cohort had a lower frequency of immune-mediated toxicities such as colitis and pneumonitis (Table 1.4.3-2).

Similarly, the percentage of subjects who reported treatment-related AEs, ≥ Grade 3 treatment-related events, or related AEs leading to discontinuation of investigational product was lower when durvalumab 20 mg/kg Q4W was combined with tremelimumab 1 mg/kg (n = 11) versus tremelimumab 3 mg/kg (n = 6)(Table 1.4.3-4). The clinical summary of the cohort treated with durvalumab 20 mg/kg Q4W and tremelimumab 3 mg/kg regimen is presented in Section 1.4.3.

Table 1.4.3-4 Rate Summary of All Adverse Events in the Q4W Cohorts, As-treated Population, Study D4190C00006

Adverse Event Outcome (MedDRA V17.1)	M3/T1 (N = 3) n (%)	M10/T1 (N = 3) n (%)	M10/T3 (N = 3) n (%)	M15/T1 (N = 12) n (%)	M15/T3 (N = 11) n (%)	M15/T10 (N = 9) n (%)	M20/T1 (N = 11) n (%)	M20/T3 (N = 6) n (%)	Total (N = 58) n (%)
1 or more event	3 (100)	3 (100)	3 (100)	12 (100)	11 (100)	9 (100)	7 (63.6)	6 (100)	54 (93.1)
1 or more Grade 3 event	0	2 (66.7)	3 (100)	9 (75.0)	5 (45.5)	7 (77.8)	3 (27.3)	6 (100)	35 (60.3)
1 or more Grade 4 event	0	1 (33.3)	1 (33.3)	1 (8.3)	0	0	1 (9.1)	1 (16.7)	5 (8.6)
1 or more serious event	1 (33.3)	2 (66.7)	2 (66.7)	7 (58.3)	7 (63.6)	7 (77.8)	2 (18.2)	6 (100)	34 (58.6)
1 or more event leading to discontinuation of study drug	1 (33.3)	1 (33.3)	2 (66.7)	2 (16.7)	5 (45.5)	3 (33.3)	0	5 (83.3)	19 (32.8)
Death	0	1 (33.3)	0	1 (8.3)	2 (18.2)	0	0	2 (33.3)	6 (10.3)
1 or more related event	1 (33.3)	3 (100)	3 (100)	7 (58.3)	9 (81.8)	8 (88.9)	7 (63.6)	5 (83.3)	43 (74.1)
1 or more ≥ Grade 3 related event	0	2 (66.7)	2 (66.7)	5 (41.7)	4 (36.4)	4 (44.4)	2 (18.2)	5 (83.3)	24 (41.4)
1 or more related serious event	0	1 (33.3)	2 (66.7)	3 (25.0)	5 (45.5)	4 (44.4)	2 (18.2)	5 (83.3)	22 (37.9)
1 or more related event leading to discontinuation of study drug	0	1 (33.3)	2 (66.7)	1 (8.3)	4 (36.4)	3 (33.3)	0	4 (66.7)	15 (25.9)
Death related to study drug	0	1 (33.3)	0	0	0	0	0	1 (16.7)	2 (3.4)

MedDRA = Medical Dictionary for Regulatory Activities; M(x)/T(y) = durvalumab (x) mg/kg and tremelimumab (y) mg/kg; Q4W = every 4 weeks.

The overall pattern and frequency of AEs noted in the durvalumab 10 mg/kg Q2W cohorts (Table 1.4.3-5) were similar to those seen in the Q4W cohorts. As noted above, a numerical increase in the percentage of subjects with previous mentioned types of AEs was observed in combination cohorts that included 3 mg/kg tremelimumab relative to 1 mg/kg tremelimumab (Table 1.4.3-3).

Table 1.4.3-5 Rate Summary of All Adverse Events in the Q2W Cohorts, As-treated Population, Study D4190C00006

Adverse Event Outcome (MedDRA V17.1)	M10/T1 (N = 6) n (%)	M10/T3 (N = 10) n (%)	Total (N = 16) n (%)
1 or more event	2 (33.3)	6 (60.0)	8 (50.0)
1 or more Grade 3 event	2 (33.3)	4 (40.0)	6 (37.5)
1 or more Grade 4 event	0	0	0
1 or more serious event	1 (16.7)	5 (50.0)	6 (37.5)
1 or more event leading to discontinuation of study drug	1 (16.7)	1 (10.0)	2 (12.5)
Death	1 (16.7)	1 (10.0)	2 (12.5)
1 or more related event	1 (16.7)	6 (60.0)	7 (43.8)
1 or more ≥ Grade 3 related event	0	2 (20.0)	2 (12.5)
1 or more related serious event	0	4 (40.0)	4 (25.0)
1 or more related event leading to discontinuation of study drug	0	1 (10.0)	1 (6.3)
Death related to study drug	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; M(x)/T(y) = durvalumab (x) mg/kg and tremelimumab (y) mg/kg; Q2W = every 2 weeks.

In summary, safety data in NSCLC patients from the 15 or 20 mg/kg durvalumab Q4W combination cohorts in Study D4190C0006 demonstrated a numerical increase in the frequency of treatment-related AEs and related AEs leading to discontinuation of investigational product with increasing doses of tremelimumab. In addition, the frequency of select immune-mediated toxicities was lower with 1 mg/kg tremelimumab. The overall safety profile for the durvalumab Q4W and Q2W cohorts appeared similar. The safety profile for 20 mg/kg durvalumab Q4W in combination with 1 mg/kg tremelimumab appeared comparable to the safety profile for 15 mg/kg durvalumab Q4W in combination with 1 mg/kg tremelimumab.

Summary of PK, Pharmacodynamic, and ADA Data

Refer to the current durvalumab and tremelimumab IBs for the most recent detailed descriptions of PK, pharmacodynamic, and ADA data in all studies with durvalumab and tremelimumab combination therapy.

PK (n = 55), ADA (n = 60), and soluble PD-L1 (sPD-L1; n = 69) data were collected from 10 cohorts following durvalumab Q4W or Q2W regimens. An approximately dose-proportional increase in PK exposure (maximum plasma concentration and area under the plasma drug concentration-time curve from time 0 to Day 28 post-dose) of both durvalumab and tremelimumab was observed over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W and 1 to 10 mg/kg tremelimumab Q4W.

Four of 60 subjects were ADA positive for anti- durvalumab antibodies post treatment. One of 53 subjects was ADA positive for anti-tremelimumab antibodies post treatment. No clear relationship between ADA and the dose of either durvalumab or tremelimumab was observed. No obvious association between ADA and safety or efficacy was observed.

Target engagement for durvalumab was assessed using suppression of free sPD-L1 in serum. Following treatment with the durvalumab and tremelimumab combination, complete sPD-L1 suppression (surrogate for PD-L1 targeting) was observed in almost all subjects over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. Two subjects (1 subject at 10 mg/kg durvalumab Q4W + 1 mg/kg tremelimumab Q4W and 1 subject at 15 mg/kg durvalumab Q4W + 1 mg/kg tremelimumab Q4W) showed partial sPD-L1 suppression at some visits followed by complete suppression after repeated dosing. One subject who received 15 mg/kg durvalumab Q4W + 10 mg/kg tremelimumab Q4W showed partial suppression on Day 29 and was ADA positive with an impact on PK. No clear dose-dependent changes in sPD-L1 were identified over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. There was evidence of augmented pharmacodynamic activity, most notably CD8 T cell proliferation,

relative to durvalumab monotherapy even with combination doses containing 1 mg/kg tremelimumab.

1.4.3.2 Clinical and PK Data for Combination Regimen of Durvalumab with Single Dose Schedule of Tremelimumab

The supporting data for this regimen are based on PK and pharmacodynamic data of doses of greater than 1 mg/kg from Study D4190C00006. As presented above, approximately dose-proportional increases in PK exposure and activation/proliferation markers were noted with increasing doses of tremelimumab (1, 3, and 10 mg/kg). Higher C_{max} of tremelimumab was related to a higher maximum pharmacodynamic effect in the NSCLC patient population.

Based on simulation of pharmacokinetic data, the C_{max} (78 µg/mL) post single dose administration of tremelimumab 4 mg/kg is approximately 4-fold higher than the predicted C_{max} (19 µg/mL) post the first dose of tremelimumab 1 mg/kg, and is 3-fold higher than the predicted C_{max} (25 µg/mL) post the fourth dose of tremelimumab 1 mg/kg in a Q4W × 4 doses setting. Taken together, the above evidence suggests that the combination dose of durvalumab with a single dose of tremelimumab 4 mg/kg may provide a higher pharmacodynamic effect when compared with durvalumab with 4 doses of tremelimumab 1 mg/kg.

1.4.4 Clinical Experience with Other Inhibitors of the PD-1/PD-L1 Pathway in Subjects with HCC

Nivolumab is a fully human anti-PD1 mAb that has been administered to 47 subjects with advanced HCC (n = 24 uninfected; n = 12 HCV positive; n = 11 HBV positive; El-Khoueiry et al, 2015) not amenable to curative resection at doses ranging from 0.1 to 10 mg/kg Q2W (monotherapy dose for melanoma and NSCLC is 3 mg/kg; OPDIVO, 2015). The patient population enrolled in the nivolumab study is similar to the predicted patient population for this study with 68% of subjects having a history of prior sorafenib exposure. The most common (frequency ≥ 15%) treatment-related AEs were increased AST, increased lipase, rash, increased ALT, and increased amylase, with 4% (2/47) of subjects discontinuing because of an AE. The ORR was 19% (8/42) with 2 subjects experiencing complete responses (CRs).

1.4.5 Clinical Experience with Durvalumab and VEGF Inhibitors with HCC

Bevacizumab, a mAb targeting VEGF, is approved by the FDA for the treatment of several types of cancer, including colorectal cancer, non-small cell lung cancer, glioblastoma, renal cell carcinoma, cervical cancer, ovarian cancer, fallopian tube cancer, and peritoneal cancer.

A Phase II trial evaluating the clinical and biologic effects of bevacizumab in advanced hepatocellular carcinoma (Siegel et al 2008) included 46 patients, of whom 6 had objective responses (13%; 95% CI: 3% to 23%), and 65% were progression free at 6 months. Median PFS time was 6.9 months (95% CI: 6.5 to 9.1 months); OS rate was 53% at 1 year, 28% at 2 years, and 23% at 3 years. Grade 3 to 4 AEs included hypertension (15%) and thrombosis (6%, including 4% with arterial thrombosis). Safety results showed a Grade 3 or higher haemorrhage occurred in 11% of patients, including 1 fatal variceal bleed.

Additional evidence suggests that the combination of PD-L1 inhibition with VEGF inhibition may result in synergistic activity and improved clinical benefit (Barsoum et al 2014, Voron et al 2015, Yasuda et al 2013). In a recent Phase Ib study, atezolizumab (a PD-L1 inhibitor) and bevacizumab therapy as first-line treatment in patients with HCC showed promising clinical activity, with an ORR of 65% (Stein et al 2018). Another Phase Ib study, pembrolizumab (a PD-1 inhibitor) and lenvatinib therapy in patients with advanced HCC showed an ORR of 46% (6 out of 13 patients; Ikeda et al 2018). These data indicate further evaluation of durvalumab therapy in combination with VEGF inhibitor therapy in patients with HCC concurrent with administration of TACE is warranted.

1.5 Rationale for Conducting the Study

HCC is the third-leading cause of cancer death worldwide (Parkin et al, 2005; Altekruse et al, 2009). The current treatment paradigm for HCC utilizes multimodality therapy, including surgical resection, liver transplantation and/or local regional therapies such as radiofrequency ablation with curative intent in early-stage disease. Unfortunately, those patients who do not qualify for curative treatment have limited treatments options, which primarily include bland transarterial embolization, transarterial embolization with chemo or radioactive particles, or systemic therapy with sorafenib. In the noncurative setting, sorafenib is the only option that has been shown to extend survival (median OS, 10.7 months for sorafenib vs 7.9 months for placebo). However, its benefit is primarily limited to those patients with well-preserved liver function (Child-Pugh class A; Llovet et al, 2008; Pressiani et al, 2013). Recently, regorafenib and nivolumab have been approved as second line therapy for advanced HCC in some countries/areas. Regorafenib has been shown to extend survival (median OS, 10.6 months for regorafenib vs 7.8 months for placebo) in second-line HCC patients (Bruix et al, 2017). Nivolumab has been shown encouraging response rate of 14% in patients with or without previous sorafenib and the responses are durable (El-Khoueiry et al, 2017). However, with these new treatment options, the overall outcome of patients with advanced HCC are still poor. Therefore, HCC represents a significant unmet medical need.

1.5.1 Benefit-risk Evaluation

Emerging data demonstrate encouraging clinical activity with durvalumab and tremelimumab in HCC. In the ongoing Study CD-ON- durvalumab -1108, durvalumab monotherapy prolonged SD (≥ 3 months) in 4 of 19 evaluable subjects (21%) with advanced HCC. In addition, evaluation of single-agent tremelimumab administered with a suboptimal dosing schedule (15 mg/kg every 90 days) in subjects with HCV-associated HCC demonstrated an ORR of 18% (3 of 17 subjects; Sangro et al, 2013). These data combined with emerging clinical data from other mAb inhibitors of the PD-1/PD-L1 pathway (nivolumab with ORR of 19% [8/42]; El-Khoueiry et al, 2015), as well as nonclinical and clinical data suggesting improved anticancer activity with the durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination as compared to either agent alone, make a compelling case for evaluation of this combination in HCC (Antonia et al 2016).

Bioanalytical data evaluating increasing dose levels of tremelimumab (1, 3, 10 mg/kg) in NSCLC patient population shows a dose-proportional monotonic increase in pharmacodynamic activity, suggesting that a higher dose of tremelimumab may result in higher antitumor activity. Studies evaluating tremelimumab either as a single agent or in combination with TACE/ablation in HCC population have used doses higher than 1 mg/kg Q4W of tremelimumab (15 mg/kg every 90 days as monotherapy and 3.5 or 10 mg/kg Q4W in combination with TACE/ablation) and have demonstrated a high response rate of 18% and 26%, respectively (Sangro et al 2013 and Duffy et al 2016). These data suggest that a higher dose of tremelimumab in combination with durvalumab may provide better efficacy in HCC population. Additionally, as described in Section 1.4.3.2, a single high dose of tremelimumab may provide a higher peak pharmacodynamic effect when compared with multiple lower doses while potentially avoiding the toxicity that may be associated with repeated dosing of tremelimumab. Taken together, these data support the evaluation of a higher dose of tremelimumab as a single-dose in combination with durvalumab.

Potential risks are associated with durvalumab and tremelimumab given their mechanism of action and data from studies of relevant or similar therapies. The frequency and/or severity of immune-related adverse events (irAEs) may be increased when these 2 drugs are administered in combination as compared to their monotherapy safety profiles. It is also possible that the higher doses of tremelimumab in combination with durvalumab may be associated with a higher rate and/or severity of irAEs when compared to the standard durvalumab plus tremelimumab combination regimen. For durvalumab monotherapy, the identified risks include pneumonitis, increased ALT/AST, hepatitis, diarrhea, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypopituitarism, type 1 diabetes

mellitus, increased blood creatinine, nephritis, rash, pruritus, dermatitis, and infusion-related reaction. Important potential risks are immune-mediated reactions such as pancreatitis (including elevated amylase and lipase); hypophysitis/hypopituitarism; neuropathy/neuromuscular toxicity (eg, myasthenia gravis and Guillain-Barré syndrome); other rare events such as myocarditis, pericarditis, and uveitis; hypersensitivity reactions (including anaphylaxis and allergic reaction, cytokine release syndrome, and immune complex disease); and serious infections. For tremelimumab, identified risks include diarrhea, nausea, fatigue, rash, pruritus, decreased appetite, vomiting, pyrexia, influenza-like illness, arthralgia, constipation, thrombocytopenia, injection site reaction, and increased AST. Important potential risks are immune-mediated reactions such as hepatitis, including autoimmune hepatitis and increased serum ALT and AST; respiratory tract events, including pneumonitis and interstitial lung disease (ILD); nervous system events, including encephalitis, peripheral motor and sensory neuropathies, proximal muscle weakness, and Guillain-Barré syndrome; cytopenias, including thrombocytopenia, anemia, and neutropenia; renal failure, acute kidney injury, nephritis and nephrotic syndrome, including autoimmune nephritis, and electrolyte abnormalities; autoimmune diseases, including autoimmune arthritis, Sjogren's syndrome, giant cell temporal arteritis, and ulcerative colitis; hyperglycemia, including diabetes mellitus; infusion reactions and acute immunoglobulin E (IgE)-mediated allergic reactions; dehydration; nausea; vomiting; pyrexia; and hypokalemia. Several strategies have been incorporated in the study protocol to mitigate these risks (Section 3.1.3).

Hepatocellular carcinoma subjects with HBV infection may be at an increased risk for complications from an immune-modulatory anticancer therapy. While patients with HBV and HCV, in the absence of HCC, experience hepatic flares (defined minimally by ALT > 5 × ULN), the precipitating factors, incidence, and outcome vary significantly between the 2 populations. Hepatitis B virus flares can be precipitated by a variety of agents (steroids, rituximab, anti-tumor necrosis factor [TNF] agents, and highly active antiretroviral therapy) and can lead to liver decompensation, fulminant hepatic failure, and death, particularly if viral replication is not suppressed by antiviral medications (Chang and Liaw, 2014; Perrillo et al, 2015). In contrast, HCV flares are much less common and do not lead to liver decompensation, fulminant hepatic failure, or death (Sagnelli et al, 2014). For those subjects with HCC in the setting of HBV or HCV, additional data from monotherapy administration of durvalumab (Section 1.4.1), tremelimumab (Section 1.4.2), and nivolumab (Section 1.4.4) provide reassurance with regards to the safety risk of these 2 agents in this clinical setting.

An understanding of the potential difference in benefit-risk analysis for the different HCC populations has influenced the study design in several ways:

1. Inclusion of a safety run-in evaluation of the combination of durvalumab 20 mg/kg with tremelimumab 1 mg/kg x 4 doses in a limited number of subjects in each viral population (uninfected, HCV, and HBV) prior to exposure of a larger number of subjects in the randomized portion of the study.
2. Risk-based staggered assessment of the combination of durvalumab 20 mg/kg with tremelimumab 1 mg/kg x 4 doses (in the safety run-in portion of the study) in subjects (uninfected and HCV+) who might have a better benefit-risk profile as compared to those whose safety risk could be higher (HBV+).
3. Potential for evaluation of Dose Level -1 in HBV+ subjects if the combination regimen of durvalumab 20 mg/kg with tremelimumab 1 mg/kg x 4 doses is not tolerated as assessed by prospectively defined parameters.
4. Collection of noncancerous liver tissue at screening to help guide management of any hepatotoxic AEs is also requested if it can be done safely (as judged by the investigator) during the same procedure in which the tumor tissue biopsy is obtained.
5. Specific hepatotoxicity guidelines and eligibility criteria developed in cooperation with hepatologists specializing in HBV and HCV infection.
6. Requirement for all subjects with HBV infection to be on antiviral medications for adequate viral suppression.
7. Inclusion of a safety run-in evaluation of durvalumab in combination with a higher single dose of tremelimumab in Part 2B in a limited number of subjects prior to exposure of a larger number of subjects in the randomized portion (Part 3) of the study.

Bevacizumab has been approved by the FDA for the treatment of several types of cancers, although it is not currently approved for the treatment of HCC. Several studies are currently underway in evaluating the combination of bevacizumab (VEGF inhibitor) with atezolizumab (PD-L1 inhibitor) in patients with a variety of tumor types, including HCC.

NCT02715531 is an ongoing, open-label, Phase Ib study of the safety and efficacy of atezolizumab (a PD-L1 inhibitor) and bevacizumab in patients with solid tumors, including 1 arm in patients with metastatic or advanced HCC with no prior treatment. As of the data cutoff (October 24, 2017), 26 pts were evaluable for safety. Treatment-related all grade AEs occurred in 21 patients (81%). Treatment-related Grade 3-4 AEs were seen in 9 patients (35%), most commonly hypertension (n=5 patients [19%]). No grade 5 AEs were observed. Two patients (8%) experienced 3 treatment-related Grade 3 SAEs (autoimmune encephalitis, mental status change, and intra-abdominal haemorrhage). Immune-related AEs requiring corticosteroid treatment occurred in 3 patients (12%). The combination of atezo + bev is safe and well tolerated; no new safety signals were identified beyond the established safety profile for each agent. As of the data cutoff (11 January 2018), 23 patients had a median of 10.3

months of follow up (range: 3.5 to 17.3 months). The confirmed ORR was 61% based on Investigator assessment and 65% based on independent review. Disease control was maintained for ≥6 months in 65% of all patients and 70% of responders (Stein et al 2018).

The preliminary safety of durvalumab in combination with bevacizumab has been established in NCT02802098 (unpublished data) and NCT02336165. In NCT02336165, in patients with bevacizumab-refractory, recurrent glioblastoma, durvalumab combined with continuing bevacizumab therapy was shown to be well tolerated (Reardon et al 2017).

Preclinical as well as recent clinical data support the synergistic antitumor effect of PD-L1 inhibition combined with VEGF inhibition. The preliminary safety data has been established and is generally well tolerated. Therefore, the overall benefit/risk assessment supports the proposed study to evaluate the efficacy and safety of durvalumab in combined with a VEGFR inhibitor in advanced HCC.

1.6 Research Hypothesis

Durvalumab and tremelimumab as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab can be administered to subjects with advanced HCC with adequate safety, tolerability, and efficacy.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

1. To assess the safety and tolerability of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced HCC.

2.1.2 Secondary Objectives

1. To evaluate the efficacy of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced HCC.
2. To evaluate the relationship between candidate biomarkers (eg, PD-L1 expression in the tumor microenvironment) and measures of clinical outcome of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced HCC.

2.1.3 Exploratory Objectives

CCI

2.2 Study Endpoints

2.2.1 Primary Endpoints

1. AEs, SAEs, discontinuation of investigational product(s) due to toxicity, and changes from baseline in laboratory parameters (including liver and viral laboratory tests), electrocardiograms (ECG), and vital signs.

2.2.2 Secondary Endpoints

1. Objective response rate (ORR), disease control rate (DCR), time to response (TTR), duration of response (DoR), time to progression (TTP), and progression-free survival (PFS) based on investigator assessments and Blinded Independent Central Review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al, 2009), and overall survival (OS).
2. AEs, SAEs, discontinuation of investigational product(s) due to toxicity, and changes from baseline in laboratory parameters (including liver and viral laboratory tests), ECG, and vital signs in 3 distinct HCC populations: uninfected, HBV+, and HCV+.
3. PD-L1 expression within the tumor microenvironment.

2.2.3 Exploratory Endpoints

CCI

[redacted]

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a multicenter, open-label, stratified, study designed to evaluate the safety, tolerability, and clinical activity of durvalumab and tremelimumab administered as monotherapy, and durvalumab in combination with tremelimumab or bevacizumab in subjects with advanced HCC. The study will comprise of 6 parts described below and illustrated in Figure 3.1.1-1. Approximately 655 subjects will be screened to enroll approximately 456 subjects globally, including approximately 12 subjects in Part 1A, approximately 24 subjects in Part 1B, approximately 108 subjects in Part 2A, approximately 12 subjects in Part 2B, approximately 200 subjects in Part 3, and approximately 100 subjects in Part 4.

Following protocol amendment 5, enrollment into Part 3 Arm A will be closed. Patients who have been randomized to Arm A before this protocol amendment, can continue on assigned study treatment (provided the investigator and patient think it is in the best

interests of the patient) until confirmed PD or any other discontinuation criteria as described in section 4.1.6 is met. If a patient has not completed or started all 4 doses of tremelimumab, the patient may either continue to complete the full schedule or continue with durvalumab monotherapy only.

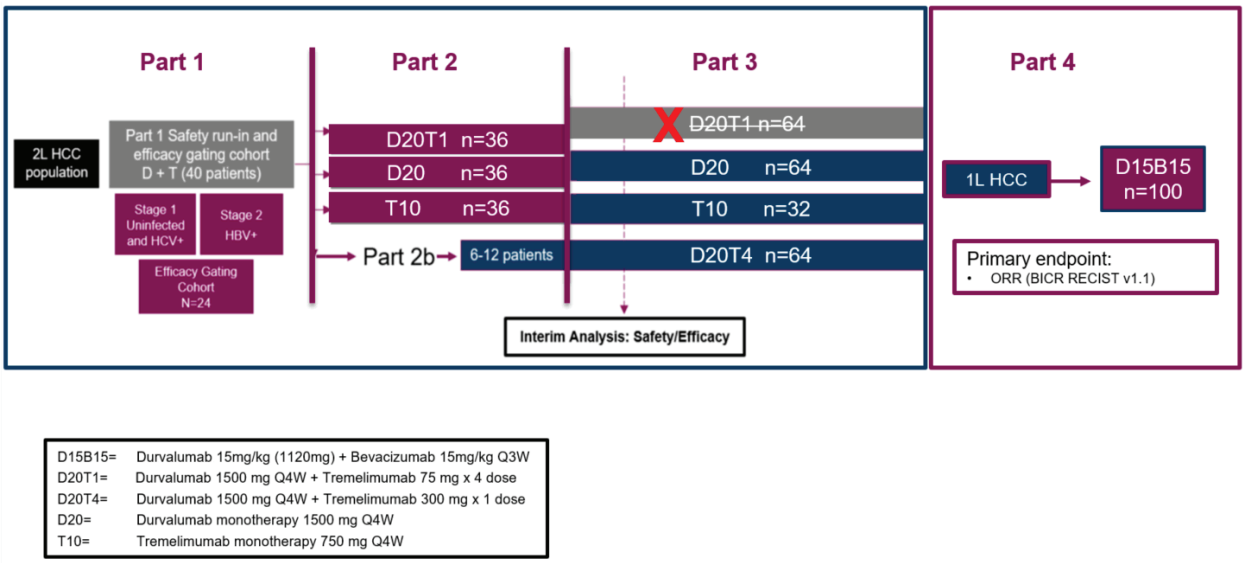

Figure 3.1.1-1 Study Flow Diagram

2L = second line; 1L = first line; HBV+ = hepatitis B virus positive; HCC = hepatocellular carcinoma; HCV+ = hepatitis C virus positive; D = durvalumab; T = tremelimumab; B = Bevacizumab

Part 1A: Safety Run-in with Durvalumab and Tremelimumab Combination Therapy

Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant of, or refused sorafenib-based therapy will be enrolled in Part 1A using a risk-based staggered approach.

- **Stage 1:** Approximately 6 subjects with advanced uninfected or HCV+ HCC will be enrolled (rationale for excluding HBV+ HCC subjects is explained in Section 1.4.4). Subjects will be administered the durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. If the frequency of AEs meeting DLT criteria is ≥ 33% for a given viral status/type, then lower dose cohorts in that specific subpopulation may be explored depending on the type and severity of the toxicities seen at this combination dose.
- **Stage 2:**

- *HBV+ Cohort:* Enrollment of 6 additional subjects with advanced HBV+ HCC may start after the first 3 subjects in Stage 1 have been observed on study for at least 4 weeks. Subjects will be administered durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. If the frequency of AEs meeting DLT criteria is ≥ 33%, then Dose Level -1 (ie, durvalumab 15 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W followed by durvalumab 15 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met) may be explored depending on the type and severity of the toxicities seen at this combination dose.
- *Dose for HBV+ HCC Subjects Administered the Durvalumab and Tremelimumab Combination:* durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W will be the dose evaluated for HBV+ subjects in Part 1B and Part 2A if the following criteria are met: (1) all 6 subjects have been observed for at least 4 weeks and the DLT frequency is < 33% (ie, < 2 of 6 subjects); AND (2) at least 3 of the 6 subjects have been observed for 6 weeks. If the DLT frequency for the Stage 2 is ≥ 33% (ie, ≥ 2 of 6 subjects), then Dose Level -1 (ie, durvalumab 15 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 15 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met) will be the dose evaluated for HBV+ subjects in Part 1B and Part 2A assuming the DLT frequency at Dose Level -1 is < 33%.

Part 1B: Efficacy Gating Cohort for Durvalumab and Tremelimumab Combination Therapy

Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant of, or refused sorafenib-based therapy will be enrolled in Part 1B.

Approximately 24 subjects (uninfected, HBV infected, or HCV infected) will be enrolled in an efficacy gating cohort to determine if there is sufficient evidence of clinical activity to warrant opening enrollment to Part 2. Refer to Section 4.8.7 for details regarding the definition of sufficient evidence. Subjects will be administered durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. After approximately 12 of the 24 subjects have been enrolled, enrollment of subjects who have progressed on or are intolerant to sorafenib may be paused in favor of subjects who have refused sorafenib to ensure a minimum enrollment of 12 subjects who have refused sorafenib in Part 1 (A and B). The total number of subjects with a specific viral status may be restricted in this cohort to ensure that all types of patients have an opportunity to enroll. For example, as enrollment proceeds if emerging data indicate

that the majority of patients enrolling are all HBV infected, enrollment of this specific viral type of HCC may be paused to allow other types of subjects (uninfected and HCV infected) to enroll.

If during Part 1B of the study, ≥ 33% of subjects with a specific viral status type discontinue therapy for treatment-related toxicity, enrollment for that specific viral status type may be paused and study data will be reviewed to determine whether additional monitoring, alternate dose levels, or treatment schedules should be evaluated prior to further enrollment of subjects with that specific viral status type.

Part 2A: Randomized Arms Evaluating Durvalumab and Tremelimumab Combination Therapy, Durvalumab Monotherapy, and Tremelimumab Monotherapy

Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant of, or refused sorafenib-based therapy, will be stratified based on viral status (uninfected, HCV infected, or HBV infected) and PD-L1 expression (positive, negative, or non-evaluable).

- Subjects may not enroll into any arm of Part 2A until sufficient evidence, as specified in Section 4.8.7 (in Part 1A and Part 1B), is observed
- Subjects will be randomized 1:1:1 within each stratum to 1 of the 3 treatment arms with approximately 36 subjects (approximately 12 subjects/viral status type) per treatment arm:
  - Arm A: Durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses followed by durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met
  - Arm B: Durvalumab 20 mg/kg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met
  - Arm C: Tremelimumab 10 mg/kg monotherapy Q4W for 7 doses followed by every 12 weeks (Q12W) until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

If during Part 2A of the study, ≥ 33% of subjects with a specific viral status type within a given arm discontinue therapy for treatment-related toxicity, enrollment for that specific viral status type may be paused and study data will be reviewed to determine whether additional monitoring, alternate dose levels, or treatment schedules should be evaluated prior to further enrollment of subjects with that specific viral status type. Enrollment into any arm of Part 2A

may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial to a given arm.

All subjects in Part 1A, Part 1B, and Part 2A will be evaluated for efficacy, as specified in the protocol (Section 4.2), and their disease status primarily analyzed according to RECIST v1.1. All subjects will be followed for survival until the end of study, as defined in section 6.3. For biomarker analysis, subjects will be required to have a fresh tumor tissue biopsy at screening, an optional post-dose biopsy, and an optional biopsy at disease progression. Collection of noncancerous liver tissue at screening should also be attempted if it can be done safely (as judged by the investigator) during the same procedure in which the fresh tumor tissue biopsy is obtained. Evaluation of PD-L1 expression status will be done in real-time while the study is ongoing.

Part 2B: Safety Run-in for Additional Treatment Regimen of Durvalumab and Tremelimumab Combination Therapy

Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant to, or have refused sorafenib-based therapy will be enrolled in Part 2B.

Approximately 6 to 12 subjects will be enrolled into Arm D evaluating a single higher dose of tremelimumab in combination with durvalumab:

- Arm D: durvalumab 1500 mg and tremelimumab 300 mg combination therapy for 1 dose followed by durvalumab 1500 mg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

A safety evaluation will be performed once 6 safety evaluable subjects have completed 4 weeks of follow-up. A safety evaluable subject is defined as a subject who has received at least 1 dose of study drug and completed at least 4 weeks of follow-up or discontinued treatment prior to the completion of 4 weeks of follow-up due to an adverse event.

Enrollment into Part 2B may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial.

For biomarker analysis, all subjects in Part 2B will be required to have a newly acquired (fresh or acquired within 3 months, preferred) or archival (< 3 years) tissue sample at screening, an optional post-dost biopsy, and an optional biopsy at disease progression.

Part 3: Randomized Arms Evaluating Durvalumab and Tremelimumab Combination Therapy, Durvalumab Monotherapy, and Tremelimumab Monotherapy

Immunotherapy-naive subjects with advanced HCC who have progressed on, are intolerant to, or have refused sorafenib-based therapy will be stratified based on viral status (uninfected, HCV infected, or HBV infected) and sorafenib-based therapy (refusers or all others). Subjects will be stratified to the HCV positive cohort if they test positive for HCV or have a history of HCV infection.

- Subjects may not enroll into any arm of Part 3 until enrollment in Part 2A and Part 2B has been completed and the safety evaluation of the first 6 subjects in Part 2B is completed.

- Subjects will be randomized at a ratio of 2:1:2 into 1 of up to 3 treatment arms with approximately 64 subjects in each of the durvalumab monotherapy or combination treatment arms (Arms B and D) and approximately 32 subjects in the tremelimumab monotherapy treatment arm (Arm C). No prerequisite number of subjects for viral status is set for any arm in Part 3:

  - Arm A (recruitment closed following protocol amendment 5): durvalumab 1500 mg and tremelimumab 75 mg combination therapy Q4W for 4 doses followed by durvalumab 1500 mg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. Following protocol amendment 5, enrollment into Part 3 Arm A will be closed. Patients who have been randomized to Arm A before this protocol amendment, can continue on assigned study treatment (provided the investigator and patient think it is in the best interests of the patient) until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met. If a patient has not completed or started all 4 doses of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only.
  - Arm B: durvalumab 1500 mg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met
  - Arm C: Tremelimumab 750 mg monotherapy Q4W for 7 doses followed by Q12W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

- Arm D: durvalumab 1500 mg and tremelimumab 300 mg combination therapy for 1 dose followed by durvalumab 1500 mg monotherapy Q4W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

All subjects in Part 3 will be evaluated for safety and efficacy as specified in the protocol, and their disease status will be primarily analyzed according to RECIST v1.1. An interim analysis will occur after approximately 10 subjects per treatment arm in Part 3 have completed 4 weeks of follow-up as described in Section 4.8.7. All subjects will be followed for survival until the end of study as defined in section 6.3.

For biomarker analysis, subjects will be required to have a newly acquired (fresh or acquired within 3 months, preferred) or archival (< 3 years) tissue sample at screening, an optional post-dost biopsy, and an optional biopsy at disease progression.

Enrollment into any arm of Part 3 may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial in a given arm.

The endpoints to be measured in this study are described in Section 2.2.

Part 4: Single Arm Evaluating Durvalumab with Bevacizumab in Combination.

Subjects with advanced HCC who have not received any prior systemic therapy can be enrolled into Part 4. Approximately 100 subjects will be enrolled into a single arm in Part 4 to evaluate the safety and efficacy of durvalumab in combination with bevacizumab:

- Durvalumab 15mg/kg (1120 mg) and bevacizumab 15 mg/kg combination therapy Q3W until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met

All subjects in Part 4 will be evaluated for safety and efficacy as specified in the protocol, and their disease status will be primarily analyzed according to RECIST 1.1. An interim analysis will occur after approximately 100 subjects in Part 4 have had the opportunity for 18 weeks of follow-up. Another interim analysis will occur after approximately 100 subjects in Part 4 have had the opportunity for 36 weeks of follow-up.

All subjects will be followed for survival until the end of study as per section 6.3.

For biomarker analysis, subjects will be required to have a newly acquired (fresh or acquired within 3 months, preferred) or archival (< 3 years) tissue sample at screening.

3.1.2 Treatment Regimen

Subjects in Part 1A, Part 1B, and Part 2A will receive weight-based dosing regimens of durvalumab and tremelimumab either as monotherapy or as combination therapy. Subjects in Part 2B and Part 3 will receive a fixed dosing regimen of durvalumab and tremelimumab either as monotherapy or as combination therapy as described in Table 3.1.2-1.

Table 3.1.2-1 Treatment and Regimens

Study Part	Dosing Regimen
Part 1A and Part 1B	
Combination therapy (see Figure 3.1.2-1)	Durvalumab 20 mg/kg (or 15 mg/kg for Dose Level -1, if needed) in combination with tremelimumab 1 mg/kg Q4W for 4 doses. After completion of the combination therapy, subjects will receive durvalumab monotherapy at 20 mg/kg Q4W until any of the discontinuation criteria in Section 4.1.6 are met. The first durvalumab monotherapy dose at 20 mg/kg Q4W will be given 4 weeks after the final dose of durvalumab and tremelimumab combination therapy. Subjects who progress on durvalumab monotherapy may be retreated with the durvalumab and tremelimumab combination as described in Section 3.1.2.1.
Part 2A	
Arm A Combination therapy (see Figure 3.1.2-1)	Durvalumab 20 mg/kg (or 15 mg/kg for Dose Level -1, if needed) in combination with tremelimumab 1 mg/kg Q4W for 4 doses. After completion of the combination therapy, subjects will receive durvalumab monotherapy at 20 mg/kg Q4W until any of the discontinuation criteria in Section 4.1.6 are met. The first durvalumab monotherapy dose at 20 mg/kg Q4W will be given 4 weeks after the final dose of durvalumab and tremelimumab combination therapy. Subjects who progress on durvalumab monotherapy may be retreated with the durvalumab and tremelimumab combination as described in Section 3.1.2.1.
Arm B Durvalumab monotherapy (see Figure 3.1.2-2)	Durvalumab monotherapy at 20 mg/kg Q4W until any of the discontinuation criteria in Section 4.1.6 are met.
Arm C Tremelimumab monotherapy (see Figure 3.1.2-3)	Tremelimumab monotherapy at 10 mg/kg, Q4W for 7 doses and then every 12 weeks until any of the discontinuation criteria in Section 4.1.6are met.
Part 2B	
Arm D Combination therapy (see Figure 3.1.2-4)	Durvalumab 1500 mg in combination with tremelimumab 300 mg for 1 dose. After completion of the combination therapy, subjects will receive durvalumab monotherapy at 1500 mg Q4W until any of the discontinuation criteria in Section 4.1.6 are met. The first durvalumab monotherapy dose at 1500 mg Q4W will be given 4 weeks after the final dose of durvalumab and tremelimumab combination therapy. Subjects who progress on durvalumab monotherapy may be retreated with the durvalumab and tremelimumab combination as described in Section 3.1.2.1.

Table 3.1.2-1 Treatment and Regimens

Study Part	Dosing Regimen
Part 3	
Arm A (recruitment closed following protocol amendment 5) Combination therapy (see Figure 3.1.2-1)	Durvalumab 1500 mg in combination with tremelimumab 75 mg Q4W for 4 doses. After completion of the combination therapy, subjects will receive durvalumab monotherapy at 1500 mg Q4W until any of the discontinuation criteria in Section 4.1.6 are met. The first durvalumab monotherapy dose at 1500 mg Q4W will be given 4 weeks after the final dose of durvalumab and tremelimumab combination therapy. Subjects who progress on durvalumab monotherapy may be retreated with the durvalumab and tremelimumab combination as described in Section 3.1.2.1. **Following protocol amendment 5, enrollment into Part 3 Arm A will be closed. Patients who have been randomized to Arm A before this protocol amendment, can continue on assigned study treatment (provided the investigator and patient think it is in the best interests of the patient) until confirmed PD or any other discontinuation criteria as described in Section 4.1.6 is met.** If a patient has not completed or started all 4 doses of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only.
Arm B Durvalumab monotherapy (see Figure 3.1.2-2)	Durvalumab monotherapy at 1500 mg Q4W until any of the discontinuation criteria in Section 4.1.6 are met.
Arm C Tremelimumab monotherapy (see Figure 3.1.2-3)	Tremelimumab monotherapy at 750 mg, Q4W for 7 doses and then every 12 weeks until any of the discontinuation criteria in Section 4.1.6 are met
Arm D Combination therapy (see Figure 3.1.2-4)	Durvalumab 1500 mg in combination with tremelimumab 300 mg for 1 dose. After completion of the combination therapy, subjects will receive durvalumab monotherapy at 1500 mg Q4W until any of the discontinuation criteria in Section 4.1.6 are met. The first durvalumab monotherapy dose at 1500 mg Q4W will be given 4 weeks after the final dose of durvalumab and tremelimumab combination therapy. Subjects who progress on durvalumab monotherapy may be retreated with the durvalumab and tremelimumab combination as described in Section 3.1.2.1.
Part 4	
Combination Therapy (see Figure 3.1.2-5)	Durvalumab 15mg/kg (1120 mg) in combination with Bevacizumab 15 mg/kg Q3W until any of the discontinuation criteria in Section 4.1.6 are met. Subjects who progress on this combination therapy may not be retreated.

Q4W = every 4 weeks, Q12W = every 12 weeks, Q3W = every 3 weeks

The treatment regimen for durvalumab and tremelimumab combination therapy for Part 1A, Part 1B, and Part 2A Arm A is illustrated in Figure 3.1.2-1 below.

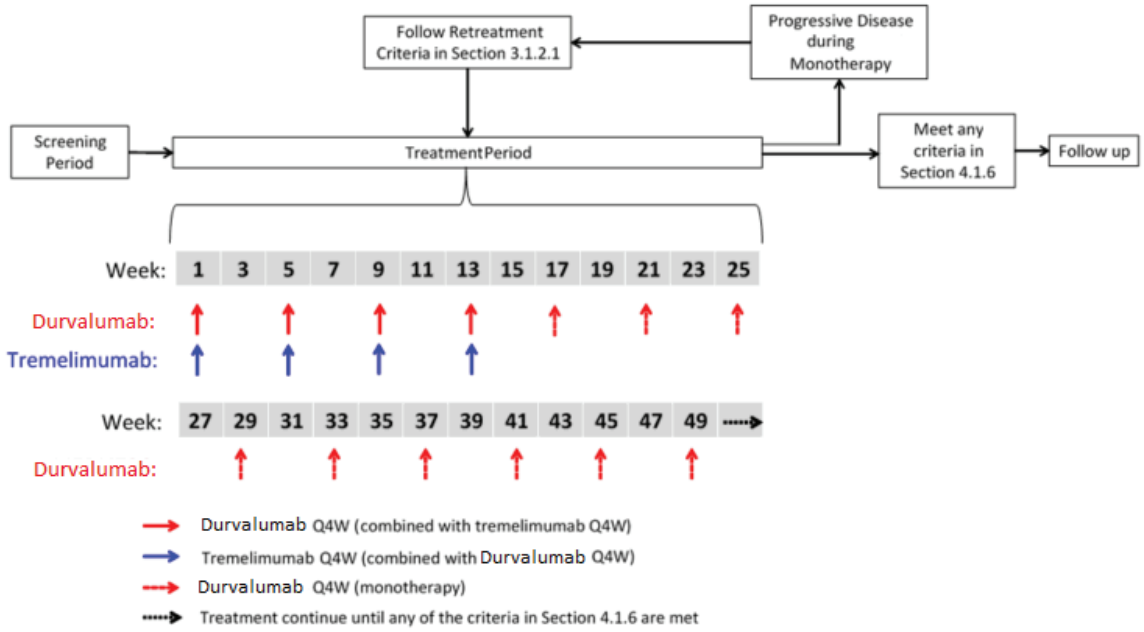

Figure 3.1.2-1 Durvalumab and Tremelimumab Combination Therapy Treatment Schedule

Q4W = every 4 weeks.

The treatment regimen for durvalumab monotherapy (Part 2A Arm B and Part 3 Arm B) is illustrated in Figure 3.1.2-2.

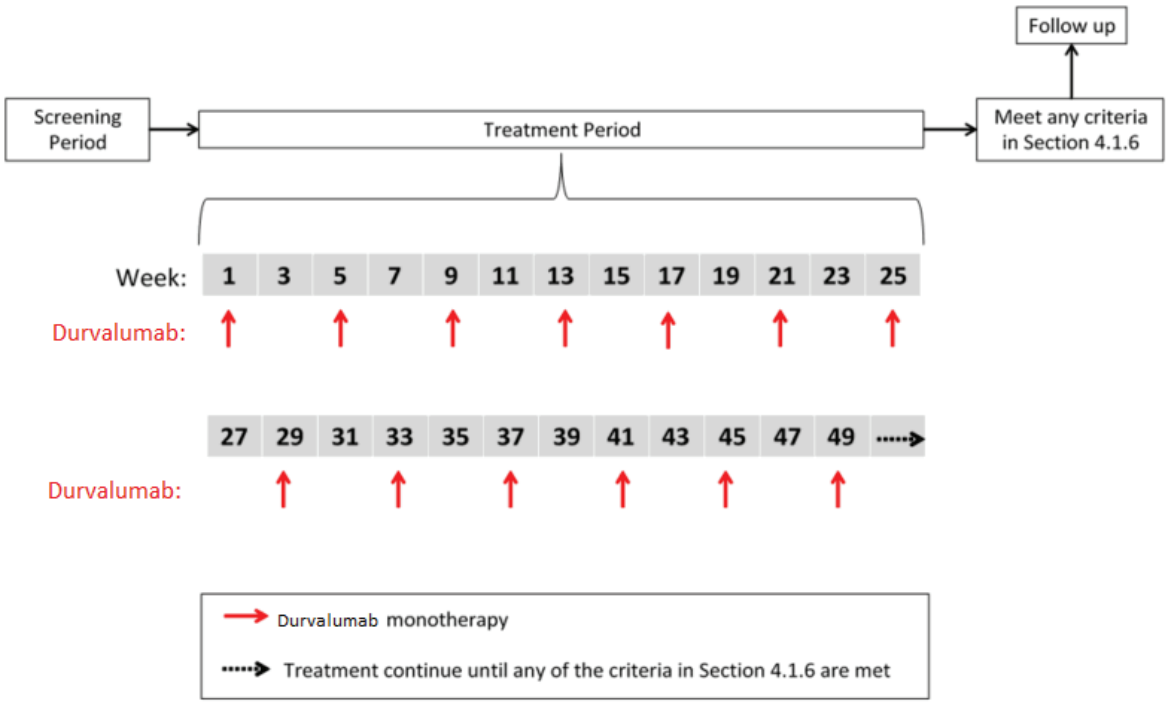

Figure 3.1.2-2 Durvalumab Monotherapy Treatment Schedule

Q4W = every 4 weeks.

The treatment regimen for tremelimumab monotherapy (Part 2A Arm C and Part 3 Arm C) is illustrated in Figure 3.1.2-3.

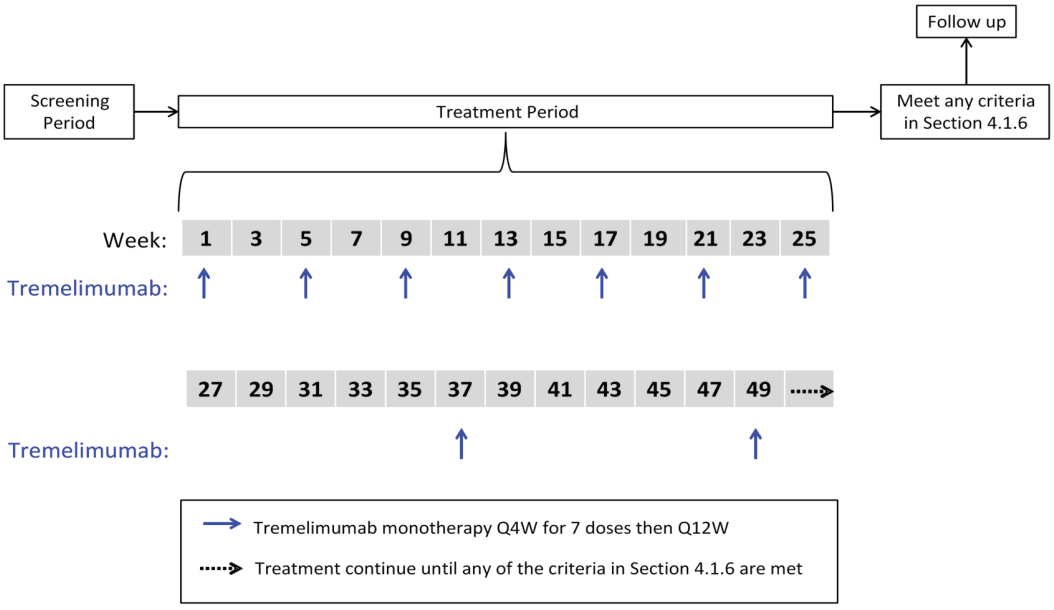

Figure 3.1.2-3 Tremelimumab Monotherapy Treatment Schedule

Q4W = every 4 weeks: Q12W = every 12 weeks.

The treatment regimen for durvalumab and tremelimumab combination therapy for Part 2B Arm D and Part 3 Arm D is shown in Figure 3.1.2-4.

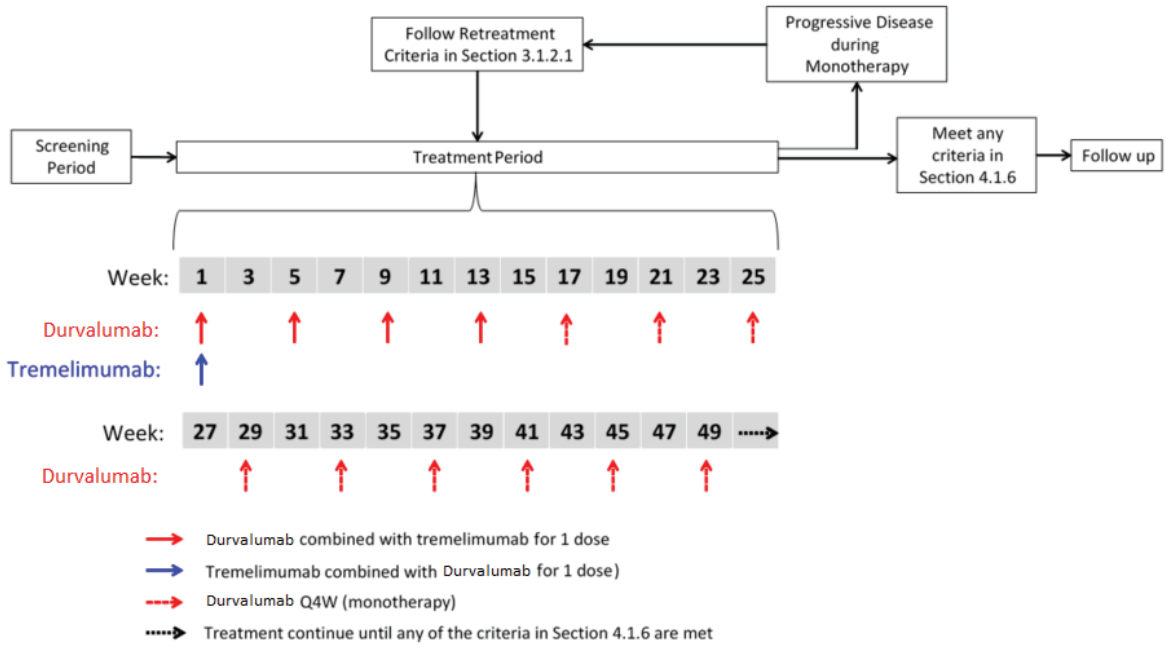

Figure 3.1.2-4 Durvalumab and Tremelimumab Combination Therapy Treatment Schedule

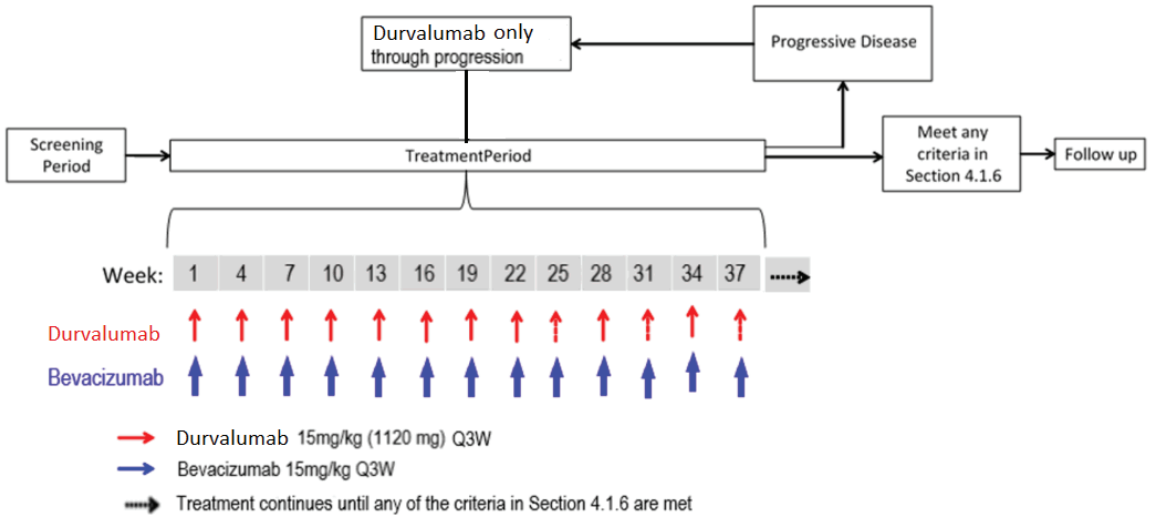

Figure 3.1.2-5 Durvalumab and Bevacizumab Combination Therapy Treatment Schedule

Q4W = every 4 weeks.
Q3W = every 3 weeks.

3.1.2.1 Duration of Treatment and Criteria for Treatment Through Progression and for Retreatment

All treatment will be administered beginning on Day 1 unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (Section 4.1.6).

Treatment through progression is permitted for subjects with durvalumab and bevacizumab combination in Part 4. However, only durvalumab can be continued through progression while bevacizumab should be discontinued at initial radiological progression. Re-treatment is not permitted for subjects in Part 4.

Subjects with rapid tumor progression (based on investigator opinion) or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible for continuing durvalumab and tremelimumab combination therapy.

For all subjects who are treated through progression, the investigator should ensure subjects do not have any significant, unacceptable or irreversible toxicities that indicate continuing or restarting treatment would not further benefit the subjects.

Subjects enrolled in the durvalumab and tremelimumab combination therapy arms meeting the retreatment criteria below will follow the same treatment guidelines followed during the

original treatment period, including the same dose and frequency of treatments and the same schedule of assessments. Subjects who meet the criteria for retreatment for their respective treatment arm may only receive retreatment once. Crossover within the study is not permitted, except for patients in Part 3 Arm A, who can be retreated with the durvalumab 1500mg + tremelimumab 300mg x 1 dose, with prior approval from the AstraZeneca Study Physician.

Subjects randomized to any durvalumab and tremelimumab combination therapy arm may undergo retreatment as described below:

- Subjects who complete the specified dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per investigator judgment), but subsequently have evidence of PD during the durvalumab portion of the combination regimen, with or without confirmation according to investigator assessments using RECIST v1.1, may restart treatment with the combination.

For all subjects who are treated through progression and for subjects who are restarting durvalumab and tremelimumab combination therapy, the investigator should ensure that

1. The subject does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the subject.
2. The subject does not meet any of the investigational product discontinuation criteria (Section 4.1.6).
3. There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in World Health Organization/Eastern Cooperative Oncology Group (WHO/ECOG) performance status to >1.
4. There is absence of rapid PD or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.
5. The subject still fulfills the eligibility criteria for this study (Section 4.1.2 and 4.1.3) with the exception of inclusion criteria 4, 9, and 10 and exclusion criteria 5 and 17. Subjects must also agree to re-consent to restart durvalumab and tremelimumab combination therapy and treatment through progression.
6. The subject has not used additional immunosuppression other than corticosteroids for the management of an AE, has not experienced recurrence of an AE if re-challenged, and does not currently require maintenance doses > 10 mg prednisone or equivalent per day.

Subjects in the immunotherapy arms will not be permitted to continue immunotherapy if progression occurs after confirmed response (CR or PR as defined by investigator assessments using RECIST v1.1) to immunotherapy treatment in the target lesions

(regardless of the appearance of new lesions), ie, the response and progression events both occurred in the target lesions while receiving immunotherapy during the same period.

Subjects who the sponsor and the investigator determine may not continue treatment after PD will be followed up for survival. Subjects who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

3.1.2.2 Dose-limiting Toxicity

A DLT will be defined as any Grade 3 or higher treatment-related toxicity that occurs during the first 4 weeks of treatment, including:

- Any Grade 4 irAE
- Any Grade 3 colitis
- Any Grade 3 noninfectious pneumonitis irrespective of duration
- Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 7 days of the initiation of maximal supportive care
- Any other Grade 3 irAE (excluding colitis or pneumonitis), that does not downgrade to Grade 2 within 7 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- AST or ALT > 3 × ULN with concurrent increase in total bilirubin > 2 × ULN without evidence of cholestasis or alternative explanations, eg, viral hepatitis, disease progression in the liver, etc (Hy's Law)
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition 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 subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes)
- Concurrent vitiligo or alopecia of any AE 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 7 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Isolated Grade 3 thrombocytopenia that is not associated with clinically significant bleeding and does not require medical intervention
- 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
- Isolated Grade 3 amylase or lipase abnormalities that are not associated with clinical signs/symptoms or findings on imaging consistent with pancreatitis

Immune-related AEs are defined as events of immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

An AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.

DLT is only applicable for Part 1.

3.1.3 Management of Study Medication Related Toxicities

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. When in doubt, the investigator should consult with the medical monitor. If the investigator has any question in regards to an AE being an irAE, the investigator should immediately contact the medical monitor.

Specific toxicity management and dose modification for durvalumab and tremelimumab

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, the occurrence of irAEs that are either overlapping or greater than each of these drugs when used as monotherapy is possible. Potential irAEs may be similar to those seen with the use of ipilimumab, nivolumab, or the combination thereof and may include immune-mediated enterocolitis, dermatitis, pneumonitis, hepatitis (hepatotoxicity), neurotoxicity, and endocrinopathies (Hodi et al, 2010; Brahmer et al, 2012; Topalian et al, 2012; Wolchok et al, 2013). Subjects should be monitored for signs and symptoms of irAEs in any organ. In the absence of an alternate etiology (eg, infection, HBV or HCV hepatic flare, or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, pneumonitis, dermatitis, hepatitis, neurotoxicity, pancreatitis, cytopenias, and endocrinopathies.

Treatment modifications will not be required for AEs that are clearly not attributed to durvalumab or tremelimumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dose reductions of durvalumab or tremelimumab are not permitted. Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab and tremelimumab monotherapy and durvalumab + tremelimumab combination therapy are provided in the Dosing Modification and Toxicity Management Guidelines. The most current version of these guidelines is to be maintained within the Site Master File. In addition, a version of the current Dosing Modifications and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Please contact your clinical trial associate for information on how to gain access to this website. Hepatotoxicity management guidelines are provided below.

Specific toxicity management and dose modification for bevacizumab

Subjects receiving durvalumab and bevacizumab combination therapy who, in the opinion of the investigator, have an AE attributed to bevacizumab that meets interruption or discontinuation criteria for bevacizumab, may continue durvalumab dosing regimen as scheduled. However, if an AE is attributed to durvalumab and meets the interruption or discontinuation criteria for durvalumab, both durvalumab and bevacizumab should be interrupted or discontinued according to toxicity management guideline. For management of toxicities due to bevacizumab, please refer to the local approved regulatory prescribing information for bevacizumab or manage in accordance with institutional guidelines.

3.1.3.1 Management of Hepatotoxicity

Management of hepatotoxicity should take into consideration the viral status of the subject as well as the type of toxicity observed. In general, while both ALT and AST will be monitored, ALT is considered to be more liver-specific; therefore, changes in ALT should be the primary driver for dose modification and management decisions. In addition, isolated increases in ALT without other signs of hepatotoxicity (such as fever, hyperbilirubinemia, and worsening ascites), which have been observed in subjects treated with tremelimumab monotherapy (Sangro et al, 2013), should be considered to be of a different risk-benefit profile than increases in ALT associated with other signs of hepatotoxicity.

General guiding principles for select subject populations:

1. Uninfected HCC: Interpretation of hepatic laboratory results not confounded by underlying viral infection. Management should focus on ruling out non-immune-related AEs and early intervention with steroids and/or other immunosuppressive agents as clinically appropriate
2. HCV+ or HBV+ HCC: Differential diagnosis for isolated increases in ALT could include:
    a. Activation of the immune system resulting in increased immune response to HCV or HBV manifesting as decreases in viral replication, decreases in HCV viral load, or decreases in HBsAg
    b. Changes in immune response to HCV or HBV leading to increased HCV or HBV viral replication, increases in HCV viral load, or increases in HBV viral load/HBsAg (primarily a hypothetical risk given the mechanism of action of durvalumab and tremelimumab)
    c. Non-irAEs unrelated to HCV or HBV
    d. irAEs such as autoimmune hepatitis

Increases in ALT attributable to changes in HCV status do not necessarily require immediate immunosuppression. Rather, only in the setting of irAEs would immunosuppression (eg, corticosteroids) be considered. Antiviral therapy may be considered in the setting of an ALT increase due to increased HCV viral replication.

Increases in ALT attributable to changes in HBV viral replication do not necessarily require immediate intervention and/or immunosuppression, with the exception of increases in HBV viral load. Increases in HBV viral load suggest onset of resistance to anti-HBV therapy which should precipitate a change in anti-HBV therapy. Only in the setting of irAEs would immunosuppression (eg, corticosteroids) be considered.

Liver biopsy is recommended soon after the AE is reported as a way to understand the underlying pathology and determine the best type of intervention. Suggested laboratory tests to monitor liver status include AST, ALT, total bilirubin, direct bilirubin, albumin, alkaline phosphatase, gamma-glutamyltransferase, and international normalized ratio. Subjects should be monitored/evaluated for etiologies (eg, viral hepatitis, disease progression, concomitant medications, herbals, over-the-counter medications, supplements) other than immune-related hepatotoxicity before the initiation of dose modifications and immunosuppression.

3.2 Study Design and Dose Rationale

3.2.1 Dose Rationale

Durvalumab Monotherapy (20 mg/kg)

The dose and schedule for durvalumab monotherapy (20 mg/kg Q4W) were selected based on 2 sets of data: (1) the safety analysis of doses administered in Study CD ON durvalumab-1108 (a Phase 1/2 study to evaluate the safety, tolerability, and PK of durvalumab given as monotherapy in subjects with advanced solid tumors [see Section 1.4.1]); and (2) PK profile simulations described above indicating that durvalumab administered using a 10 mg/kg Q2W schedule and 20 mg/kg Q4W schedule are predicted to have similar PK profiles.

Tremelimumab Monotherapy (10 mg/kg)

The dose and schedule for tremelimumab monotherapy (10 mg/kg Q4W for 7 doses and then Q12W until any of the criteria outlined in Section 4.1.6 are met) is currently being evaluated in Study D4880C00003, an ongoing double-blind, randomized, global Phase 2b study in subjects with mesothelioma (NCT01843374).

Durvalumab 20 mg/kg (or 1500 mg fixed dose) in Combination with Tremelimumab 1 mg/kg (or 75 mg fixed dose) x 4 doses

The dose and schedule for 20 mg/kg durvalumab Q4W and 1 mg/kg tremelimumab Q4W was selected based on PK, pharmacodynamics, safety and efficacy data from Study D4190C0006, as described in Section 1.4.3. The goal of dose selection was to identify an optimal dose of durvalumab that would yield sustained target suppression, optimize synergy of the combination, while maintaining the balance of safety in combination with tremelimumab.

The observed PK exposures of both durvalumab and tremelimumab following combination therapy were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents. A low incidence of ADA was observed with no obvious association with dose and safety. Following treatment with the durvalumab and tremelimumab combination in all cohorts, complete sPD-L1 suppression (surrogate for PD-L1 targeting) was observed in all but 3 subjects who received durvalumab at doses of 10 and 15 mg/kg Q4W. Complete sPD-L1 suppression was maintained in all subjects receiving 20 mg/kg Q4W durvalumab. Based on PK/pharmacodynamics (monotherapy and combination) and preliminary efficacy data (from combination), durvalumab doses of 3 and 10 mg/kg Q4W combination cohorts were excluded from further development. Pharmacokinetic simulations indicated that a similar AUC at steady state (4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W durvalumab regimens; given the similar AUC and overlapping exposure, both regimens are expected to have a similar safety and efficacy profiles. Cohorts were narrowed to 15 mg/kg Q4W and 20 mg/kg Q4W of durvalumab.

Monotonic increases in pharmacodynamic activity best illustrated by T-cell proliferation (Ki67) were observed with increasing doses of tremelimumab relative to the activity observed in subjects treated with durvalumab monotherapy. There was evidence of augmented Ki67 activity in CD4 and CD8 T cells relative to durvalumab monotherapy with combination doses containing 1 mg/kg and higher tremelimumab and with doses of 15 or 20 mg/kg durvalumab in combination with 1 mg/kg tremelimumab.

Safety data from the 15 and 20 mg/kg durvalumab Q4W cohorts demonstrated a numerical increase in the frequency of treatment-related AEs and AEs leading to discontinuation of investigational product with increasing doses (> 1 mg/kg) of tremelimumab.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to have a qualitative change with increasing doses of tremelimumab. The 15 and 20 mg/kg durvalumab Q4W cohorts demonstrated ORs at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses in some tumor types such as NSCLC or urothelial cancer. A pharmacodynamic analysis demonstrated that the peak change (%) from baseline of CD4+Ki67+ T cells was significantly increased by increasing doses of tremelimumab from 1 to 10 mg/kg in patients with NSCLC who received durvalumab and tremelimumab combination therapy (Study D4190C00006). Therefore, the optimal dose of tremelimumab at 1 mg/kg and higher based on PK/pharmacodynamics, safety, and preliminary clinical activity should be investigated.

To achieve optimal receptor occupancy with an acceptable safety profile, the dose of durvalumab 20 mg/kg Q4W was selected. The combination of 20 mg/kg durvalumab Q4W and 1 mg/kg tremelimumab Q4W has been chosen in Part 2A because it provided the optimal balance between PK/pharmacodynamics, safety, and clinical activity.

Due to the potential for increased toxicity that is associated with repeated dosing of tremelimumab in combination with durvalumab in comparison to durvalumab or tremelimumab monotherapy, and as maximal tumor shrinkage was observed during the first 8 to 16 weeks in the majority of subjects, the combination will consist of 4 monthly tremelimumab doses of 1 mg/kg in combination with durvalumab in Part 2A.

In conclusion, the selected dose and schedule of the combination therapy for Part 2A weight-based dosing regimen is 20 mg/kg durvalumab and 1 mg/kg tremelimumab Q4W for 4 doses, followed by 20 mg/kg durvalumab monotherapy Q4W. For Part 3 of this study, a fixed dose equivalent of the above dose (1500 mg durvalumab and 75 mg tremelimumab Q4W for 4 doses, followed by 1500mg durvalumab monotherapy Q4W) will be used. The justification for using the fixed dose regimen of durvalumab and tremelimumab is provided below.

Durvalumab 1500 mg in Combination with Tremelimumab 300 mg x 1 dose

The PK/pharmacodynamic data supporting a single high dose of tremelimumab in combination with durvalumab are presented in Section 1.4.3.2. The 4 mg/kg × 1 dose of tremelimumab, while maintaining a similar overall exposure, has a 3- to 4-fold higher C_{max} compared with the 1 mg/kg × 4 doses of tremelimumab. Therefore, this single administration of the higher dose of tremelimumab may have the potential for better antitumor activity while potentially avoiding the cumulative toxicity associated with repeated dosing of the 1 mg/kg tremelimumab. This hypothesis will be tested by evaluating the safety and preliminary efficacy on this regimen in the current study. The justification for using the fixed dose equivalent of durvalumab and tremelimumab combination regimen is provided below.

Rationale for Utilizing a Fixed Dose Regimen of Durvalumab in Combination with Tremelimumab

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). Similarly, a population PK model was developed for tremelimumab using data from

Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) (Wang et al 2014).

Population PK analysis indicated only minor impact of body weight on the PK of durvalumab and also tremelimumab (coefficient of ≤ 0.5). The weight-based versus fixed dosing (based on median body weight of ~75 kg) regimens of both durvalumab and tremelimumab were compared using predicted PK concentrations (5th, median, and 95th percentiles) using a population PK model. A total of 1000 patients were simulated using body weight distribution of 40 kg to 120 kg. Simulation results demonstrate that body weight-based versus fixed dosing regimens of both durvalumab and tremelimumab yield similar median steady-state PK concentrations with slightly less overall between-subject variability.

Similar findings have been reported by others (Ng et al, 2006, Wang et al, 2009, Zhang et al, 2012, Narwal et al, 2013). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al, 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK/pharmacodynamic parameters (Zhang et al, 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg durvalumab (equivalent to 20 mg/kg) and a fixed dose of 75 and 300 mg tremelimumab (equivalent to 1 and 4 mg/kg) is included in the current study.

In conclusion, the selected doses and schedules of the combination therapy for fixed dosing regimens are 1500 mg durvalumab and 75 mg tremelimumab Q4W for 4 doses, followed by 1500 mg durvalumab monotherapy Q4W and 1500 mg durvalumab and 300 mg tremelimumab for 1 dose, followed by 1500 mg durvalumab monotherapy Q4W.

Dose Rationale for Bevacizumab

The dose regimen for bevacizumab in this study (ie, bevacizumab 15 mg/kg) is consistent with the regimen that has been approved by the FDA for treatment of several types of cancers and with the dose of bevacizumab used in combination with atezolimumab evaluated in patients with HCC, which showed promising early efficacy and acceptable tolerability (Stein et al 2018).

Dose Rationale for Durvalumab in Combination with Bevacizumab

The proposed dosing regimen of durvalumab 1120 mg Q3W is aligned with the fixed doing of durvalumab 1500 mg Q4W, which is supported by efficacy and safety as well as tolerability data in ongoing and prior durvalumab clinical studies. To conform to the bevacizumab schedule in the study, we propose to use standard durvalumab dose and ratio at a Q3W dosing interval, rather than the standard Q4W schedule.

The safety of a Q3W dosing schedule in combination with chemotherapy has been explored in the Study D419SC00001 (refer to the current durvalumab IB for more information), where tremelimumab is administered at 75 mg in combination with 1120 mg durvalumab Q3W followed by 1120 mg durvalumab Q3W. The combination has been declared tolerable and manageable. The 1120 mg dose of durvalumab is the Q3W equivalent of the standard 1500mg Q4W dose.

Based on available PK data from Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W and 15 mg/kg Q3W (dose-escalation), 10 mg/kg Q2W (dose expansion), and 20 mg/kg Q4W (dose-exploration), similar overall exposure is expected following both 15mg/kg Q3W and 20 mg/kg Q4W regimens. Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of $\leqslant$0.5). Based on average body weight of 75 kg, a fixed dose of 1120 mg Q3W durvalumab is included in the current study.

The weight-based dosing of durvalumab of 15 mg/kg is applied if a patient's weight falls to 30 kg or below to maintain similar median steady state PK concentrations in comparison with fixed dosing regimen.

3.2.2 Rationale for Study Population

The proposed study population, comprising adult subjects with advanced HCC, represents a high unmet medical need. This tumor indication, described below, presents an opportunity for novel treatment approaches that may lead to improved clinical outcomes.

Globally, HCC is the third-leading cause of cancer death (Parkin et al, 2005; Altekruse et al, 2009). The incidence of HCC in males is more than twice (2.4) that of females (Parkin et al, 2005; Miamen et al, 2012). Approximately 80% of the global HCC burden is accounted for in the high-incidence (> 20 per 100,000) regions of East Asia and sub-Saharan Africa, with 55% occurring in China alone (Parkin et al, 2005). However, even in the low-incidence (< 5 per 100,000) regions of North America and Europe, the incidence of HCC is increasing (El-Serag, 2012). In the United States (US) alone, HCC incidence rates

have more than tripled in the past 30 years (Miamen et al, 2012). The global variation in HCC incidence reflects geographic differences in risk factors, particularly chronic infections with HBV and HCV (Montalto et al, 2002; Llovet et al, 2003). Worldwide, it is estimated that HBV is responsible for 50% to 80% of HCC cases, while HCV is responsible for 10% to 25% of cases (Block et al, 2003; Anthony, 2001). In the Asia-Pacific region where HBV is endemic, an estimated 70% of HCC patients have chronic HBV infections and 20% have chronic HCV infections. These rates are approximately reversed in non-HBV endemic areas such as North America, Europe, and Japan, where HCV and alcoholic cirrhosis are considered the main risk factors (Llovet et al, 2003).

Treatment options for HCC depend on a number of factors including resectability, liver function, and patient performance status. Current treatment options include resection and transplantation, ablative therapy, and systemic therapy. However, upon initial diagnosis, only 20% of HCC patients with advanced disease are considered eligible for surgical resection (Kantar Health, 2013). As a result, HCC patients face a poor prognosis with a median OS of less than 1 year (Frenette and Gish, 2012), and less than 10% of patients are expected to survive 5 years after initial diagnosis (Kantar Health, 2013). Since 2007, sorafenib has been the global standard of care systemic therapy for advanced HCC after demonstrating a modest increase in median OS from 7.9 to 10.7 months when compared to placebo in a Phase 3 clinical study (Llovet et al, 2008). In addition, the benefit of sorafenib is primarily limited to those patients whose liver function is well preserved (Child-Pugh class A; Llovet et al, 2008; Pressiani et al, 2013). For those patients whose disease progresses on, or who are intolerant to sorafenib, there are no other standard of care options. Therefore, it appears a significant unmet need exists for new and improved systemic therapies in HCC (Villanueva and Llovet, 2011).

Clinical evidence suggests HCC may be particularly susceptible to immunotherapy. HCC has shown the highest rate of spontaneous regression among all tumors through what is believed to be an antitumor immune response mechanism (Oquinena et al, 2009). Objective tumor responses have previously been reported following adoptive immunotherapy with dendritic cells pulsed with tumor lysate (Palmer et al, 2009) and lymphokine-activated killer cells combined with recombinant interleukin (IL)-2 (Takayama et al, 2000). In addition, overexpression of PD-L1 in HCC patient samples was found to be significantly associated with tumor aggressiveness and postoperative recurrence (Gao et al, 2009). Similarly, PD-L1 expression on tumor-infiltrating monocytes increased with disease progression and was associated with high mortality and reduced survival in HCC patients (Kuang et al, 2009). In a study of HBV-infected HCC patients, upregulation of circulating and intratumoral PD-1 and PD-L1 expression was found to promote $CD8^+$ T-cell apoptosis and postoperative recurrence

(Shi et al, 2011). Furthermore, the 2 leading causes of HCC, HBV and HCV infection, have also been shown to upregulate the PD-L1/PD-1 pathway as a mechanism to evade antiviral immunity (Peng et al, 2008; Golden-Mason et al, 2007).

In addition, clinical experience exists with both durvalumab monotherapy (10 mg/kg Q2W) and nivolumab (El-Khoueiry et al, 2015) in advanced stage HCC patients, including those with HBV or HCV infection. In Study CD-ON- durvalumab-1108, 4 of the 19 evaluable (21%) HCC subjects treated at the recommended durvalumab monotherapy dose demonstrated prolonged SD (≥ 3 months), while 8 of 42 (19%) treated with nivolumab demonstrated either partial or complete responses (El-Khoueiry et al, 2015). In addition, tremelimumab (15 mg/kg every 90 days) has previously been explored in HCC patients (n = 20) with chronic HCV and demonstrated a manageable safety profile as well as antitumor and antiviral effects (Sangro et al, 2013). No AEs required systemic steroids for management and 3 of 17 evaluable subjects (17.6%) demonstrated PR. The antitumor and antiviral effects of dual blockade of CTLA-4 and PD-L1 have yet to be explored in patients with advanced HCC with or without an underlying chronic viral infection. The current study provides a novel opportunity to test this combination in populations with high unmet need.

3.2.3 Rationale for Endpoints

Primary Endpoint: Safety

Although safety of the recommended Phase 2 dose (RP2D) for the durvalumab and tremelimumab combination was established in subjects with NSCLC, the safety profile of the combination in the NSCLC population is not directly generalizable to subjects with HCC. Based on the eligibility criteria for subjects with NSCLC treated with the durvalumab and tremelimumab combination, these subjects will not have HBV or HCV infections, or cirrhosis with compromised liver function/reserve. Therefore, careful risk-based exploration of the dose using sequential enrollment in a "safety run-in" in the HCC subject population is appropriate. In addition, a thorough understanding of the safety profile through monitoring and analysis of AEs, SAEs, ECGs, laboratory values (including liver and virology measurements), vital signs, and histologic information from biopsies of fresh tumor tissue and noncancerous liver tissue has been incorporated into assessments throughout the study.

Secondary Endpoints

Efficacy

The gold standard measurement of efficacy in an oncology Phase III study is OS. Given that the median OS of subjects with HCC treated with sorafenib is 10.7 months, it is expected that

subjects enrolled in this trial (progressed on, intolerant of, or refused sorafenib) will have an even shorter median OS. Therefore, additional efficacy endpoints of TTP, DoR, DCR, ORR, and PFS will be evaluated to support OS.

Candidate Biomarkers

Identification of a predictive biomarker could optimize the risk-to-benefit ratio for an immunotherapy combination, which has been associated with life-threatening toxicities. Given that durvalumab is a PD-L1 antagonist, understanding how the expression of the drug target correlates with tumor response is critical.

Exploratory Endpoints

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

3.2.4 Rationale for Interim Analysis Criteria

The goal of the interim analysis following completion of Part 1 enrollment is to determine if the durvalumab and tremelimumab combination has an appropriate benefit-risk ratio compared with either durvalumab or tremelimumab monotherapies. Given that the combination is expected to have a less desirable safety profile compared with the monotherapies, the combination must offer increased benefit compared with the monotherapies to adequately balance this risk. Therefore, the clinically "interesting" ORR has been set to ≥ 20% which is greater than the ORR observed for durvalumab monotherapy (5.7%; see durvalumab IB) or tremelimumab monotherapy (17.6%; Sangro et al, 2013). This ORR is also substantially greater than the ORR observed for sorafenib (2%; Llovet et al, 2008), the only approved agent for the treatment of HCC.

A subsequent interim analysis will be performed to assess futility and safety of the monotherapy arms (Arms B and C) and safety of the additional durvalumab and tremelimumab combination therapy arm (Arm D). The futility criteria as described in Section 4.8.7 for the monotherapy arms (Arms B and C) was chosen such that the risk of falsely stopping an effective treatment is < 5%.

For Part 4, an interim analysis will occur after approximately 100 subjects have had the opportunity for 18 weeks of follow-up. Another interim analysis will occur after approximately 100 subjects in Part 4 have had the opportunity for 36 weeks of follow-up. The main objective of this interim analysis is to assess the safety and efficacy of durvalumab in combination with bevacizumab. The primary efficacy endpoint is ORR assessed by BICR according to RECIST 1.1.

Additional interim analyses based on similar objectives may be performed to support the ongoing Phase III HCC development for Parts 1-3. No formal adjustments will be made to the significance level used for testing. The details of each analysis will be described in the SAP prior to database lock for any interim analysis.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Approximately 12 subjects in Part 1A, approximately 24 subjects in Part 1B, approximately 108 subjects in Part 2A, approximately 12 subjects in Part 2B, approximately 200 subjects in Part 3, and approximately 100 subjects in Part 4 will be enrolled globally.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male or female subjects; age ≥ 18 years (all countries except Japan) or ≥ 20 years (Japan only) at the time of screening.
2. Written informed consent and any locally required authorization, Health Insurance and Portability and Accountability Act in the US, European Union Data Privacy Directive in the European Union obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.
3. Confirmed HCC based on histopathological findings from tumor tissues. Advanced HCC with diagnosis confirmed pathologically or with noninvasive methods (as described below).

a. Noninvasive methods: focal lesion > 1 cm with arterial hypervascularity and venous or delayed phase washout on a 4 phase multi-detector computed tomography (CT) or dynamic contrast enhanced magnetic resonance imaging (MRI; Bruix and Sherman, 2011).

4. Immunotherapy-naive and have either progressed on, are intolerant to, or refused treatment with sorafenib or another approved VEGFR TKI.

   Part 4 only: Must not have received prior systemic therapy for HCC.

5. Child-Pugh Score class A.
6. ECOG performance status of 0 or 1.
7. Patients with HBV infection [as characterized by positive hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibodies (anti-HBcAb) with detectable HBV DNA (≥10 IU/ml)] must be treated with antiviral therapy, as per institutional practice, to ensure adequate viral suppression (HBV DNA ≤ 2000 IU/mL) prior to enrollment. Patients must remain on antiviral therapy for the study duration and for 6 months after the last dose of study medication. Patients who test positive for antiHBc with undetectable HBV DNA (<10 IU/ml) do not require anti-viral therapy prior to enrollment. These subjects will be tested at every cycle to monitor HBV DNA levels and initiate antiviral therapy if HBV DNA is detected (≥10 IU/ml). HBV DNA detectable subjects must initiate and remain on antiviral therapy for the study duration and for 6 months after the last dose of study medication.
8. Patients with HCV infection must have confirmed diagnosis of HCV characterized by the presence of detectable HCV RNA or anti-HCV antibody upon enrollment (management of this disease is per local institutional practice).
9. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines. Subjects in Part 1A, Part 1B, or Part 2A must consent to pretreatment biopsies of tumor. Subjects in Part 2B, Part 3 and Part 4 must provide a newly acquired (fresh or acquired within 3 months, preferred) or archival (< 3 years) tumor sample.
10. Consent to provide a newly acquired or archival tumor tissue (< 3 years) for correlative biomarker studies.
11. Adequate organ and marrow function, as defined below. Criteria “a,” “b,” “c,” and “f” cannot be met with transfusions, infusions, or growth factor support administered within 14 days of starting the first dose.
    a. Hemoglobin ≥ 9 g/dL
    b. Absolute neutrophil count ≥ 1,000/µL
    c. Platelet count ≥75000/µL
    d. Total bilirubin (TBL) ≤ 2.0 × ULN (Upper Limit of Normal)
    e. AST and ALT ≤ 5 × ULN
    f. Albumin ≥ 2.8 g/dL
    g. International Normalized Ratio ≤ 1.6

h. Calculated creatinine clearance ≥ 50 mL/minute as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine creatinine clearance

i. **Part 4 only**: Proteinuria < 2+. For patients with proteinuria ≥ 2+, further assessment of 24-hour proteinuria should be < 1 gram.

12. Females of childbearing potential who are sexually active with a non-sterilized male partner must use a highly effective method of contraception (Table 4.1.2-1) from the time of screening, and must agree to continue using such precautions for 90 days (durvalumab and tremelimumab monotherapy) or 180 days (durvalumab combined with tremelimumab) after the final dose of investigational product(s). Male partners of a female subject must use male condom plus spermicide (or male condom in countries where spermicides are not approved or available) throughout these periods. Cessation of contraception after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the study and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female subjects should refrain from breastfeeding throughout these periods.
    a. Females of childbearing potential are defined as those who are not surgically sterile (ie, have not undergone bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause). The following age-specific requirements apply to the definition of postmenopausal:
        i. Females < 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle stimulating hormone levels in the postmenopausal range for the institution.
        ii. Females ≥ 50 years of age will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced oophorectomy with last menses > 1 year ago, had chemotherapy-induced menopause with > 1 year interval since last menses, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    b. Highly effective methods of contraception are described in Table 4.1.2-1. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette®/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills); not all of these methods are approved or available in Japan (see Table 4.1.2-1).
13. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (see Table 4.1.2-1) from Day 1 through 90 days (durvalumab and tremelimumab monotherapy) or 180 days (durvalumab combined with tremelimumab) after receipt of

the final dose of investigational product(s). Not engaging in sexual activity for the total duration of the study and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout these periods. Female partners of a male subject must use a highly effective method of contraception throughout these periods.

14. Body weight >30kg
15. Must have a life expectancy of at least 12 weeks

Table 4.1.2-1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	• Etonogestrel implants (eg, Implanon® or Norplant®) [b] • Intravaginal device (eg, ethinylestradiol and etonogestrel) • Medroxyprogesterone injection (eg, Depo-Provera®) [b] • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system [b] • Cerazette® (desogestrel) [b]

Note: A highly effective method of contraception is defined as one that results in a low failure rate (ie, < 1% per year) when used consistently and correctly.

[a] This is also considered a hormonal method.

[b] This hormonal method is not approved or available in Japan.

4.1.3 Exclusion Criteria

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

1. History of hepatic encephalopathy within past 12 months or requirement for medications to prevent or control encephalopathy (eg, no lactulose, rifaximin, etc if used for purposes of hepatic encephalopathy).
2. GI Bleeding (eg, esophageal varices or ulcer bleeding) within 12 months. (Note: For patients with a history of GI bleeding for more than 12 months or assessed as high risk for esophageal variceal by the Investigator, adequate endoscopic therapy according to institutional standards is required).
3. Clinically meaningful ascites defined as ascites requiring non-pharmacologic intervention (eg, paracentesis) to maintain symptomatic control, within 6 months prior to the first scheduled dose. Subjects on stable doses of diuretics for ascites for ≥ 2 months are eligible.

4. Main portal vein thrombosis (Vp4) as documented on imaging. (VP4 is defined as portal vein thrombosis in the main trunk of the portal vein or a portal vein branch contralateral to the primarily involved lobe (or both)).
5. Prior exposure to immunotherapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, or anti-PD-L1 mAbs.
6. Known allergy or hypersensitivity to study drug formulations.
7. Requires ongoing therapeutic anti-coagulation or anti-platelet therapy; the subject must be off either therapy for at least 7 days prior to the first dose of investigational product. Low-dose aspirin for cardiac prophylaxis/protection is permitted per local institutional standards.
8. Active or prior documented autoimmune or inflammatory disorders including inflammatory bowel disease (eg, colitis, Crohn's disease), diverticulitis, celiac disease, systemic lupus erythematosus; Wegener syndrome (granulomatosis with polyangitis); myasthenia gravis; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc. The following are exceptions to this criterion:
   a) Subjects with vitiligo or alopecia.
   b) Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
   c) Subjects with psoriasis or eczema not requiring systemic treatment.
9. Irritable bowel syndrome or other serious gastrointestinal chronic conditions associated with diarrhea within the past 3 years prior to the start of treatment.
10. Active infection including tuberculosis (TB) (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), or human immunodeficiency virus (positive human HIV 1/2 antibodies).
11. Patients co-infected with HBV and HCV, or co-infected with HBV and hepatitis D virus (HDV). HBV positive [presence of hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibodies (anti-HBcAb) with detectable HBV DNA (≥10IU/ml)]; HCV positive (presence of anti-HCV antibodies); HDV positive (presence of anti-HDV antibodies).
12. Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or the follow-up period of an interventional study.
13. Receipt of any conventional or investigational anticancer therapy not otherwise specified above within 28 days prior to the first dose of durvalumab or tremelimumab.
14. Any concurrent chemotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment with the exception of subjects on adjuvant endocrine therapy for ≥ 5 years for a history of breast cancer. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. In addition, local treatment (eg, by local surgery or radiotherapy) of isolated lesions for palliative intent is acceptable with prior consultation and in agreement with the medical monitor.
15. Any toxicity from prior therapy which has not completely resolved to baseline at the time of consent. Subjects with NCI CTCAE v4.03 Grade 1 or 2 toxicities that are deemed stable or irreversible can be enrolled on a case-by-case basis with prior consultation and agreement with the medical monitor.

16. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of IP. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical, or local steroid injections (eg, intra-articular injection).
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.
    - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).
17. History of primary immunodeficiency or solid organ transplantation.
18. Receipt of live, attenuated vaccine within 30 days prior to the first dose of investigational products (Note: Subjects, if enrolled, should not receive live vaccine during the study and 30 days after the last dose of investigational product[s]). Vaccination with a killed vaccine is permitted at any time with consultation with the medical monitor.
19. Female patients who are pregnant or breastfeeding, or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab (Durvalumab) monotherapy or 180 days after the last dose of durvalumab plus tremelimumab or bevacizumab combination therapy. Not engaging in sexual activity, as per the patient's preferred and usual lifestyle, for the total duration of the treatment and washout periods is an acceptable practice.
20. Major surgery (as defined by the investigator) within 28 days prior to first dose of IP or still recovering from prior surgery. Local procedures (eg, core needle biopsy, and prostate biopsy) are allowed if completed at least 3 days prior to the administration of the first dose of study treatment.
21. History of leptomeningeal carcinomatosis
22. Other invasive malignancy within 2 years except for noninvasive malignancies such as cervical carcinoma in situ, in situ prostate cancer, nonmelanomatous carcinoma of the skin, lobular or ductal carcinoma in situ of the breast that has been surgically cured.
23. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension (defined as systolic blood pressure $\geq$ 150 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg, with or without antihypertensive medication), unstable angina pectoris, cardiac arrhythmia, vena cava thrombosis, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from IP, or compromise the ability of the subject to give written informed consent.
24. Any condition that, in the opinion of the investigator or sponsor, would interfere with evaluation of the investigational products or interpretation of subject safety or study results.
25. Subjects who are involuntarily incarcerated or are unable to willingly provide consent or are unable to comply with the protocol procedures.
26. History of, or current, brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT, each preferably with IV contrast of the brain prior to study entry.

Additional Exclusion Criteria Specific to Part 4 Only

27. Clinically significant (eg, active) cardiovascular disease, including:
    - Myocardial infarction or unstable angina within ≤6 months of randomization
    - New York Heart Association Grade≥ 2 congestive heart failure
    - Poorly controlled cardiac arrhythmia despite medication (patient with rate controlled atrial fibrillation are eligible), or any clinically significant abnormal finding on resting ECG
    - Peripheral vascular disease Grade ≥3 (eg, symptomatic and interfering with activities of daily living requiring repair or revision)
    - Previous cerebrovascular accident, transient ischemic attack, or sub-arachnoids hemorrhage within 6 months prior to randomization
28. Known hereditary predisposition to bleeding or thrombosis; History of arterioembolic event including a stroke or myocardial infarction
29. Non-healing wound, active ulcer, or bone fracture. Patients with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection are eligible but require wound examinations every 3 weeks.

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive response system [IXRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not receive investigational products. There can be no exceptions to this rule. Subjects who are screening failures should be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is randomized in error or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately

documented, and that the potential benefit:risk profile remains positive for the patient.

If sites want to re-screen a screen failed patient, sites should discuss with study physician first. Patients may be rescreened a single time, but they may not be re-randomized. If a screen failed patient is re-screened, a new subject number must be assigned.

Refer to Section 4.6.1 for assignment of treatment groups.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator. AEs will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.5.1 Survival Status for Withdrawn Consent and Lost to Follow-Up Patients

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 6.3), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status.
- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product(s) if any of the following occur in the subject in question:

1. Withdrawal of consent from further participation in the study
2. Lost to follow-up
3. An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
4. Any AE that meets criteria for discontinuation as defined in Section 3.1.3 and in the Dosing Modification and Toxicity Management Guidelines. In the opinion of investigator, if the AE is attributed to bevacizumab, only bevacizumab should be discontinued. If the AE is attributed to durvalumab, both durvalumab and bevacizumab should be discontinued.
5. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational product(s) might constitute a safety risk
6. Pregnancy or intent to become pregnant
7. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
8. Initiation of alternative anticancer therapy including another investigational agent
9. Confirmed PD and subject not eligible for retreatment. [Note: subjects with confirmed PD who, in the investigator's opinion, continue to receive benefit from their assigned treatment and meet the criteria for treatment through progression may continue to receive their assigned therapy after discussion with study physician.]

Subjects who are permanently discontinued from receiving investigational product(s) regardless of the reason (withdrawal of consent from further treatment, due to an AE, other), will be identified as having permanently discontinued treatment and will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn specifically from further study participation; the subject is lost to follow-up.

All subjects will be followed for survival until the end of the study. Subjects who decline to return to the site for evaluations should be contacted by phone every 3 months to assess for survival unless consent is withdrawn.

4.1.7 Replacement of Subjects

Subjects in Part 1A who do not remain on study for the 4-week observation period will be replaced. Subjects in Part 1B, Part 2A, and Part 2B of the study may be replaced if they discontinue prior to receiving the first dose of study medication. Subjects randomized in Part 3 and Part 4 will not be replaced.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Genetic Research or Future Research

Samples obtained for genetic research or future research will be labeled with a sample identification number linked to the SID number but will not be labeled with personal identifiers such as the subject's name. If the subject withdraws consent for participating in the genetic research or future research, the sponsor will locate the subject's sample and destroy it. Genetic research refers to the analysis of germline DNA in the blood and does not include assessment of mutations specific for the tumor that are part of the main study. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her sample(s) used for genetic research or future research, this additional research may not start immediately and may start at any time during the storage period. CCI [redacted] Samples obtained for future use will not be subject to any unknown, experimental research that is not related to the objectives of this study and that is not specified in the protocol. Subjects will not be asked to provide samples for future research that are not requested as part of the conduct of the main study. CCI [redacted] The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for genetic research or future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for genetic research or future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research or future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

If sites want to re-screen a screen failed patient, sites should discuss with study physician first. Patients may be rescreened a single time, but they may not be re-randomized. If a screen failed patient is re-screened, a new subject number must be assigned.

Table 4.2.1-1 shows all procedures to be conducted at the screening visit.

Table 4.2.1-1 Schedule of Screening/Baseline Procedures

Procedure	Screening/Baseline
	Days -14 to -1
Written informed consent/assignment of SID number [a]	X
Verify eligibility criteria	X
Tumor and disease assessments	
History of prior cancer treatment	X
Disease assessment by investigator assessments using RECIST v1.1 (CT or MRI) [a] including appropriate tumor markers (eg, CCI	X
BCLC classification	X
Study procedures and examinations	
Demographics (including age, sex, race, ethnicity) and alcohol use	X
Medical history	X
Assessment of Child-Pugh Score	X
Physical examination, including height, weight	X
ECOG performance status	X
12-lead ECG [b]	X
Vital signs (temperature, BP, respiratory rate, heart rate, pulse oximetry)	X
Assessment of AEs/SAEs (related to study/baseline procedures)	X
Concomitant medications	X
Laboratory tests	
Serum chemistry (Section 4.3.4)	X

Table 4.2.1-1 Schedule of Screening/Baseline Procedures

Procedure	Screening/Baseline
	Days -14 to -1
Hematology (Section 4.3.4)	X
Coagulation (PT, INR)	X
Thyroid function tests (TSH, free T_3, and free T_4)	X
Urinalysis	X
Markers of menopause for females who require laboratory testing per inclusion criterion #12, Section 4.1.2	X
Serum pregnancy test (for women of childbearing age)	X
Subjects with known diagnosis of hepatitis B: qualitative HBsAg, qualitative HBeAg, anti-HBc, anti-HBs, anti-HBe, quantitative HBV DNA, anti-HCV, and anti-HDV	X
Subjects with known diagnosis of hepatitis C: HCV RNA, HCV genotype [c], anti-HCV, qualitative HBsAg, and anti-HBc	X
Subjects without known diagnosis of hepatitis B or C: HCV RNA, anti-HCV, qualitative HBsAg, quantitative HBV DNA, anti-HBc, and anti-HBs	X
HIV	X
Vitamin D	X
Other laboratory tests and assays	
Archival tumor sample (if available)	X
Fresh tumor tissue biopsy [a,d]	X
Fresh noncancerous liver tissue biopsy [a,d,e]	X
CCI [redacted]	

AE = adverse event; CCI [redacted] anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; BP = blood pressure; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HIV = human immunodeficiency virus; INR = international normalized ratio; CCI [redacted] MRI = magnetic resonance imaging; CCI [redacted] PT = prothrombin; RECIST = Response Evaluation Criteria in Solid Tumors; CCI [redacted] SAE = serious adverse event; SID = subject identification; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] Informed consent, disease assessments, and collection of fresh biopsy samples can be performed from Days -28 to -1; informed consent must be obtained prior to the subject undergoing any screening procedures; however, if laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization. Subjects enrolled in Part 2B or Part 3 are required to submit a newly acquired (fresh or acquired within 3 months, preferred) or archival (< 3 years) tumor sample.

[b] ECGs should be obtained after the subject has been in a supine position for 5 minutes and recorded while the subject remains in that position.

[c] Only for subjects without a known genotype at screening.

Table 4.2.1-1 Schedule of Screening/Baseline Procedures

Procedure	Screening/Baseline
	Days -14 to -1

[d] Collection of noncancerous liver tissue at screening is also requested if it can be done safely (as judged by the investigator) during the same procedure in which the fresh tumor tissue biopsy is obtained.

[e] CCI [redacted]

[f] Part 4 only: flow cytometry will not be collected for patients enrolled into Part 4.

4.2.2 Treatment Period

Procedures to be conducted during the treatment period are presented in Table 4.2.2-1 for Weeks 1 to 25 and in Table 4.2.2- for Week 29 through end of treatment. At study visits when subjects do not receive investigational product(s), all of the pre-treatment assessments will be performed.

The timing of ECGs and vital sign assessments should be such that it allows the blood draw CCI [redacted] to occur at the exact nominal time. All samples are collected pre-dose unless otherwise indicated. If a subject undergoes retreatment with the combination of durvalumab and tremelimumab, the timing and type of assessments "resets" to Week 1, Day 1. CCI [redacted]

Table 4.2.2-1 Schedule of Treatment Period Study Procedures Weeks 1 to 25 - Parts 1-3 ONLY

Study Period	Treatment Period: Weeks 1 to 25												
Week/Day	**W1 D1**	**W3 D1 ± 1D**	**W5 D1 ± 3D**	**W7 D1 ± 3D**	**W9 D1 ± 3D**	**W11 D1 ± 3D**	**W13 D1 ± 3D**	**W15 D1 ± 3D**	**W17 D1 ± 3D**	**W19 D1 ± 3D**	**W21 D1 ± 3D**	**W23 D1 ± 3D**	**W25 D1 ± 3D**
Randomization/enrollment	X												
Tumor and disease assessments													
Disease assessment by RECIST v1.1(CT or MRI) [a]					X				X				X
Tumor markers CCI	X [c]	X	X	X	X	X	X	X	X	X	X	X	X
Fresh tumor biopsy (optional) [b]			X										
Study procedures and examinations													
Physical examination	X [c]	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Child-Pugh Score	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X [c]				X				X				X
12-lead ECG [d]	As clinically indicated												
Vital signs [e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests													
Serum chemistry (see Section 4.3.4 for a list of tests)	X [c]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology (see Section 4.3.4 for a list of tests)	X [c]	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation (PT, INR)	X [c]	X	X	X	X	X	X	X	X	X	X	X	X
CCI and qualitative HBeAg [f], anti-HBe [g] (HBV+ subjects only)	X [h, c]		X		X		X		X		X		X
CCI			X		X		X		X		X		X
Thyroid function tests (TSH, free T_3, free T_4)	X [c]		X		X		X		X		X		X
Urinalysis	X [c]		X		X		X		X		X		X

Table 4.2.2-1 Schedule of Treatment Period Study Procedures Weeks 1 to 25 - Parts 1-3 ONLY

Study Period	Treatment Period: Weeks 1 to 25												
Week/Day	**W1 D1**	**W3 D1 ± 1D**	**W5 D1 ± 3D**	**W7 D1 ± 3D**	**W9 D1 ± 3D**	**W11 D1 ± 3D**	**W13 D1 ± 3D**	**W15 D1 ± 3D**	**W17 D1 ± 3D**	**W19 D1 ± 3D**	**W21 D1 ± 3D**	**W23 D1 ± 3D**	**W25 D1 ± 3D**
Urine or serum pregnancy test (for females of childbearing potential)	X [c]		X		X		X		X		X		X
CCI													
CCI													
Other laboratory tests and assays													
CCI													

Table 4.2.2-1 Schedule of Treatment Period Study Procedures Weeks 1 to 25 - Parts 1-3 ONLY

Study Period	Treatment Period: Weeks 1 to 25												
Week/Day	**W1 D1**	**W3 D1 ± 1D**	**W5 D1 ± 3D**	**W7 D1 ± 3D**	**W9 D1 ± 3D**	**W11 D1 ± 3D**	**W13 D1 ± 3D**	**W15 D1 ± 3D**	**W17 D1 ± 3D**	**W19 D1 ± 3D**	**W21 D1 ± 3D**	**W23 D1 ± 3D**	**W25 D1 ± 3D**
Investigational product(s) administration													
Durvalumab administration (monotherapy and combination therapy) [n]	X		X		X		X		X		X		X
Tremelimumab administration (as monotherapy) [n]	X		X		X		X		X		X		X
Tremelimumab administration (combination therapy, Tx4)	X		X		X		X						
Tremelimumab administration (combination therapy, Tx1)	X												

AE = adverse event; [CCI] anti-HBe = hepatitis B e antibody; CT = computed tomography; D = day; [CCI] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; HBeAg = hepatitis B e antigen; [CCI] INR = international normalized ratio; [CCI] MRI = magnetic resonance imaging; [CCI] PT = prothrombin; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; T = tremelimumab; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone; W = week.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of durvalumab /tremelimumab unless otherwise indicated. On nontreatment days, all of the pre-treatment assessments will be performed.

Note: [CCI]

[a] Disease assessments should occur ± 7 days of visit. Imaging of the chest and abdomen (head and neck, and pelvic scans are optional unless disease is known to be present at these sites at baseline) will be performed. Imaging of hepatic tumors should be collected in the hepatic arterial, portal venous, and delayed phases following IV contrast administration. Subjects who meet the criteria for retreatment will have disease assessments performed at the same schedule as the original treatment period.

[b] Post-dose noncancerous liver tissue biopsies are not required.

[c] If assessments are performed within 3 days prior to Dose 1, they do not need to be repeated.

[d] Any clinically significant abnormalities detected require triplicate ECG results.

[e] Vital signs (temperature, blood pressure, pulse rate, pulse oximetry, and respiratory rate) will be measured on durvalumab and tremelimumab (monotherapy and combination) treatment days. Vital signs will be measured within 30 minutes prior to the start of infusion for all subjects in all treatment arms. For subjects receiving either durvalumab or tremelimumab as monotherapy (Arms B and C of Part 2A and Arms B and C of Part 3, or

Table 4.2.2-1 Schedule of Treatment Period Study Procedures Weeks 1 to 25 - Parts 1-3 ONLY

Study Period	Treatment Period: Weeks 1 to 25												
Week/Day	W1 D1	W3 D1 ± 1D	W5 D1 ± 3D	W7 D1 ± 3D	W9 D1 ± 3D	W11 D1 ± 3D	W13 D1 ± 3D	W15 D1 ± 3D	W17 D1 ± 3D	W19 D1 ± 3D	W21 D1 ± 3D	W23 D1 ± 3D	W25 D1 ± 3D

combination arms after the last dose of tremelimumab), vital signs will be measured every 15 minutes (± 5 minutes) during the infusion (eg, 15-, 30-, and 45-minute collection times), at EOI (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI. For subjects receiving combination treatment (Part 1A; Part 1B; Arm A of Part 2A; Part 2B; and Arms A and D of Part 3 prior to last dose of tremelimumab), vital signs will be measured every 15 minutes (± 5 minutes) during the infusion of tremelimumab, at EOI of tremelimumab (+ 5 minutes), and at 30 and 60 minutes post EOI of tremelimumab (immediately prior to the start of the durvalumab infusion). For subjects receiving combination treatment, vital signs will also be measured every 15 minutes (± 5 minutes) during the infusion of durvalumab, at EOI durvalumab (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI of durvalumab. For the first day of administration of investigational product, an additional 2-hour (± 15 minutes) post EOI period of observation will be required following the 60 minutes (± 5 minutes) post EOI assessment of vital signs for all arms. For subjects receiving combination treatment, this will occur following the 60 minutes (± 5 minutes) post EOI assessment of vital signs of durvalumab. For subsequent doses, the additional 2-hour observation period will not be required unless clinically indicated (eg, subject experiences an infusion reaction).

f Only required if test was positive at baseline.

g Only required if subject is HBeAg positive at baseline.

h CCI

i CCI

j CCI

k CCI

l CCI

m CCI

n See Section 4.5.1.4 for description of investigational product administration.

o CCI

p CCI

Table 4.2.2-1 Schedule of Treatment Period Study Procedures Weeks 1 to 25 - Parts 1-3 ONLY

Study Period	Treatment Period: Weeks 1 to 25												
Week/Day	W1 D1	W3 D1 ± 1D	W5 D1 ± 3D	W7 D1 ± 3D	W9 D1 ± 3D	W11 D1 ± 3D	W13 D1 ± 3D	W15 D1 ± 3D	W17 D1 ± 3D	W19 D1 ± 3D	W21 D1 ± 3D	W23 D1 ± 3D	W25 D1 ± 3D
CCI													
q CCI													
r CCI													

Table 4.2.2-2 Schedule of Treatment Period Study Procedures Weeks 1 to 25 – PART 4 ONLY

Study Period	Treatment Period: Weeks 1 to 25								
Week/Day	W1 D1	W4 D1 ± 1D	W7 D1 ± 3D	W10 D1 ± 3D	W13 D1 ± 3D	W16 D1 ± 3D	W19 D1 ± 3D	W22 D1 ± 3D	W25 D1 ± 3D
Randomization/enrollment	X								
Tumor and disease assessments									
Disease assessment by RECIST v1.1(CT or MRI) [a]				X			X		
Tumor markers CCI	X [c]	X	X	X	X	X	X	X	X
Study procedures and examinations									
Physical examination	X [c]	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Assessment of Child-Pugh Score	X	X	X	X	X	X	X	X	X
ECOG performance status	X [c]		X		X		X		X

Table 4.2.2-2 Schedule of Treatment Period Study Procedures Weeks 1 to 25 – PART 4 ONLY

Study Period	Treatment Period: Weeks 1 to 25								
Week/Day	**W1 D1**	**W4 D1 ± 1D**	**W7 D1 ± 3D**	**W10 D1 ± 3D**	**W13 D1 ± 3D**	**W16 D1 ± 3D**	**W19 D1 ± 3D**	**W22 D1 ± 3D**	**W25 D1 ± 3D**
12-lead ECG [d]	As clinically indicated								
Vital signs [e]	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Laboratory tests									
Serum chemistry (see Section 4.3.4 for a list of tests)	X [c]	X	X	X	X	X	X	X	X
Hematology (see Section 4.3.4 for a list of tests)	X [c]	X	X	X	X	X	X	X	X
Coagulation (PT, INR)	X [c]	X	X	X	X	X	X	X	X
CCI and qualitative HBeAg [f], anti-HBe [g] (HBV+ subjects only)	X [c]	X	X	X	X	X	X	X	X
CCI		X	X	X	X	X	X	X	X
Thyroid function tests (TSH, free T_3, free T_4)	X [c]	X	X	X	X	X	X	X	X
Urinalysis[k]	X [c]	X	X	X	X	X	X	X	X
Urine or serum pregnancy test (for females of childbearing potential)	X [c]	X	X	X	X	X	X	X	X
CCI									
CCI									
Other laboratory tests and assays									
CCI									

Table 4.2.2-2 Schedule of Treatment Period Study Procedures Weeks 1 to 25 – PART 4 ONLY

Study Period	Treatment Period: Weeks 1 to 25								
Week/Day	W1 D1	W4 D1 ± 1D	W7 D1 ± 3D	W10 D1 ± 3D	W13 D1 ± 3D	W16 D1 ± 3D	W19 D1 ± 3D	W22 D1 ± 3D	W25 D1 ± 3D
CCI [redacted]									
Durvalumab and bevacizumab administration [i]	X	X	X	X	X	X	X	X	X

AE = adverse event; CCI [redacted] anti-HBe = hepatitis B e antibody; CT = computed tomography; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; HBeAg = hepatitis B e antigen; CCI [redacted] INR = international normalized ratio; CCI [redacted] MRI = magnetic resonance imaging; CCI [redacted] PT = prothrombin; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone; W = week.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of durvalumab /bevacizumab unless otherwise indicated. On nontreatment days, all of the pre-treatment assessments will be performed.

[a] Disease assessments should occur ± 7 days of visit. Imaging of the chest and abdomen (head and neck, and pelvic scans are optional unless disease is known to be present at these sites at baseline) will be performed. Imaging of hepatic tumors should be collected in the hepatic arterial, portal venous, and delayed phases following IV contrast administration. Subjects who meet the criteria for retreatment will have disease assessments performed at the same schedule as the original treatment period.

[b] If assessments are performed within 3 days prior to Dose 1, they do not need to be repeated.

[c] Any clinically significant abnormalities detected require triplicate ECG results.

[d] Vital signs (temperature, blood pressure, pulse rate, pulse oximetry, and respiratory rate) will be measured within 30 minutes prior to the start of infusion. BP and pulse will be measured every 15 minutes (± 5 minutes) during the infusion of bevacizumab, at EOI of bevacizumab (+ 5 minutes), and at 30 and 60 minutes post EOI of bevacizumab (immediately prior to the start of the durvalumab infusion). BP and pulse will also be measured every 15 minutes (± 5 minutes) during the infusion of durvalumab, at EOI durvalumab (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI of durvalumab. For the first day of administration of investigational products, an additional 2-hour (± 15 minutes) post EOI period of observation will be required, i.e. total 3-hour observation after EOI of durvalumab. For subsequent doses, the additional 2-hour observation period will not be required unless clinically indicated (eg, subject experiences an infusion reaction).

Table 4.2.2-2 Schedule of Treatment Period Study Procedures Weeks 1 to 25 – PART 4 ONLY

Study Period	Treatment Period: Weeks 1 to 25								
Week/Day	W1 D1	W4 D1 ± 1D	W7 D1 ± 3D	W10 D1 ± 3D	W13 D1 ± 3D	W16 D1 ± 3D	W19 D1 ± 3D	W22 D1 ± 3D	W25 D1 ± 3D

[e] Only required if test was positive at baseline.

[f] Only required if subject is HBeAg positive at baseline.

[g] CCI [redacted]

[h] See Section 4.5.1.4 for description of investigational product administration.

[i] CCI [redacted]

[j] Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Table 4.2.2-3 Schedule of Treatment Period Study Procedures Week 29 to End of Study - Parts 1-3 ONLY

Study Period	Treatment Period: Week 29 to End of Study						
Week/Day	**W29 D1 ± 3D**	**W33 D1 ± 3D**	**W37 D1 ± 3D**	**W41 D1 ± 3D**	**W45 D1 ± 3D**	**W49 D1 ± 3D**	**Continua-tion**
Tumor and disease assessments							
Disease assessment by RECIST v1.1 (CT or MRI) [a]		X		X		X	Q8W
Tumor markers CCI	X	X	X	X	X	X	Q4W
Study procedures and examinations							
Physical examination	X	X	X	X	X	X	Q4W
Assessment of Child-Pugh Score	X	X	X	X	X	X	Q4W
ECOG performance status		X		X		X	Q8W
Vital signs (durvalumab monotherapy) [b]	X	X	X	X	X	X	Q4W
Vital signs (tremelimumab monotherapy and combination therapy) [b]	X	X	X	X	X	X	Q4W
Assessment of AEs/SAEs (durvalumab monotherapy)	X	X	X	X	X	X	Q4W
Assessment of AEs/SAEs (tremelimumab monotherapy and combination therapy)	X	X	X	X	X	X	Q4W
Concomitant medications (durvalumab monotherapy)	X	X	X	X	X	X	Q4W
Concomitant medications (tremelimumab monotherapy and combination therapy)	X	X	X	X	X	X	Q4W
Laboratory tests							
Serum chemistry (durvalumab monotherapy; see Section 4.3.4 for a list of tests)	X	X	X	X	X	X	Q4W
Serum chemistry (tremelimumab monotherapy and combination therapy; see Section 4.3.4 for a list of tests)	X	X	X	X	X	X	Q4W
Hematology (durvalumab monotherapy; see Section 4.3.4 for a list of tests)	X	X	X	X	X	X	Q4W

Table 4.2.2-3 Schedule of Treatment Period Study Procedures Week 29 to End of Study - Parts 1-3 ONLY

Study Period	Treatment Period: Week 29 to End of Study						
Week/Day	**W29 D1 ± 3D**	**W33 D1 ± 3D**	**W37 D1 ± 3D**	**W41 D1 ± 3D**	**W45 D1 ± 3D**	**W49 D1 ± 3D**	**Continuation**
Hematology (tremelimumab monotherapy and combination therapy; see Section 4.3.4 for a list of tests)	X	X	X	X	X	X	Q4W
Coagulation (PT, INR) (durvalumab monotherapy)	X	X	X	X	X	X	Q4W
Coagulation (PT, INR) (tremelimumab monotherapy and combination therapy)	X	X	X	X	X	X	Q4W
CCI qualitative HBeAg [c], anti-HBe [d] (HBV+ subjects only)	X	X	X	X	X	X	Q4W
CCI	X	X	X	X	X	X	Q4W
Thyroid function tests (TSH, free T_3, free T_4)	X	X	X	X	X	X	Q4W
Urinalysis	X	X	X	X	X	X	Q4W
Urine or serum pregnancy test (for females of childbearing potential)	X	X	X	X	X	X	Q4W
Investigational product(s) administration							
Durvalumab administration (monotherapy and combination therapy)	X	X	X	X	X	X	Q4W
Tremelimumab administration (as monotherapy)			X			X	Q12W

AE = adverse event; CCI anti-HBe = hepatitis B e antibody; CT = computed tomography; D = day; DNA = deoxyribonucleic acid; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; HBeAg = hepatitis B e antigen; CCI INR = international normalized ratio; MRI = magnetic resonance imaging; CCI PT = prothrombin; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone; W = week.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of durvalumab /tremelimumab unless otherwise indicated.

[a] Disease assessments should occur ± 7 days of visit. Imaging of the chest and abdomen (head and neck, and pelvic scans are optional unless disease is known to be present at these sites at baseline) will be performed. Imaging of hepatic tumors should be collected in the hepatic arterial, portal venous, and delayed phases following IV contrast administration. Subjects who meet the criteria for retreatment will have disease assessments performed at the same schedule as the original treatment period.

[b] Vital signs (temperature, blood pressure, pulse rate, pulse oximetry, and respiratory rate) will be measured on durvalumab and tremelimumab (monotherapy and combination) treatment days. Vital signs will be measured within 30 minutes prior to the start of infusion for all subjects in all treatment arms. For subjects receiving either durvalumab or tremelimumab as monotherapy (Arms B and C of Part 2A and Arms B and C of Part 3 or combination arms after the last dose of tremelimumab), vital signs will be measured every 15 minutes (± 5 minutes) during the infusion (eg, 15-, 30-, and 45-minute collection times), at EOI (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI. For subjects receiving combination treatment (Part 1A; Part 1B; Arm A of Part 2A; Part 2B; and Arms A and D of Part 3 prior to last dose of tremelimumab), vital signs will be measured every 15 minutes (± 5 minutes) during the infusion of tremelimumab, at EOI of tremelimumab (+ 5 minutes), and at 30 and 60 minutes post EOI of tremelimumab (immediately prior to the start of the durvalumab infusion). For subjects receiving combination treatment, vital signs will also be measured every 15 minutes (± 5 minutes) during the infusion of durvalumab, at EOI durvalumab (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI of durvalumab. For subsequent doses, the additional 2-hour observation period will not be required unless clinically indicated (eg, subject experiences an infusion reaction).

[c] Only required if test was positive at baseline.

[d] Only required if subject is HBeAg positive at baseline.

[e] CCI

[f] CCI

Table 4.2.2-4 Schedule of Treatment Period Study Procedures Week 28 to End of Study – PART 4 ONLY

Study Period	Treatment Period: Week 28 to End of Study							
Week/Day	W28 D1 ± 3D	W31 D1 ± 3D	W34 D1 ± 3D	W37 D1 ± 3D	W40 D1 ± 3D	W43 D1 ± 3D	W46 D1 ± 3D	Continuation
Tumor and disease assessments								
Disease assessment by RECIST v1.1 (CT or MRI) [a]	X			X			X	Q9W
Tumor markers CCI	X	X	X	X	X	X	X	Q3W
Study procedures and examinations								
Physical examination	X	X	X	X	X	X	X	Q3W
Weight	X	X	X	X	X	X	X	Q3W
Assessment of Child-Pugh Score	X	X	X	X	X	X	X	Q3W
ECOG performance status		X		X		X		Q6W
Vital signs [b]	X	X	X	X	X	X	X	Q3W
Assessment of AEs/SAEs	X	X	X	X	X	X	X	Q3W
Concomitant medications	X	X	X	X	X	X	X	Q3W
Laboratory tests								
Serum chemistry (see Section 4.3.4 for a list of tests)	X	X	X	X	X	X	X	Q3W
Hematology (see Section 4.3.4 for a list of tests)	X	X	X	X	X	X	X	Q3W
Coagulation (PT, INR)	X	X	X	X	X	X	X	Q3W
CCI qualitative HBeAg [c], anti-HBe [d] (HBV+ subjects only)	X	X	X	X	X	X	X	Q3W
CCI	X	X	X	X	X	X	X	Q3W
Thyroid function tests (TSH, free T_3, free T_4)	X	X	X	X	X	X	X	Q3W
Urinalysis	X	X	X	X	X	X	X	Q3W
Urine or serum pregnancy test (for females of childbearing potential)	X	X	X	X	X	X	X	Q3W
Investigational product(s) administration								
Durvalumab and Bevacizumab administration	X	X	X	X	X	X	X	Q3W

AE = adverse event; CCI anti-HBe = hepatitis B e antibody; CT = computed tomography; D = day; CCI ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; HBeAg = hepatitis B e antigen; CCI INR = international normalized ratio; MRI = magnetic resonance imaging; CCI PT = prothrombin; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone; W = week.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of durvalumab/bevacizumab unless otherwise indicated.

[a] Disease assessments should occur ± 7 days of visit. Imaging of the chest and abdomen (head and neck, and pelvic scans are optional unless disease is known to be present at these sites at baseline) will be performed. Imaging of hepatic tumors should be collected in the hepatic arterial, portal venous, and delayed phases following IV contrast administration. Subjects who meet the criteria for retreatment will have disease assessments performed at the same schedule as the original treatment period.

[b] Vital signs (temperature, blood pressure, pulse rate, pulse oximetry, and respiratory rate) will be measured on durvalumab and bevacizumab treatment days. Vital signs will be measured within 30 minutes prior to the start of infusion for all subjects in all treatment arms. Vital signs will be measured every 15 minutes (± 5 minutes) during the infusion of bevacizumab, at EOI of bevacizumab (+ 5 minutes), and at 30 and 60 minutes post EOI of bevacizumab (immediately prior to the start of the durvalumab infusion). Vital signs will also be measured every 15 minutes (± 5 minutes) during the infusion of durvalumab, at EOI durvalumab (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI of durvalumab. For subsequent doses, the additional 2-hour observation period will not be required unless clinically indicated (eg, subject experiences an infusion reaction).

[c] Only required if test was positive at baseline.

[d] Only required if subject is HBeAg positive at baseline.

[e] CCI

4.2.3 Follow-up Period

Table 4.2.3-1 shows all procedures to be conducted during the end of treatment visit and follow-up period. Subjects will complete the end of treatment visit at the time the decision is made to discontinue treatment.

All subjects are to complete the end of treatment visit, all follow-up visits and be contacted for survival status in accordance with the Schedule of Study Procedures. However, if a subject discontinues from treatment and moves onto alternative anticancer treatment, the follow-up visits will no longer be required; however, survival follow-up assessments would be required as indicated in the Schedule of Study Procedures unless the subject withdraws consent for further survival follow-up. Survival follow-up will continue until the end of study as defined in Section 6.3.

Table 4.2.3-1 Schedule of End of Treatment and Follow-up Procedures

Study Period	EOT	Follow-up Period				
Procedure / Study Day or Month		**Day 30 Post-last Dose ± 3 Days**	**Day 60 Post-last Dose ± 3 Days**	**Day 90 Post-last Dose ± 7 Days**	**Q3M After Day 90 Post-last Dose up to Month 12 Post-last Dose ± 7 Days**	**Q6M After Month 12 Post-last Dose ± 14 Days**
Disease assessments						
Disease assessment by RECIST v1.1 (CT or MRI) [a]	X			X	X	X
Tumor markers CCI	X	X	X	X	X	X
Fresh tumor biopsy	X [b]					
Collect information regarding subsequent anticancer therapy		X	X	X	X	X
Survival status		X	X	X	X	X
Study procedures and examinations						
Physical examination	X	X	X	X		
Assessment of Child-Pugh Score	X	X	X	X		
ECOG performance status				X	X	X
Vital signs (temperature, blood pressure, pulse rate, pulse oximetry, and respiratory rate)	X	X	X	X		
Assessment of AEs/SAEs	X	X	X	X		
Concomitant medications	X	X	X	X		
Laboratory tests						
Serum chemistry (see Section 4.3.4 for a list of tests)	X	X	X	X		
Hematology (see Section 4.3.4 for a list of tests)	X	X	X	X		
Coagulation (PT, INR)	X	X	X	X		

Table 4.2.3-1 Schedule of End of Treatment and Follow-up Procedures

Study Period	EOT	Follow-up Period				
Procedure / Study Day or Month		**Day 30 Post-last Dose ± 3 Days**	**Day 60 Post-last Dose ± 3 Days**	**Day 90 Post-last Dose ± 7 Days**	**Q3M After Day 90 Post-last Dose up to Month 12 Post-last Dose ± 7 Days**	**Q6M After Month 12 Post-last Dose ± 14 Days**
CCI qualitative HBeAg [c], and anti-HBe [d] (HBV+ subjects only)	X	X	X	X		
CCI	X	X	X	X		
Thyroid function tests (TSH, free T_3, free T_4)	X	X	X	X		
Urinalysis	X	X	X	X		
Urine or serum pregnancy test (for women of childbearing potential)	X					
CCI						

AE = adverse event; CCI anti-HBe = hepatitis B e antibody; CT = computed tomography; CCI ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HBeAg = hepatitis B e antigen; CCI INR = international normalized ratio; MRI = magnetic resonance imaging; PD = progressive disease; CCI

Table 4.2.3-1 Schedule of End of Treatment and Follow-up Procedures

Study Period		Follow-up Period				
Procedure / Study Day or Month	EOT	Day 30 Post-last Dose ± 3 Days	Day 60 Post-last Dose ± 3 Days	Day 90 Post-last Dose ± 7 Days	Q3M After Day 90 Post-last Dose up to Month 12 Post-last Dose ± 7 Days	Q6M After Month 12 Post-last Dose ± 14 Days

PT = prothrombin; Q3M = every 3 months; Q6M = every 6 months; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

[a] Imaging of the chest and abdomen (head and neck, and pelvic scans are optional unless disease is known to be present at these sites at baseline) will be performed. Imaging of hepatic tumors should be collected in the hepatic arterial, portal venous, and delayed phases following IV contrast administration. Disease assessment will not be performed if EOT is for PD.

[b] Optional tumor biopsy collected once upon confirmed PD.

[c] Only required if test was positive at baseline.

[d] Only required if subject is HBeAg positive at baseline.

[e] CCI [redacted]

[f] The 90-day post-last dose of tremelimumab will be drawn at Week 25 Day 1 for subjects who complete all 4 cycles of tremelimumab dosing in combination with durvalumab. For subjects enrolled in Arm D of Part 2B and Arm D of Part 3 who receive only 1 dose of tremelimumab, the blood sample collected on Week 13 Day 1 will serve as the 90-day post-last dose sample for tremelimumab subjects who receive only 1 dose of tremelimumab in combination with durvalumab. Subjects who complete beyond 25 weeks of treatment will not be required to provide an additional 90-day post-last dose blood sample collection for tremelimumab during the designated follow-up period.

[g] CCI [redacted]

[h] CCI [redacted]

[i] CCI [redacted]

4.3 Description of Study Procedures

4.3.1 Efficacy

Tumor assessments will be based on investigator and BICR assessments according to RECIST v1.1 (Eisenhauer et al, 2009) and will be performed according to the schedule presented in Section 4.2. All subjects will be followed for survival according to the schedule in Table 4.2.3-1 through the end of the study as defined in section 6.3.

All original images used for RECIST tumor assessments, including unscheduled visit scans, are to be stored on digital hard media (e.g., CDs) at the Investigative site as source documents. Guidelines for image acquisition, de-identification, and transfer to an Imaging Contract Research Organization (CRO) appointed by AstraZeneca will be provided in a separate document by the imaging CRO. All images will be collected, quality checked, and stored centrally by the Imaging CRO. Images will be used for Blinded Independent Central Review (BICR) of tumors by RECIST 1.1 for Part 1, Part 2, and Part 3 patients, and will be retained for a potential future BICR by RECIST 1.1 for Part 4. The management of patients will be based in part on the results of the RECIST 1.1 assessments conducted by the Investigator.

Tumor assessments should include the following evaluations: physical examination (palpation) and CT or MRI scan of the chest and abdomen (head and neck, and pelvic scans are optional unless disease is known to be present at these sites at baseline). The choice of imaging for hepatic tumors should follow local institutional practice, eg, 3-phase CT or multiphase MRI. The same method is preferred for all subsequent tumor assessments.

Tumor markers specific for the disease under study (eg, CCI should be collected (at a minimum) as outlined in Section 4.2.

If the subject has known CNS metastases, a brain MRI with IV contrast is required at screening and at each post baseline assessment. If a subject becomes neurologically symptomatic during treatment outside of the setting where the subject has known CNS metastases, a brain MRI with IV contrast is required.

Tumor Evaluations

CT scan with contrast of the chest and abdomen (head and neck, and pelvis optional)

- CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.
- Head and neck, and pelvis scans are optional unless disease is known to be present at these sites at baseline. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.
- CT images of hepatic tumors should be collected in the hepatic arterial, portal venous, and delayed phases following IV contrast administration.
- If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study, then the recommended methods are as follows: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If an MRI cannot be performed, then CT without IV contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

MRI scans

- MRI of the chest and abdomen (head and neck, and pelvic scans are optional unless disease is known to be present at these sites at baseline) is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. MRI scans of hepatic tumors should be performed in the precontrast, hepatic arterial, portal venous, and delayed phases.
- The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen (and other anatomies such as head and neck and pelvis) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression, and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. CT of the chest is typically recommended over MRI due to significant motion artifacts (eg, heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this protocol to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Body scans should be performed with breath-hold scanning techniques if possible.

Isotopic bone scans (scintigraphy)

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

FDG-PET scan for RECIST v1.1 new lesions

- ^{18}F-Fluoro-deoxyglucose positron emission tomography (FDG-PET)/CTs may be used as a method for identifying new RECIST v1.1 lesions, according to the following algorithm: new lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose (FDG) uptake not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI then follow-up CT/MRI assessments should be continued, scheduled as per protocol, or clinically indicated in order to confirm new lesions.
- At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically-based efficacy assessments. It is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CTs for tumor measurements by RECIST v1.1. In exceptional situations, if a site can document that the CT performed as part of PET/CT examination is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT, then the CT portion of the PET/CT can be used for RECIST measurements. However, this is not recommended because the PET portion of the CT introduces additional PET data that may bias an investigator if it is not routinely or serially performed.

Physical examination

- Lesions detected by physical examination (palpation) will only be considered as non-target lesions if superficial, eg, skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (CT/MRI scan slice thickness recommended to be no greater than 5 mm)
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm in short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- **Target Lesions -** All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It is encouraged to prioritize selection of up to 2 arterial enhancing liver lesions over non-enhancing liver lesions as target lesions. Lymph nodes are collectively considered as a single organ. Bilateral organs (eg, adrenal glands) are considered as a single organ. Mutilobular or segmented organs (eg, liver) are considered as a single organ. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions -** It is possible to record multiple non-target lesions involving the same organ as a single item on the electronic case report form (eCRF; eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

4.3.1.1 Evaluation of Response by Response Evaluation Criteria in Solid Tumors

Tumor response will be assessed by RECIST v1.1. All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to the sponsor-appointed Contract Research Organization for quality control review and storage. A BICR of the images will be performed for part 1, part 2 and part 3 patients (the centralized storage of images from Part 4 will be retained for a potential future BICR). Results of these independent reviews will not be communicated to the investigators, and the management of subjects will be based solely upon the results of the RECIST v1.1 assessment conducted by the investigator.

Evaluation of Target Lesions

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).

- **Partial Response -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease -** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions may be considered progression.)
- **Stable Disease -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response -** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm in short axis).
- **Non-complete Response/Non-progressive Disease -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease -** Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in nonmeasurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from “trace” to “large,” an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of unequivocal new lesions is considered PD according to RECIST v1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive study treatment until confirmed PD as defined below.

Evaluation of Overall Response

Confirmation of CR, PR, as well as PD is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. If the next protocol scheduled scan is due within 2 weeks after the confirmatory scan was obtained, the protocol-scheduled scan does not need to be done. For subjects who are clinically stable, treatment will continue between the initial assessment of PD and an immediate subsequent scan with PD

(confirmation of immediate prior PD) (which is not required by RECIST v1.1; see below). These subjects may continue to receive durvalumab in combination with tremelimumab beyond confirmed PD (see below) and if investigators consider that subjects continue to receive benefit from treatment. In the absence of clinical deterioration, such modifications to the RECIST criteria may discourage the early discontinuation of durvalumab in combination with tremelimumab and provide a more complete evaluation of durvalumab in combination with tremelimumab antitumor activity than would be seen with conventional response criteria.

Table 4.3.1.1-1 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 4.3.1.1-1 Evaluation of Overall Response at a Single Timepoint by RECIST V1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response	No	Complete response
No target lesion [a]	Complete response	No	Complete response
Complete response	Not evaluable [b]	No	Partial response
Complete response	Non-complete response/ non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable [b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable
No target lesion [a]	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Defined as no target lesions at baseline.

[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

Confirmation of Progression

Confirmed objective PD refers to either of the following scenarios: 1) clinical progression/deterioration confirmed by a radiological scan if clinically feasible or 2) in the absence of significant clinical deterioration, radiologic PD by RECIST v1.1 followed by a second radiologic confirmation scan with an assessment of PD according to the specific confirmation of progression criteria listed below. RECIST v1.1 modified for confirmation of progression refers to scenario 2 above. The confirmatory scan should occur at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of PD according to RECIST v1.1.

Immediate prior radiologic progression would be considered confirmed if any of the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum of the diameters of target lesions compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in the sum of the diameters compared with the nadir
- *and/or* significant progression (worsening) of non-target lesions and/or of pre-existing new lesions at the immediate subsequent ("confirmatory") scan timepoint compared with the immediate prior timepoint
- *and/or* additional new unequivocal lesions at the immediate subsequent ("confirmatory") scan timepoint

Note: In order to have confirmed objective PD, there should be 2 consecutive assessments of PD; the first PD should be assessed by RECIST v1.1, and the second PD should be assessed using the confirmation of progression criteria listed above. If the first PD by RECIST v1.1 is not confirmed, assessments should continue until the next PD by RECIST v1.1, which, in turn, will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression. If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression. **If the first assessment of PD is not confirmed by the immediate subsequent scan, the investigator should not change the PD assessment of the prior scan.**

If a subject discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, the subject should still continue to be followed until confirmed objective disease progression.

If progression is not confirmed, in the absence of significant clinical deterioration, the subject should continue study drug and on-treatment assessments until the next assessment of PD, which will also require a follow-up confirmation scan.

4.3.1.2 CCI [redacted]

CCI [redacted]

[redacted]

4.3.2 Tissue Biopsies

4.3.2.1 Fresh Tissue Biopsies

Fresh tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible as determined by the investigator and are not obtained from sites that require significant risk procedures, which include, but are not limited to, biopsies of the brain, lung, mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel wall [refer to the definition of a significant risk device under §812.3(m) in the Investigational Device Exemptions regulation (21 CFR 812)].

At baseline, fresh tumor tissue biopsies will be attempted prior to administration of the first dose of investigational product(s) for all subjects in Part 1A, Part 1B, and Part 2A. For subjects in Part 2B and Part 3, newly acquired (fresh or acquired within 3 months, preferred) or archival (< 3 years) tumor samples will be required. Noncancerous liver tissue biopsies should also be attempted if they can be done safely (as judged by the investigator) during the same procedure in which the pretreatment fresh tumor tissue biopsies are obtained.

In addition, fresh tumor biopsies (noncancerous liver tissue is NOT required) will be obtained on Week 5 Day 1 (± 3 days) (optional) and upon confirmed PD (optional) if clinically feasible (ie, repeat biopsy does not pose unacceptable medical risk to a subject as determined by the investigator). Additional biopsies may also be performed if clinically indicated (eg, for mixed responses). For subjects requiring serial image-guided core needle tumor biopsy, those biopsies will be performed according to institutional practice.

If clinically practical, at each fresh tumor biopsy timepoint, subjects will undergo 4 core biopsies, but a minimum of at least 1 core biopsy is required. The first and third (if available) core biopsies will be placed in formalin and processed for formalin-fixed, paraffin-embedded blocks, while the second and fourth core biopsies (if available) will be immediately frozen in liquid nitrogen or equivalent method and then stored at -80°C (-112°F). In exceptional cases,

excisional or punch biopsies are permitted and may be substituted for the required minimum of 1 core biopsy if sufficiently large (4 mm or greater in diameter).

Baseline noncancerous liver tissue biopsies are requested to provide information regarding the histological status of the liver prior to administration of investigational product(s). If clinically feasible at the same procedure in which pretreatment fresh tumor tissue biopsies are obtained, subjects should undergo biopsy of noncancerous liver tissue per individual institutional standards. The noncancerous liver tissue biopsy will be processed per local institutional standards.

Tumor biopsies will be stored at MedImmune or an appropriate vendor selected by MedImmune. Core (tumor) biopsies may be used for correlative studies such as IHC, tumor DNA analysis (non-germline), RNA analysis, proteomic/protein analysis, and immunodiversity. Additional details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

4.3.2.2 Archival Tumor Samples

If possible, initial and subsequent archival tumor tissue should be provided. Archival tumor samples must be formalin fixed and embedded in paraffin blocks for IHC and additional correlative markers (eg, tumor DNA analysis [non-germline], RNA analysis, and immunodiversity). When an archival tumor block cannot be provided for this study, then only freshly cut sections should be provided as described in the Laboratory Manual.

4.3.3 Medical History, Physical Examination, Electrocardiogram, ECOG Performance Status, Child-Pugh Score, and Vital Signs

4.3.3.1 Medical History and Physical Examination

Physical examinations will be performed according to institutional guidelines on study days noted in Section 4.2, and will include assessments of weight; and height (at screening only).

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade and recorded as AEs in the eCRF. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the prestudy grade or below.

4.3.3.2 Electrocardiograms

ECGs (12-lead) will be recorded at screening and as clinically indicated throughout the study as noted in Section 4.2. ECGs should be obtained after the subject has been in a supine position for 5 minutes and recorded while the subject remains in that position. In case of

clinically significant ECG abnormalities, including a QT interval corrected using Fridericia's formula (QTcF) value > 470 milliseconds, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 5.1.

The same recorder will be used for each subject at each timepoint, if possible. Date and time settings should be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

Skin preparations should be thorough and electrode positions should be according to standard 12-lead ECG placement.

In this study lead V2 will be analyzed and reported as primary. Lead V5 will be analyzed, for all visits, as backup for the individual where analysis in lead V2 is not deemed possible for pre-dose or significant parts of whole visits or whole visits.

The following variables will be reported: heart rate, PR, RR, QRS and QT intervals from the primary lead of the digital 12-lead ECG.

4.3.3.3 ECOG Performance Status

Performance status as determined by the ECOG scale (Oken et al, 1982; Table 4.3.3.3-1) will be recorded in the eCRF per the schedule in Section 4.2.

Table 4.3.3.3-1 Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status Criteria
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, eg, light house work or 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

4.3.3.4 Child-Pugh Score

Cirrhosis severity as determined by the Child-Pugh score (Pugh et al, 1973) will be recorded in the eCRF per the schedule in Section 4.2.

Table 4.3.3.4-1 shows the modified Child-Pugh classification of liver disease severity according to the degree of ascites, serum concentrations of bilirubin and albumin, prothrombin time, and degree of encephalopathy. The severity of cirrhosis is classified as follows:

- Child-Pugh class A (well-compensated disease): score of 5 to 6
- Child-Pugh class B (significant functional compromise): score of 7 to 9
- Child-Pugh class C (decompensated disease): score of 10 to 15

Table 4.3.3.4-1 Child-Pugh Classification of Cirrhosis Severity

Parameter	Points Assigned		
	1	2	3
Ascites *	Absent	Slight	Moderate
Bilirubin	< 2 mg/dL (< 34.2 µmol/L)	2 to 3 mg/dL (34.2 to 51.3 µmol/L)	> 3 mg/dL (> 51.3 µmol/L)
Albumin	> 3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	< 2.8 g/dL (< 28 g/L)
Prothrombin time			
Seconds over control	< 4	4 to 6	> 6
INR	< 1.7	1.7 to 2.3	> 2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

INR = international normalized ratio.
*For Child-Pugh classification, ascites should be assessed primarily based on physical examination. For example, a thin rim of ascites detected only on CT scan but not detectable on physical examination by the treating investigator would be assigned to "Absent, 1 point" per standard clinical practice. However, if radiological findings are substantially inconsistent with physical examination, the ascites should be re-assessed carefully to confirm appropriate Child-Pugh classification for ascites.

4.3.3.5 Vital Signs

Vital signs (temperature, blood pressure [BP], pulse rate, pulse oximetry, and respiratory rate) will be measured on study days noted in Section 4.2.

4.3.4 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study. If the subject has completed any safety laboratory tests within 72 hours before Week 1 Day 1, they will not need to be repeated.

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed according to the schedules of procedures in Section 4.2:

Serum Chemistry

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Bicarbonate (not required in countries where this is not standard)
- AST
- ALT
- Alkaline phosphatase (ALP)
- Total bilirubin
- Direct bilirubin
- Lipase
- Gamma glutamyl transferase
- Lactic dehydrogenase
- Uric acid
- Creatinine
- Blood urea nitrogen
- Glucose
- Albumin
- Total protein
- Triglycerides
- Cholesterol
- Amylase
- Thyroid stimulating hormone, free thyroxine (T_4), free triiodothyronine (T_3)

Note for serum chemistries: Tests for AST, ALT, ALP, direct bilirubin, and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology

- White blood cell count with differential
- Hemoglobin
- Prothrombin time/international normalized ratio
- Activated partial thromboplastin time
- Platelet count
- Fibrinogen

Coagulation

- Prothrombin (PT)
- INR

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin
- Serum beta-human chorionic gonadotropin

Other Safety Tests

- HBsAg, HBeAg, hepatitis B core antibody, hepatitis B surface antibody, hepatitis B e antibody, IgM hepatitis B core antibody, hepatitis C antibody, hepatitis D antibody, hepatitis B DNA, hepatitis C RNA
- Human immunodeficiency virus antibodies

Other Tests

- CCI (only as outlined in Section 4)
- Vitamin D (to be collected and held for later testing)

4.3.5 CCI

CCI

4.3.6 CCI

CCI

4.3.7 CCI

CCI

CCI

[redacted]

4.3.8 Estimate of Volume of Blood to Be Collected

A total of approximately 51 mL of blood will be collected during the 14-day screening period for all screening tests performed in subjects without a known diagnosis of either HBV or HCV infection. No more than approximately 51 mL of blood will be drawn at any one protocol visit during treatment of this subpopulation of subjects.

For subjects with a known diagnosis of either HCV or HBV, approximately 51 and 52 each subgroup, respectively. No more than approximately 54 mL of blood will be drawn at any one protocol visit during treatment for both the HCV positive and HBV positive subjects, with the highest blood draws occurring on CCI collection days. At all other treatment visits no more than approximately 39 mL of blood is expected to be drawn for any subject. All tests

performed at the end of treatment visit will draw no more than approximately 25 mL of blood for all subjects. During the follow-up period, no more than approximately 38 mL of blood will be collected at any one follow-up visit in any of the subpopulations. The total volume to be collected will depend on the length of subject participation in the study as well as to which investigational treatment arm of study they are enrolled.

4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or terminate this study (or site) at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2. Subject enrollment is unsatisfactory
3. Noncompliance that might significantly jeopardize the validity or integrity of the study
4. Enrollment into Part 2 may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial to a given treatment

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory

authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centers.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Durvalumab	MedImmune	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0
Tremelimumab	MedImmune	Formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine HCl, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM EDTA, pH 5.5.
Bevacizumab	Roche	400-mg vial solution for infusion 25 mg/mL.

EDTA = ethylenediaminetetraacetic acid; HCl = hydrochloride; w/v = weight per volume.

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Commercially available 0.9% (weight per volume [w/v]) saline or 5% dextrose in water (D5W) will be supplied by each site. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy. All investigational products should be kept in a secure and dry place.

4.5.1.1 Dose Calculation

The dose will be calculated using the subject's Week 1 Day 1 weight for subjects enrolled in Part 1A, Part 1B, and Part 2A, and Part 4. Dose adjustments for each dose are only needed

for greater than 10% change in weight. Dosing day weight may be used for dose calculations instead of weight at Week 1 Day 1 per institutional standard.

For fixed-dose regimens: If a patient's weight falls to 30kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to *dosing specified below*, after consultation between the investigator and/or study physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the original assigned fixed

- Arm A, B, and D: durvalumab 1500 mg (20 mg/kg if weight ⩽30 kg)
- Arm A: Tremelimumab 75 mg (1 mg/kg if weight ⩽30 kg)
- Arm C: Tremelimumab 750 mg (10 mg/kg if weight ⩽30 kg)
- Arm D: Tremelimumab 300 mg: Not applicable
- Part 4: durvalumab 1120 mg (15mg/kg if weight ⩽30 kg)
- Part 4: bevacizumab 15mg/kg

Durvalumab

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

$$\text{Dose (mL)} = \frac{[\text{subject weight (kg)} \times \text{durvalumab dose level (mg/kg)}]}{50 \text{ mg/mL}}$$

Or for fixed dose:

$$\text{Dose (mL)} = \frac{\text{durvalumab dose level (mg)}}{50 \text{ mg/mL}}$$

where 50 mg/mL is durvalumab concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). If no institutional standard on dose calculations exists, then dose adjustments for each cycle are only needed for a greater than 10% change in weight.

Tremelimumab

The dose will be calculated using the following formula:

$$\text{Dose (mL)} = \frac{[\text{subject weight (kg)} \times \text{tremelimumab dose level (mg/kg)}]}{20 \text{ mg/mL}}$$

Or for fixed dose:

$$\text{Dose (mL)} = \frac{\text{tremelimumab dose level (mg)}}{\text{20 mg/mL}}$$

where 20 mg/mL is tremelimumab concentration.

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL). If no institutional standard on dose calculations exists, then dose adjustments for each cycle are only needed for a greater than 10% change in weight.

Bevacizumab

The dose will be calculated using the following formula:

$$\text{Dose (mL)} = \frac{[\text{subject weight (kg)} \times \text{bevacizumab dose level (mg/kg)}]}{\text{25 mg/mL}}$$

where 25 mg/mL is bevacizumab concentration.

4.5.1.2 Investigational Product Dose Preparation

Durvalumab

Durvalumab will be supplied by AstraZeneca 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 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. 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

Select the IXRS-assigned number of vials of investigational product required to prepare the subject's dose. The dose will be administered using an IV bag containing 0.9% weight/volume (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2 μm or 0.22 μm filter. Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard. The calculated volume of durvalumab is added to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag. Note for a fixed dose of 1500 mg, patient weight should be >30 kg.

Standard infusion time is one hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400 mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine-hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate and 0.02% (w/v) polysorbate 80; it has a pH of 5.5. The nominal fill volume is 20.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Product preparation of tremelimumab for administration with an IV bag

The dose of tremelimumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the tremelimumab vial to 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

Select the IXRS-assigned number of vials of investigational product required to prepare the subject's dose. The dose will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 μm or 0.22 μm filter.

Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard. The volume of tremelimumab is added to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. Note for a fixed dose of 75 mg, patient weight should be >30 kg.

Standard infusion time is one hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

Bevacizumab

Bevacizumab 15 mg/kg should be administered according to bevacizumab prescribing information and clinical practice. The total in-use storage time from needle puncture of bevacizumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If the in-use storage time exceeds these limits, a new dose must be prepared from new vials. Bevacizumab does not contain preservatives, and any unused portion must be discarded.

The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/mL (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 to 16.5 mg/mL. In the majority of the occasions, the necessary amount of bevacizumab can be diluted with 0.9% sodium chloride solution for injection to a total volume of 100 mL.

4.5.1.3 Investigational Product Inspection

Investigational products will be supplied to the site in vials in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton). Each vial selected for dose preparation should be inspected. If there are any defects noted with the investigational product(s), the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.6) for further instructions.

If there are any defects noted with the investigational products, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.6) for further instructions.

4.5.1.4 Treatment Administration

The first day of dosing is considered Day 1. The duration of durvalumab administration will be 1 hour (± 15 minutes) in duration. The IV infusion of tremelimumab will be 1 hour (± 15 minutes) in duration.

For durvalumab and tremelimumab combination therapy, tremelimumab will be administered first. durvalumab infusion will start 1 hour (± 15 minutes) after the end of the tremelimumab infusion.

Bevacizumab 15 mg/kg should be administered according to bevacizumab prescribing information and clinical practice. The initial bevacizumab dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. It should not be administered as an IV push or bolus. The bevacizumab infusion should start approximately 1 hour (maximum 2 hours) after the end of the Durvalumab infusion.

4.5.1.5 Monitoring of Dose Administration

Subjects will be monitored prior to, during, and after infusion of durvalumab, tremelimumab and bevacizumab. Vital signs (temperature, BP, pulse rate, pulse oximetry, and respiratory rate) will be measured on durvalumab and tremelimumab (monotherapy and combination), and durvalumab with bevacizumab combination treatment days as specified in Section 4.2.2.

In the event of ≤ Grade 2 infusion-related reaction, the infusion rate of durvalumab and tremelimumab may be decreased by 50% or temporarily interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing ≤ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate.

Primary prophylaxis against infusion-related reactions is not permitted during this study in order to avoid obscuring a potential safety signal and to enable a future assessment regarding whether premedications should be required for all subjects in future studies. However, at the discretion of the investigator, secondary prophylaxis (ie, prevention of infusion-related reaction following initial episode) is appropriate and will be permitted. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered per institutional standard at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, treatment with durvalumab and tremelimumab will be discontinued.

As with any mAb, allergic reactions to dose administration are possible. Therefore, 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.

All dosing visits are initially scheduled based on the date of Week 1 Day 1 dosing. Future dosing visits can be recalibrated based on actual dosing dates when necessary.

Subjects are to receive durvalumab monotherapy, durvalumab and tremelimumab combination therapy, tremelimumab monotherapy, or durvalumab with bevacizumab combination therapy doses within a 3-day visit window (unless dosing needs to be held for toxicity reasons). If the subject experiences a related toxicity, the management guidelines provided in Section 3.1.3 and the Dosing Modification and Toxicity Management Guidelines should be followed.

4.5.1.6 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department/AstraZeneca Japan representative (Japan only) by the site with further notification to the site monitor. All defects will be communicated to MedImmune/AstraZeneca Japan (Japan only) and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints (except Japan):

Email: PPD

Phone:

Fax:

Mail: MedImmune, LLC
Attn: Product Complaint Department
PPD
Gaithersburg, MD 20878, USA

4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local languages, as required (except Japan). For Japan, details are specified in the document explaining reconstitution and other handling procedures for the investigational products.

4.5.4 Storage

Store durvalumab, tremelimumab and bevacizumab at 2°C to 8°C (36°F to 46°F). Do not freeze.

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.5.6 Accountability

For all countries except Japan, the investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

For Japan, investigational product provided for this study will be used only as directed in the study protocol. The Investigational Product Storage Manager is responsible for managing investigational product from receipt by the study site until the return or destruction of all unused investigational product to the MedImmune representative.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

An IXRS will be used for assignment of investigational product. A subject is considered enrolled into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of investigational product to the subject.

Subjects in Part 2A of the study will be stratified based on viral status (HBV vs HCV vs uninfected) and PD-L1 expression (positive, negative, or non-evaluable) and assigned randomly 1:1:1 within each stratum to 1 of the 3 treatment arms (Arms A, B, and C) according to a randomization schedule. Subjects in Part 2B will be assigned to Arm D. Subjects in Part 3 will be stratified based on viral status (uninfected, HCV infected, or HBV infected) and TKI-based therapy (refusers or all others) and assigned randomly in a ratio of 2:2:1:2 to 1 of up to 4 treatment arms (Arms A, B, C, and D). Following protocol amendment 5, subjects in Part 3 will be assigned randomly in a ratio of 2:1:2 to 1 of up to 3 treatment arms (Arms B, C, and D). The randomization code will be produced by an independent statistician who is not part of study team. The IXRS will manage the number of HBV, HCV, uninfected, PD-L1-positive, and PD-L1-negative subjects randomized. Once approximately 36 subjects for one viral status cohort have been randomized into Part 2A, the IXRS will not allow enrollment of additional subjects for that viral status cohort.

The time between randomization/enrollment and the initiation of treatment should be as short as possible and no more than 1 business day. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

4.6.2 Methods for Ensuring Blinding

This is an open-label study.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 4.7.2. Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management [including palliative radiotherapy to non-target lesions after discussion with the medical monitor, etc]) should be used when necessary for all subjects. Inactivated viruses, such as those in the influenza vaccine are permitted.

4.7.2 Prohibited Concomitant Medications

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

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

1. Any investigational anticancer therapy other than those under investigation in this study
2. Monoclonal antibodies (mAbs) against CTLA-4, PD-1, or PD-L1 (other than those under investigation in this study)
3. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy after consultation with the medical monitor), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses 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 subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections

(eg, intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, food allergies, CT scan contrast hypersensitivity, chronic obstructive pulmonary disease, radiation, nausea, etc) are acceptable upon discussion with the medical monitor

5. Live attenuated vaccines during the study through 30 days after the last dose of investigational product
6. Drugs with laxative properties and herbal and natural remedies for constipation should be used with caution through 90 days after last dose of tremelimumab.
7. Herbal and natural remedies which may have immune-modulating effects should not be given concomitantly unless agreed by the Sponsor.
8. **Part 4 only**: Any anticoagulants and anti-platelet agents (Low molecular heparin is permitted).
9. Sunitinib should not be given concomitantly or through 90 days after the last dose of tremelimumab.
10. EGFR TKIs should not be given concomitantly and should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

4.8 Statistical Evaluation

4.8.1 General Considerations

For the purpose of generating the clinical study report, the final analysis for this study, which will include all study endpoints, will be performed 12 months after the first dose to the last patient in the study. The study populations are defined as follows:

- **As-treated Population** is defined as subjects who receive any dose of either investigational product(s).
- **Response Evaluable Population** is defined as all treated subjects who have a baseline tumor assessment and have measurable disease at baseline.

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan (SAP).

4.8.2 Sample Size and Power Calculations

The study consists of 5 parts. Part 1A is a safety run-in with initial enrollment of 6 uninfected or HCV+ subjects and staggered enrollment of 6 to 12 additional subjects

(3+3 dose-escalation design) with HBV+ disease as outlined above. The sample sizes for Part 1A were determined empirically and are consistent with those used in clinical studies to evaluate the safety of a proposed administered dose in a new patient population. There is a 47% to 91% probability of observing an AE from 6 subjects if the true incidence rate is 10% to 33%.

For Part 1B, approximately 24 subjects will be enrolled. For the combined sample size of approximately 36 subjects for Part 1A and Part 1B, there is an 84% to 98% probability of observing at least one AE if the true incidence rate is 5% to 10%. The sample size of 36 subjects is chosen to obtain a preliminary assessment of antitumor activity. Table 4.8.2-1 provides the estimated ORR and the 95% confidence interval (CI) based on the exact probability method for a range of possible responses out of 36 subjects. The preliminary assessment of antitumor activity will help determine if there is sufficient evidence of clinical efficacy to warrant continued enrollment of subjects in Part 2.

Table 4.8.2-1 Estimated Objective Response Rate and 95 Percent Confidence Interval Out of 36 Subjects

Number (%) of Responses	2 (5.6)	4 (11.1)	6 (16.7)	8 (22.2)	10 (27.8)	12 (33.3)	14 (38.9)
Lower limit of 95% CI	0.7%	3.1%	6.4%	10.1%	14.2%	18.6%	23.1%
Upper limit of 95% CI	18.7%	26.1%	32.8%	39.2%	45.2%	50.9%	56.5%

CI = confidence interval.

Part 2A dose-expansion analysis cohort will include the approximately 108 subjects who are enrolled as a part of the global recruitment. The subjects will be stratified in a 1:1:1 ratio based on viral status (HBV vs HCV vs uninfected) and PD-L1 status, and assigned randomly within each stratum in a 1:1:1 ratio to 1 of the 3 treatment arms (Arms A, B, and C). With 12 subjects (per viral status cohort) treated with durvalumab or tremelimumab monotherapy respectively, there is a 72% to 86% probability of observing at least 1 AE from 12 subjects if the true incidence rate is 10% to 15%. Details of the China-specific analysis will be specified in the China supplementary SAP and China-specific amendment.

Part 2B is a safety cohort for the evaluation of durvalumab in combination with a higher single-dose of tremelimumab (Arm D) in which approximately 6 to 12 subjects will be enrolled.

Part 3 is a dose-expansion cohort in which approximately 200 subjects will be randomized in a 2:2:1:2 ratio to 1 of up to 4 treatment arms (Arms, A, B, C, and D). Following protocol amendment 5, subjects in Part 3 will be assigned randomly at a ratio of 2:1:2 into 1 of 3 treatment arms (Arms B, C, and D). There is a 96% probability of observing at least 1 AE

from 64 subjects if the true incidence rate is 5%. To evaluate the efficacy in terms of ORR of durvalumab and tremelimumab administered as monotherapy and in combination to subjects with advanced HCC, data from Part 2 and Part 3 will be analyzed for each part separately and for both parts combined. If the true ORR is 20% in the combination therapy of durvalumab 1500 mg and tremelimumab 75 mg Q4W for 4 doses (or durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses), a sample size of 100 subjects will provide at least 95% power to test the hypothesis that ORR is greater than 7% at a 0.05 significance level

Part 4 is a single arm cohort to evaluate safety and efficacy of durvalumab in combination with bevacizumab. The primary efficacy endpoint is ORR assessed by BICR according to RECIST 1.1.If the true ORR is 32%, a sample size of 100 subjects will provide at least 83% power to test the hypothesis that ORR is greater than 18.8% (Kudo et al 2018) at a 0.05 (2-sided) significance level. Other hypothesized ORRs and corresponding power values are given in the table below.

Power Calculations to detect difference between True ORR versus Control ORR=18.8%, n=100						
ORR	30%	31%	32%	33%	34%	35%
Power	70%	77%	83%	88%	92%	94%

Based on Exact Binominal Test, Alpha = 0.05 (2 sided)
With 100 patients, the precision of the estimation of ORR in the overall study population will be within:

• +/- 8% if the ORR is 10% (i.e. 95% CI 4.9%, 17.6%)
• +/- 9% if the ORR is 15% (i.e. 95% CI 8.6%, 23.5%)
• +/-11% if the ORR is 35% (i.e. 95% CI 25.7%, 45.2%)

There is a 99% probability of observing at least 1 AE from 100 subjects if the true incidence rate is 5%.

To evaluate the efficacy in terms of ORR of durvalumab and tremelimumab administered as monotherapy and in combination to subjects with advanced HCC, data from Part 2 and Part 3 will be analyzed for each part separately and for both parts combined. If the true ORR is 20% in the combination therapy of durvalumab 1500 mg and tremelimumab 75 mg Q4W for 4 doses (or durvalumab 20 mg/kg and tremelimumab 1 mg/kg combination therapy Q4W for 4 doses), a sample size of 100 subjects will provide at least 95% power to test the hypothesis that ORR is greater than 7% at a 0.05 significance level.

During the course of the study, subjects' tumor samples (archival and/or from fresh biopsies) will be analyzed for PD-L1 expression and the prevalence of PD-L1-positive expression for this population will be evaluated.

4.8.3 Efficacy

Primary analysis of response-related endpoints and corresponding time-to-event endpoints will be based on BICR assessments (for at least part 1 patients) according to RECIST v1.1. Sensitivity analysis of these endpoints will be performed using investigator assessments according to RECIST v1.1.

4.8.3.1 Efficacy Endpoint Definitions

The definitions of the efficacy endpoints and associated analyses are described below. Details will be provided in the SAP.

- **Objective response rate** is defined as the rate of best overall response of CR or PR according to RECIST v1.1. The best overall response is defined as the best response (in the order of CR, PR, SD, PD, and not evaluable) among all overall responses recorded from the start of treatment until progression (per RECIST v1.1), or the last evaluable disease assessment in the absence of PD prior to the initiation of subsequent anticancer therapy or the discontinuation from the study, whichever occurs first. The best overall response of CR or PR must be confirmed, which means a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.
- **Progression-free survival** is defined as the time from the date of first dosing to the first documentation of radiographic disease progression (per RECIST v1.1) or death due to any cause, whichever occurs first. Subjects who are alive with no documented PD by the data cutoff date for PFS analysis will be censored at the date of their last evaluable disease assessment.
- **Time to disease progression** is defined as the time from the date of first dosing to the first documentation of radiographic disease progression (per RECIST v1.1). Subjects with no documented PD by the data cutoff date for TTP analysis will be censored at the date of their last evaluable disease assessment.
- **Time to response** is defined as the time from the first dose of investigational product to the first documentation of a subsequently confirmed objective response. Only subjects who have achieved objective response (confirmed CR or confirmed PR) will be evaluated for TTR.
- **Duration of response** is defined for responders as the period from the first documentation of objective response to the first documented disease progression (per RECIST v1.1) or death from any cause, whichever occurs first. For subjects who are

alive and no documented PD at the time of data cutoff for analysis, DoR will be censored at the last evaluable disease assessment date.

- **Disease control rate** is defined as the rate of best overall response of CR, PR or SD according to RECIST v1.1. Disease control rate at 24 weeks is defined as the rate of best overall response of CR, PR or having SD with duration of SD lasting 24 weeks.
- **Overall survival** is defined as the time from the date of first dosing until death due to any cause. If there is no death reported for a subject by the data cut-off date for overall survival analysis, OS will be censored at the last known alive date. If the last known date alive is after the data cutoff date for the OS analysis, the last known date alive will be truncated at the data cutoff date.

4.8.3.2 Analysis of Efficacy

Efficacy data will be analyzed on the Response Evaluable Population, which will include all treated subjects who have a baseline tumor assessment and measureable disease at baseline. Summaries and analyses will be performed for each part separately and for Part 2 and Part 3 combined. Efficacy data will be presented by treatment arm.

The efficacy endpoints of ORR and DCR will be estimated based on their 2-sided 95% CIs using an exact probability method. DCR at 24 weeks will be estimated along with its 2-sided 95% exact CI.

Time-to-event endpoints, including DoR, TTR, TTP, PFS, and OS, will be analyzed using the Kaplan-Meier method. The median of each time-to-event endpoint and its 95% CI will be estimated based on the Kaplan-Meier curves. Only subjects with an OR (best overall response of complete response or partial response) will be included in the analysis of DoR. The landmark 6-month PFS, 6-month TTP, and 1-year OS rates will be estimated based on Kaplan-Meier curves along with their 95% CIs.

Tumor samples (archival and/or from fresh biopsies) will be analyzed to determine the expression level of selected immune-related pathways (eg, PD-L1 protein expression as determined by IHC) that may predict increased frequency of response or longer disease stabilization. CCI [redacted]

CCI [redacted]

4.8.4 Safety

Safety summaries will be performed for each part separately and for Part 2 and Part 3 combined. Safety data will be presented by treatment arm.

The safety data will include AEs, SAEs, discontinuation of investigational product due to toxicity, and changes from baseline in laboratory parameters (including liver and viral labs), ECGs, and vital signs. These data will be summarized by treatment arm for each viral status cohort (HBV vs HCV vs uninfected) in the As-treated Population.

4.8.4.1 Analysis of Adverse Events

The number and percentage of subjects reporting treatment-emergent AEs will be summarized overall and by the worst NCI CTCAE grade, system organ class, and preferred term. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs and treatment-emergent AE/SAEs considered related to investigational product will be summarized. At each level of subject summarization, a subject will be counted once using the highest grade and level of causality if one or more occurrences of the same system organ class/preferred term is reported. AEs will be graded according to the NCI CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Laboratory abnormalities will be graded according to the NCI CTCAE v4.03, if applicable. Frequencies of maximum observed grade will be presented for each laboratory parameter as well as the rates of subjects with Grade 3-4 toxicities. A shift table, presenting the 2-way frequency tabulation for baseline and post-baseline grade at scheduled time of evaluation as well as the worst post-baseline grade, will be provided for clinical laboratory tests.

4.8.4.3 Analysis of Vital Signs

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation and by treatment arm including end of treatment visit as well as for the maximum and minimum post-baseline values.

4.8.4.4 Analysis of Electrocardiograms

Electrocardiogram parameters (PR, RR, QRS, QT, QT corrected using Bazett's formula [QTcB], and QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by treatment arm by scheduled time of evaluation including end of treatment visit as well as for the maximum post-baseline values. The QTcF will be considered as the primary correction method to assess subject cardiac safety.

The notable ECG interval values in maximum absolute QTcF and QTcB intervals (new > 450 milliseconds, new > 480 milliseconds, new > 500 milliseconds) and the maximum absolute uncorrected QT intervals (new > 500 milliseconds) over all post-baseline evaluations, as well as in QTcF and QTcB maximum changes from baseline (> 30 and > 60 milliseconds) over all post-baseline evaluations will be summarized by treatment. "New" means the category of the QTc abnormality was not present at baseline and became present at least one post-baseline ECG assessment.

4.8.4.5 Analysis of ECOG Performance Status

Descriptive statistics will be provided for the ECOG performance status assessments and changes from baseline by scheduled time of evaluation and by treatment arm including end of treatment visit.

4.8.5 CCI

4.8.5.1 CCI

CCI

4.8.5.2 CCI

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CCI

4.8.6 CCI

CCI

4.8.7 Interim Analysis

An interim analysis is planned to occur when Part 1A and Part 1B are fully enrolled and subjects have been followed for at least 16 weeks. The purpose of the interim analysis is to determine whether there is sufficient evidence to open Part 2 enrollment. As described in Section 3.2.4, the clinically "interesting" ORR is ≥ 20%. Therefore, if the probability of ORR ≥ 20% is < 20%, then enrollment in Part 2 will not proceed; if the probability of ORR ≥ 20% is > 80%, then Part 2 will open for enrollment. The probability is computed based on Bayesian approach. Under the rule, based on 36 subjects, including 12 subjects from Part 1A and 24 subjects from Part 1B, if ≤ 4 responses (confirmed PR or better) out of the 36 subjects are observed, then enrollment in Part 2 will be terminated, and if ≥ 9 responses (confirmed PR or better) out of the 36 subjects are observed then enrollment will begin in Part 2. If the number of responses is 5, 6, 7 or 8 out of 36 subjects, then all available data (AEs, SAEs, duration of response, DCR, changes in CCI etc) will be evaluated by the sponsor and investigators to determine if the benefit-risk profile supports enrollment of Part 2. The

probabilities of different scenarios for different true response rates can be found in Table 4.8.7-1.

Table 4.8.7-1 Probabilities of Different Scenarios for Different True Response Rates

True Response Rate	Probability of Terminating Enrollment	Probability of Continuing Enrollment	Probability of Further Evaluation
0.05	97%	0%	3%
0.10	71%	1%	28%
0.15	36%	8%	56%
0.20	13%	28%	59%
0.25	3%	56%	40%
0.30	1%	80%	20%
0.35	0%	93%	7%

Another interim analysis will occur after approximately 10 subjects per treatment arm in Part 3 have completed 4 weeks of follow-up. All available data from Part 2 and Part 3 will be included in the analysis. The goal of this interim analysis is to potentially terminate 1 or more of the 2 monotherapy arms (Arms B and C) for futility or safety and the additional durvalumab and tremelimumab combination therapy arm (Arm D) for safety. The monotherapy arms will be terminated for futility if no confirmed complete or partial response is observed in the treated subjects. This criterion was chosen given that a monotherapy is considered effective if the true ORR is at least 10%. If the true response rate is 10%, the probability of stopping a treatment arm based on 36 subjects is 2%. A monotherapy is considered effective if the true ORR is at least 10%, which is greater than the ORR observed for sorafenib (2%, Llovet et al, 2008).

For Part 4, an interim analysis will occur after approximately 100 subjects have had the opportunity for 18 weeks of follow-up. Another interim analysis will occur after approximately 100 subjects in Part 4 have had the opportunity for 36 weeks of follow-up. The main objective of this interim analysis is to assess the safety and efficacy of durvalumab in combination with bevacizumab. The primary efficacy endpoint is ORR assessed by BICR according to RECIST 1.1.

Additional interim analyses based on similar objectives may be performed to support the ongoing Phase III HCC development (in Part 1-3). No formal adjustments will be made to the significance level used for testing. The details of each analysis will be described in the SAP prior to database lock for any interim analysis.

In addition, recruitment may be stopped in any arm if emerging data (safety and/or efficacy) suggest that it will no longer be developed. This may include data from other ongoing trials.

The final analysis for this study, which will include all study endpoints, will be performed 12 months after the first dose to the last patient in the study.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. The term disease progression should not be reported as an AE or SAE, however, medically significant individual events and/or laboratory abnormalities associated with disease progression (see definition of disease progression below) that fulfill the AE or SAE definition should be reported. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

AEs may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not

worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

Adverse Events Associated with Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of a new metastasis or progression of existing metastasis related to the primary cancer under study should not be considered an AE. Death clearly resulting from disease progression should NOT be reported as an SAE (see reporting guidelines in Section 5.5).

New Cancers

The development of a new cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the investigational product and have been identified after the subject's inclusion in the study. New metastatic lesion(s) of the subject's known cancer should NOT be reported as a new cancer.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious. 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.

The AESIs for durvalumab ± tremelimumab 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 irAE is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. 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/medical monitor.

AESIs observed with durvalumab ± tremelimumab include:

- Diarrhea/Colitis and intestinal perforation
- Pneumonitis/ILD
- Hepatitis/transaminase increases
- Neuropathy/neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Endocrinopathies (ie, events of hypophysitis, hypopituitarism, adrenal insufficiency, hyperthyroidism, hypothyroidism, and type 1 diabetes mellitus)
- Rash/Dermatitis
- Nephritis/blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis

- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

In addition, infusion-related reactions (Section 5.3.1) and hypersensitivity /anaphylactic reactions (Section 5.3.2) with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in Section 3.1.3 (hepatotoxicity) and in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the sponsor to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the investigational product/study regimen by the reporting investigator.

For management of toxicities due to bevacizumab, please refer to the local approved regulatory prescribing information or manage in accordance with institutional guidelines.

5.3.1 Infusion-related Reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to the sponsor and are defined, for the purpose of this protocol, as all AEs occurring from the start of the study treatment infusion up to 48 hours after the infusion start time. Guidelines for management of infusion-related reactions are provided in the Dosing Modification and Toxicity Management Guidelines.

5.3.2 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al, 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Infusion of biological products is commonly associated with infusion-related reactions. Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion-related reactions are commonly observed during or shortly after the first time exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion-related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to durvalumab and tremelimumab, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the investigator's convenience and in order to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Appendix 4 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis. Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in the Dosing Modification and Toxicity Management Guidelines.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor (see Section 5.5). See Section 5.2 for the definition of SAEs and Appendix 3 Additional Safety Guidance for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE eCRF.

5.4.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from the time of the patient signing the informed consent form through 90 days after the last dose of durvalumab and tremelimumab. If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

5.4.2 Follow-up of Unresolved Adverse Events

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

5.4.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- Death clearly the result of disease progression or a complication of disease progression should be reported at the next visit and documented in the eCRF but should **not** be reported as an SAE.
- Where death is not due (or not clearly due) to disease progression, the AE causing the death must be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to the sponsor representative within the usual timeframes (refer to Section 5.5 for additional information).

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started post the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug then it should also be reported as an SAE.

5.4.4 Safety Data to be Collected following the Final DCO of the Study

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab toxicity management guidelines. All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of Serious Adverse Events, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 5.5.

5.5 Reporting of Serious Adverse Events

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

If any SAE occurs during the course of the study, investigators or other site personnel must inform the appropriate sponsor representative(s) within 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all the necessary information is provided to the sponsor Patient Safety data entry site within 24 hours of initial receipt of fatal and life-threatening events and within 5 calendar days of initial receipt of all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up should be undertaken immediately. Investigators or other site personnel should inform the appropriate sponsor representative(s) of any follow-up information on a previously reported SAE within 24 hours of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture system, an automated email alert is sent to inform the designated sponsor representative(s).

If the electronic data capture system is not available, the investigator or other study site personnel reports an SAE to the appropriate sponsor representative(s) by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the IBs, unless otherwise specified in this protocol.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel should inform the appropriate sponsor representative(s) within 24 hours of when he or she becomes aware of it. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 5.4 and Section 5.5 for additional information). MedImmune does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

5.6.2 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to the sponsor are defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN (ie, Hy's Law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE.

Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the appropriate sponsor representative(s) as an SAE using the eCRF (see Section 5.5 for additional information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

- If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to investigational product, permanent discontinuation of dosing for the study subject should be considered.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor. If the etiology of the event remains unconfirmed and/or is considered related to investigational product (see Appendix 3 Additional Safety Guidance), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune safety review committee (or equivalent) to determine whether continued dosing of current study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune safety review committee (or equivalent) is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities IRBs/IECs will be notified of any actions taken with the study.

5.6.3 Pregnancy

If pregnancy occurs in a female subject who has received investigational product, the investigator or other site personnel informs the appropriate sponsor study representative(s) within 24 hours of when he or she becomes aware of it.

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

If the pregnancy results in an SAE, the designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's Patient Safety data entry site within the timeframes outlined above in Section 5.5. For pregnancies that do NOT result in an SAE, all relevant information should be provided to the sponsor's Patient Safety data entry site within 30 days. The same timelines apply when outcome information is available.

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported ***within 24 hours of knowledge of the event*** to the appropriate sponsor representative(s) using the pregnancy form. The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

5.6.4 Medication Error

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

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

Medication error includes situations where an error.

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

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

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

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging

- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.
If an medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error and within 30 days for all other medication errors.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a sponsor representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately and timely recorded in the eCRFs, biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

Original images are stored on hard media (eg, optical disk, film, avi file, or hardcopy) as source documents. If images are acquired at a remote imaging facility, copies on hard media should be stored at the investigative site as source documents.

6.2.2 Study Agreements

The principal investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the Clinical Study Agreement, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the principal investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the end of the study (defined below), regardless of the number of doses of investigational product that was received.

The end of the study ("study completion") is defined when the last patient discontinues study treatment.

Post final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab toxicity management guidelines.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab (in Parts 1-3) may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits assessment per its protocol. Any patient that would be proposed to move to such study would be given a new Informed Consent.

6.4 Data Management

Data management will be performed according to the Data Management Plan.

A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

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

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the principal investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider

requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

7.2 Subject Data Protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune medical monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC and to the study site staff in all countries except Japan. In Japan, the head of the study site will distribute the documents to the applicable IRB/IEC and to the principal investigator who will then distribute the documents to the site staff and any sub-investigators as appropriate.

The opinion of the IRB/IEC should be given in writing. For all countries except Japan, the investigator should submit the written approval to MedImmune before enrollment of any subject into the study. For Japan, the head of the study site should submit a notification of direction/determination as well as a copy of the IRB/IEC written approval to the MedImmune representative and the principal investigator before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

MedImmune should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

For Japan only: the head of the study site should seek the opinion of the IRB/IEC with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The principal investigator should submit progress reports to the IRB/IEC via the head of the study site at the time of the protocol re-approval.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune representatives will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide regulatory authorities, IRB/IEC, and principal investigators or head of study site (Japan only) with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

Each principal investigator or head of study site (Japan only) is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune representatives will provide this information to the principal investigator so that he/she can meet these reporting requirements.

7.4 Informed Consent

The principal investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the principal investigator or head of study site (Japan only) and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

MedImmune representatives will distribute any subsequent amendments and new versions of the protocol to each principal investigator(s). For distribution to IRB/IEC, see Section 7.3.

If a protocol amendment requires a change to a site's ICF, MedImmune representatives and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

7.6 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are summarized below.

1. Synopsis: The synopsis was updated to align with the body of the protocol.
2. Section 1.4.4 (Clinical Experience with Other Inhibitors of the PD-1/PD-L1 Pathway in Subjects with HCC): Added this section to present nivolumab in HCC data.
3. Section 1.5.1 (Benefit-risk Evaluation): Updated section as follows:
   a. Referenced the nivolumab data presented in Section 1.4.4.
   b. Clarified that Dose Level -1 may be evaluated if RP2D is not tolerated as assessed by prospectively designed parameters.
   c. Specified that pre-dose noncancerous liver tissue biopsy will be requested if the biopsy can be done safely during the same procedure used to obtain tumor biopsies.
4. Section 3.1.1 (Overview): Updated section as follows:
   a. Reduced total number of subjects to be enrolled from “129” to “120”.
   b. Part 1, Stage 1: Reduced sample size from “9” to “6”.
   c. Part 1, Stage 2: Revised this section to indicate that if DLTs exceed the limit at the RP2D, then subjects will be treated at Dose Level -1.
   d. Part 2: Reduced minimum number of subjects with HCV+ HCC that may enroll in Part 2 after Part 1, Stage 1 has been observed for at least 6 weeks from “6” to “3”. In addition, indicated that HBV+ HCC subjects may not enroll in Part 2 until a RP2D has been identified based on subjects enrolled in Part 1, Stage 2 (instead of Part 1, Stage 1).

e. Specified that pre-dose (screening) noncancerous liver tissue biopsy will be requested if the biopsy can be done safely during the same procedure used to obtain tumor biopsies. In addition, noted that post-dose fresh tumor biopsy is optional.

5. Section 3.1.2.1 (durvalumab in Combination with Tremelimumab [Part 1 and Arm A of Part 2): Updated section as follows:
   a. Specified that durvalumab 15 mg/kg (Dose Level -1) will be administered if needed.
   b. Revised the duration of treatment so that durvalumab monotherapy at 20 mg/kg Q4W will continue until any of the study discontinuation criteria are met.
   c. Added that subjects who progress on durvalumab monotherapy may be retreated with the durvalumab and tremelimumab combination.
   d. Updated the treatment schema (Figure 3.1.2.1-1) to reflect the change in treatment duration.
6. Section 3.1.2.2 (durvalumab Monotherapy [Arm B of Part 2): Revised the duration of treatment so that durvalumab monotherapy at 20 mg/kg Q4W will continue until any of the study discontinuation criteria are met. Updated the treatment schema (Figure 3.1.2.2-1) to reflect the change in treatment duration.
7. Section 3.1.3.2 (Tremelimumab Monotherapy [Arm B of Part 2): Revised the duration of treatment so that tremelimumab monotherapy Q12W will continue until any of the study discontinuation criteria are met. Updated the treatment schema (Figure 3.1.2.3-1) to reflect the change in treatment duration.
8. Section 3.1.2.4 (Criteria for Treatment Beyond Progression and Retreatment): Removed retreatment during the follow-up period.
9. Section 3.2.1 (Dose Rationale): Revised text to reflect the change in treatment duration outlined in Section 3.1.2.
10. Section 3.2.2 (Rationale for Study Population): Added nivolumab data in HCC.
11. CCI [redacted]
12. Section 4.1.1 (Number of Subjects): Reduced number of subjects in Part 1 from "15 to 20" to "12".
13. Section 4.1.2 (Inclusion Criteria): Revised the following criteria:
   a. For inclusion criterion #8, specified that noncancerous liver tissue biopsy will be requested if the biopsy can be done safely during the same procedure used to obtain pretreatment tumor biopsies. In addition, clarified that on-treatment tumor biopsies are encouraged but not required.
   b. For inclusion criterion #11, specified that subjects should continue contraception and abstain from sperm/egg cell donation for 90 days after the last dose of durvalumab or tremelimumab and for 180 days after the last dose(s) of durvalumab in combination with tremelimumab.
14. Section 4.2.1 (Enrollment/Screening Period): Updated Table 4.2.1-1 as follows:
   a. Specified that "qualitative" HBeAg will be assessed.
   b. CCI [redacted]

c. Revised footnote "a" to include collection of fresh tumor biopsy samples.
d. Revised footnote "d" to indicate that noncancerous liver tissue biopsy will be requested if the biopsy can be done safely during the same procedure used to obtain pretreatment tumor biopsies.

15. Section 4.2.2 (Treatment Period): Updated section as follows:
    a. CCI
    b. CCI
    c. CCI
16. Section 4.2.3 (Follow-up Period): Updated section as follows:
    a. Removed text that referenced 12-month treatment duration.
    b. In Table 4.2.3, specified vital signs parameters and indicated that "qualitative" HBeAg will be assessed. Removed footnotes that referenced 12-month treatment duration as well as footnotes for specific CCI In addition, revised table title from "Schedule of Follow-up Procedures" to "Schedule of End of Treatment and Follow-up Procedures".
17. Section 4.3.1 (Efficacy): Specified that MRI scans of the chest and abdomen are acceptable and that scans of the head, neck, and pelvis are optional.
18. Section 4.3.2.1 (Fresh Tissue Biopsies): Specified that noncancerous liver tissue biopsy will be requested if the biopsy can be done safely during the same procedure used to obtain pretreatment tumor biopsies. In addition, indicated that fresh tumor biopsies are now optional rather than mandatory and number of core biopsies was reduced from "3" to "1".
19. Section 4.3.3.4 (Vital Signs): Indicated that pulse oximetry will be assessed at all timepoints where vital signs are assessed and not just at screening.
20. Section 4.3.8 (Estimate of Volume of Blood to be Collected): Reduced blood volumes.
21. Section 4.5.1 (Identity of Investigational Product[s]), Section 4.5.1.2 (Investigational Product Dose Preparation), and Section 4.5.1.4 (Treatment Administration): Added D5W as another diluent option for durvalumab.
22. Section 4.5.1.5 (Monitoring of Dose Administration): Changed durvalumab /tremelimumab combination therapy and tremelimumab monotherapy treatment window from "7" to "3" days.
23. Section 4.8.2 (Sample Size and Power Calculation): Reduced the number of subjects in Part 1 from "9" to "6"
24. Section 5 (Assessment of Safety): Updated entire section to be consistent with revised safety template language.

25. Appendix 2 (Management of Study Medication Related Toxicities): Updated all tables in this section based on the current version of the guidelines (02Jul2015).

9.2 Protocol Amendment 2

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Major changes to the protocol are summarized below.

1. Protocol Synopsis: The synopsis was updated to align with the body of the protocol.
2. CCI Section 4.2.1 (Enrollment/Screening Period; Table 4.2.1-1 [Schedule of Screening/Baseline Procedures]); Section 4.2.2 (Treatment Period; Table 4.2.2-1 [Schedule of Treatment Period Study Procedures Weeks 1 to 25] and Table 4.2.2-2 [Schedule of Treatment Period Study Procedures Week 29 and Beyond]); Section 4.2.3 (Follow-up Period; Table 4.2.3-1 [Schedule of End of Treatment and Follow-up Procedures]); Section 4.3.1 (Efficacy); Section 4.3.4 (Clinical Laboratory Tests); and Section 4.8.3.2 (Analysis of Efficacy): Added the tumor marker, CCI which is standard of care for these subjects to allow for potential consideration of tumor marker levels in conjunction with RECIST response in evaluating the overall clinical response of the HCC subjects enrolled in this study.
3. Section 3.1.1 (Overview); Section 3.1.2 (Treatment Regimen); Section 4.1.1 (Number of Subjects); Section 4.1.2 (Inclusion Criteria); Section 4.1.3 (Exclusion Criteria); Section 4.1.7 (Replacement of Subjects); Section 4.3.1 (Efficacy); Section 4.8.2 (Sample Size and Power Calculations); and Section 4.8.7 (Interim Analysis): Changed the original Part 1 to Part 1A and added Part 1B (Combination Efficacy Gating Cohort). The rationale for adding Part 1B is to determine if there is sufficient evidence of clinical activity for the combination of durvalumab and tremelimumab in subjects with HCC to warrant opening a randomized Phase 2 evaluation of the combination and each monotherapy component (Part 2). Sample size was increased to account for the enrollment of approximately 24 subjects in the newly added Part 1B.
4. Section 3.1.2.4 (Criteria for Treatment Beyond Progression, Retreatment, and Treatment After an Immune-related Adverse Event): Added criteria (from Study D4190C00010) to allow continuing treatment with durvalumab monotherapy after a toxicity on durvalumab and tremelimumab combination therapy.
5. Section 3.2.4 (Rationale for Interim Analysis Criteria): Added this section to describe the rationale for the interim analysis criteria.
6. Section 4.1.2 (Inclusion Criteria): Revised the following criteria:
   - Criterion 1: Added a higher minimum age limit (≥ 20 years) for Japan subjects.
   - Criterion 4: Excluded subjects who received systemic therapies other than sorafenib to allow enrollment of a more homogenous population. This change was made to decrease the confounding factor that could occur in interpreting efficacy data from a single arm study where patients exposed to a variable number of prior therapies can enroll.

- Criterion 5: Excluded patients with Child-Pugh Score class ≥ B7 which will restrict enrollment to those patients with the most robust liver function thereby optimizing the risk-benefit profile.
- Criterion 11d: Changed bilirubin criterion to exclusively include total bilirubin ≤ 2.0 × ULN which will be easier for sites to implement and restrict enrollment to those patients with the most robust liver function thereby optimizing the risk-benefit profile.
- Criteria 12 and 13, and Table 4.1.2-1 (Highly Effective Methods of Contraception): Revised contraception language to align with current standard MedImmune safety language. In addition, made changes to meet Japan requirements.

7. Section 4.1.3 (Exclusion Criteria): Revised Criterion 3 to reflect a more conservative definition of exclusionary ascites to optimize the risk-benefit ratio.
8. Section 4.1.8 (Withdrawal of Informed Consent for Data and Biological Samples): Revised the language for Samples Obtained for Genetic Research or Future Research to clarify that the samples collected will only be used for future research already specified in the protocol.
9. Section 4.2.1 (Enrollment/Screening Period; Table 4.2.1-1 [Schedule of Screening/Baseline Procedures]): In footnote ‘a’ of Table 4.2.1-1, changed the duration of the screening period from “Days -14 to -1” to “Days -28 to -1” only for informed consent, disease assessment and fresh biopsy collection to allow flexibility with scheduling and ease potential burden on the subjects. In addition, markers of menopause for females who require laboratory testing (according to inclusion criterion #12) were added to the schedule of screening/baseline procedures.
10. Section 4.2.1 (Enrollment/Screening Period; Table 4.2.1-1 [Schedule of Screening/Baseline Procedures]) and Section 4.2.2 (Treatment Period; Table 4.2.2-1 [Schedule of Treatment Period Study Procedures Weeks 1 to 25] and Table 4.2.2-2 [Schedule of Treatment Period Study Procedures Week 29 and Beyond]): To be consistent with Section 4.1.2 (Inclusion Criteria), specified that pregnancy testing will only apply to females of childbearing potential.
11. Section 4.2.1 (Enrollment/Screening Period; Table 4.2.1-1 [Schedule of Screening/Baseline Procedures]); Section 4.2.2 (Treatment Period; Table 4.2.2-1 [Schedule of Treatment Period Study Procedures Weeks 1 to 25] and Table 4.2.2-2 [Schedule of Treatment Period Study Procedures Week 29 and Beyond]); Section 4.2.3 (Follow-up Period; Table 4.2.3-1 [Schedule of End of Treatment and Follow-up Procedures]); and Section 4.3.3.4 (Child-Pugh Score): Added assessment of Child-Pugh Score (which is standard of care for this class of patients) to schedule of procedures as this was inadvertently omitted in the previous version of the protocol. Added Section 4.3.3.4 (Child-Pugh Score) to describe the Child-Pugh classification of cirrhosis severity.
12. CCI [redacted]

CCI [redacted]

13. Section 4.3.4 (Clinical Laboratory Tests): Specified that bicarbonate testing is not required in countries where this is not standard.
14. Section 4.3.8 (Estimate of Volume of Blood to be Collected): Updated to align with changes to assessments in Section 4.2.
15. Section 4.5.1.4 (Treatment Administration): Clarified window for infusion duration to decrease confusion with site interpretation of text.
16. Section 4.5.1.6 (Reporting Product Complaints); Section 4.5.3 (Labeling); Section 4.5.6 (Accountability); Section 7.3 (Ethics and Regulatory Review); and Section 7.5 (Changes to the Protocol and Informed Consent Form): Revised to meet Japan requirements.
17. Section 4.8.1 (General Considerations) and Section 4.8.3.2 (Analysis of Efficacy): Replaced "Full Analysis Set" with "Response Evaluable Population" to align with current nomenclature within MedImmune biostatistics group.
18. Section 5.3 (Definition of Adverse Events of Special Interest): Added new AESI language in order to align with standard MedImmune language.
19. Appendix 2 (Management of Study Medication Related Toxicities): Updated the toxicity management guidelines to align with the current 02Oct2015 version.

9.3 Protocol Amendment 3

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. Major changes to the protocol are summarized below.

1. Title Page: Updated the medical monitor and associated contact information.
2. Protocol Synopsis: The synopsis was updated to align with the body of the protocol.
3. Section 1.4 (Summary of Clinical Experience): Updated the clinical experience of durvalumab in combination with tremelimumab to support the additional treatment arms and to remind the site personnel to refer to the IBs for current study drug information.
4. Section 1.5.1 (Benefit-risk Evaluation): Updated risks associated with study drugs to be consistent with the current IBs. Added mitigation of risk for the higher tremelimumab dose by including a safety run-in cohort (Part 2B).
5. Section 2.1.2 (Secondary Objectives) and Section 2.2.2 (Secondary Endpoints): Revised the secondary efficacy objective and its corresponding endpoint to add clarification on the parameters for evaluating clinical activity, including ORR, DC, DoR, TTP, PFS, and OS, based on investigator assessments and BICR according to RECIST v1.1.
6. CCI [redacted]
7. CCI [redacted]

CCI [redacted]

8. Section 3.1.1 (Overview); Section 3.1.2 (Treatment Regimen); and Section 4.1.1 (Number of Subjects): Part 2B has been added to evaluate the safety of an additional treatment regimen of durvalumab in combination with a higher single dose of tremelimumab. Part 3 is a 4 arm randomized comparison of the treatment arms assessed in Part 2A (using a corresponding fixed-based dose) and Part 2B. Part 3 has been included to more thoroughly assess the efficacy of the treatment arms along with CCI [redacted] evaluation. The following revisions were made based on the additional treatment arms:
   - Arm D Part 2B: durvalumab 1500 mg in combination with tremelimumab 300 mg for 1 dose as combination therapy followed by durvalumab 1500 mg Q4W as monotherapy (approximately 6 to 12 subjects)
     Arm A Part 3: durvalumab 1500 mg in combination with tremelimumab 75 mg Q4W for 4 doses as combination therapy followed by durvalumab 1500 mg Q4W as monotherapy (approximately 64 subjects)
     Arm B Part 3: durvalumab 1500 mg Q4W as monotherapy (approximately 64 subjects)
     Arm C Part 3: Tremelimumab 750 mg Q4W for 7 doses then Q12W as monotherapy (approximately 32 subjects)
     Arm D Part 3: durvalumab 1500 mg in combination with tremelimumab 300 mg for 1 dose as combination therapy followed by durvalumab 1500 mg Q4W as monotherapy (approximately 64 subjects)
   - Dosing information for Part 1A, Part 1B, and Part 2A was added to the description of each part in Section 3.1.1 for clarity.
   - The reference to RP2D was removed because this study will be investigating additional treatment regimens.
   - The presentation of the treatment regimens was updated to table format for clarification and the associated figures were updated to show the additional dosing regimens.
   - The number of subjects and the Study Flow Diagram (Figure 3.1.1-1) were updated to reflect the additional treatment arms.
9. Section 3.1.1 (Overview); Section 4.1.1 (Number of Subjects); Section 4.8.2 (Sample Size and Power Calculations); and Section 4.8.8 (Analysis of Chinese Subjects in Part 2A): Allowance for additional Chinese subjects to enroll into Part 2A was added. The corresponding statistics for Part 2A were updated and Section 4.8.8 was added to further detail the statistical analysis for the additional Chinese cohort.
10. Section 3.1.1 (Overview); Section 3.2.3 (Rationale for Endpoints); Section 4.2.1 (Enrollment/Screening Period; Table 4.2.1-1 [Schedule of Screening/Baseline Procedures]); and Section 4.3.2.1 (Fresh Tissue Biopsies): Added a statement to clarify that subjects enrolled in Part 2B or Part 3 must provide a newly acquired (fresh or acquired within 3 months, preferred) or archival (< 3 years) tumor sample at screening.
11. Section 3.1.2.1 (Criteria for Treatment Beyond Progression, Retreatment, and Treatment After a Treatment-related AE): The retreatment section was updated to allow all subjects who receive combination therapy in any arm to be retreated with the same combination

regimen as previously assigned if they experience PD while on durvalumab monotherapy or if retreated after a treatment-related AE.

12. Section 3.2.1 (Dose Rationale) and Section 8 (References): Rationale to support the additional fixed dosing regimens was added along with the appropriate references.
13. Section 3.2.4 (Rationale for interim analysis) and Section 4.8.7 (Interim analysis): Added language to allow for another interim analysis after approximately 10 subjects per treatment arm in Part 3 have been enrolled. This analysis will be used to test for futility for the monotherapy arms (Arms B and C) and for safety in the higher single-dose combination therapy arm (Arm D).
14. Section 4.1.2 (Inclusion Criteria): Revised the following criteria:
    - Criterion 7: Revised text to clarify that all subjects in all arms of the study with confirmed HBV infection (defined as HBsAg positive or HBV DNA detectable) must be treated with antiviral therapy prior to enrollment, must remain on antiviral therapy for the duration of treatment, and continue antiviral therapy for 6 months after the last dose of study treatment.
    - Criterion 8a: Revised text to clarify that a previously irradiated lesion can be considered a target lesion only if no other non-irradiated measureable lesions exist.
    - Criterion 9: Added text to clarify that subjects in Part 2B and Part 3 must provide a tumor sample, which may be an archival tumor tissue sample (< 3 years) if the subject cannot provide a newly acquired (fresh or acquired within 3 months, preferred) tumor tissue sample.
    - Criterion 3: specified for part c that management of the disease is per local institutional practice
15. Section 4.1.3 (Exclusion Criteria): Revised the following criteria:
    - Criteria 12 and 13: Revised text to clarify that all subjects in all arms of the study will not be eligible if they are co-infected with hepatitis viruses.
16. Section 4.1.7 (Replacement of Subjects): Updated text to indicate that subjects in Part 1B, Part 2A, and Part 2B of the study may be replaced if they discontinue prior to receiving the first dose of study medication. Subjects randomized in Part 3 will not be replaced.
17. Section 4.2.1 (Enrollment/Screening Period; Table 4.2.1-1 [Schedule of Screening/Baseline Procedures]): Revised the following assessment:

    CCI [redacted]

    - Added BCLC classification at screening
18. Section 4.2.2 (Treatment Period; Table 4.2.2-1 [Schedule of Treatment Period Study Procedures Weeks 1 to 25]): Revised the following assessments and footnotes:

    CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Footnote ‘a’ was revised to include imaging instructions.
- Footnote ‘e’ vital signs collection instructions were revised to include the new treatment arms.
- CCI [redacted]
- CCI [redacted]
- Added footnote ‘l’ to tremelimumab administration to indicate that tremelimumab will be administered in combination with durvalumab for 1 dose only to subjects enrolled in Arm D of Part 2B and Arm D of Part 3.

19. Section 4.2.2 (Treatment Period; Table 4.2.2-2 [Schedule of Treatment Period Study Procedures Week 29 to End of Study]): Revised the title to indicate an end to the study. Revised the following footnotes:
    - CCI [redacted]
    - Footnote ‘b’ vital signs collection instructions were revised to include the new treatment arms.
20. Section 4.2.3 (Follow-up Period; Table 4.2.3-1 [Schedule of End of Treatment and Follow-up Procedures]): Revised the following footnotes:
    - CCI [redacted]
    - Removed the 6 month sample collection timepoint and associated footnote for CCI [redacted] and qualitative HBeAg and anti-HBe.
    - Revised footnote ‘a’ to include imaging instructions and to clarify that disease assessments will only be discontinued if the EOT visit is for PD.
    - Revised footnote ‘g’ to include new combination dosing arms (Arm A of Part 3) for tremelimumab end of treatment procedures and to indicate the end of treatment date as 90 days after the last dose for subjects in Arm D of Part 2B and Arm D of Part 3 who receive only 1 dose of tremelimumab.

21. CCI [redacted]
22. Section 4.5.1.1 (Dose Calculation) and Section 4.5.1.2 (Investigational Product Dose Preparation): The calculation for the additional fixed doses was added for both study drugs.
23. Section 4.6.1 (Methods for Assigning Treatment Groups): Revised text to state that subjects enrolled in Part 2B will be assigned to Arm D and subjects in Part 3 will be randomized in a ratio of 2:2:1:2 to 1 of up to 4 treatment arms (Arms A, B, C, and D).
24. Section 4.8.1 (General Considerations): Updated the timing of the main efficacy analysis to occur 12 months after the last patient is randomized.
25. Section 4.8.2 (Sample Size and Power Calculations): Revised text to include statistics for the addition of treatment arms in Part 2B and Part 3.
26. Section 4.8.3.2 (Analysis of Efficacy): Revised text to indicate that the efficacy data will be analyzed for each part separately and for Part 2 and Part 3 combined and presented by treatment arm. The efficacy analysis for the additional fixed dosing arms as well as the landmark efficacy endpoint analysis of 6-month TTP rate was added. CCI [redacted] was removed from the efficacy analysis section because it was included in the clinical laboratory tests (Section 4.3.4).
27. Section 4.8.4 (Safety): Revised text to indicate that safety summaries will be performed for each part separately and for Part 2 and Part 3 combined and presented by treatment arm.
28. CCI [redacted]
29. Section 5.3 (Definition of Adverse Events of Special Interest): Revised the AESIs observed with durvalumab in combination with tremelimumab treatment to be consistent with the current IBs.
30. Section 6.3 (Study Timetable and End of Study), Section 3.1.1 (Overview), Section 4.2.2 (Treatment Period; Table 4.2.2-2 [Schedule of Treatment Period Study Procedures Week 29 to End of Study]), Section 4.3.1 (Efficacy): The end of study definition was revised to when the last patient discontinues treatment.
31. CCI [redacted]
32. Addition of Appendix 6 Actions Required in Cases of Increases in Liver Biochemistry and Evaluations of Hy's Law to complement section 5.6.2

9.4 Protocol Amendment 4

1. Title Page and Appendix 10.1: changed global clinical lead

2. Synopsis and 6.3 Study Timetable and End of Study: Post final Data Cut Off (DCO) - Recommended update based on AZ protocol template 2.1
3. Synopsis, 4.8.3.1 Efficacy Endpoint Definitions: added in new efficacy endpoint of TTR (Time to Response), which is a standard endpoint and to compare efficacy among the different arms.
4. Table 1.4.1-1: Overview of Ongoing Clinical Studies of durvalumab in Which Subjects Have Been Treated – amended error (changed footnote b to a)
5. Section 3.1.2.1: revised the retreatment section because progressive disease should be confirmed by imaging and removed Treatment After a Treatment related AE paragraphs as sites should refer to TMG
6. Table 3.1.2.1: Revised Part 3 Arm C to correct the tremelimumab dose from "750 mg/kg" to "750 mg".
7. Section 4.1.2 Inclusion Criteria: changed inclusion criteria 3 (moved 3b to #7 and 3c to #8); inclusion criteria 7 (to provide clarification on HBV DNA detectable vs undetectable, and which patients must be treated with antiviral therapy); inclusion criteria 8 (moved 3c to 8); inclusion criteria 9 (to align with AZ protocol template 2.1 and removed requirement of "Tumor lesions used for biopsy should not be lesions used as RECIST target lesions"); inclusion criteria 11 (minor changes); and inclusion criteria 14 and 15 (to align with AZ protocol template 2.1)
8. Section 4.1.3 Exclusion Criteria: changed exclusion criteria 1, 2, 4, 10, 11 (which is now 10), 12 (which is now 11), 15 (which is now 13) and 21 (which is now 19) to provide further clarification on eligibility of patients
9. Section 4.1.6 Survival Status for Withdrawn Consent and Lost to Follow-Up Patients: recommended update based on AZ protocol 2.1
10. Table 4.2.2-1 (Schedule of Treatment Period Study Procedures Weeks 1-25): removed footnote "l" from Tremelimumab administration (for both 4 dosing cycles and 1 dosing cycle) as it was added in error; revised footnote "l" to specify the visit window for blood sample collection on Week 2 Day 1 (± 1 day) and Week 4 Day 1 (± 1 day); revised and changed placement of footnotes "I" and "k" to provide more information for patients in Arm D of part 2B and part 3; added footnote "c" to other assessments that do not need to be repeated if performed within 3 days of 1st dose; edited footnote "a" as disease assessments and dosing will not always be within 7 days of each other; and added footnote "q" for hepatitis B patients
11. Table 4.2.2-2 Schedule of Treatment Period Study Procedures Week 29 to End of Study: added footnote "f" for hepatitis B patients
12. Table 4.2.3-1 Schedule of End of Treatment and Follow-up Procedures: added footnote "h" for hepatitis B patients
13. Section 4.3.2.1 Fresh Tissue Biopsies: removed language to allow the same lesion used for baseline biopsy to also be used as a target lesion for RECIST as long as it is suitable for accurate repeated measurements.
14. Section 4.5.1.2 Investigational Product Dose Preparation: edited to reflect: 1) There are no restrictions on treme dosing material; 2) Diluent does not need to be removed from IV bag before adding drug; and 3) Dextrose can be used with either drug.

15. Section 4.5.1.5 Monitoring of Dose Administration: as per TMG, updated to not allow skipping or missing of doses; dose is just held until drug can be resumed as per (or permanently discontinued)
16. Section 4.8.3.1 Efficacy Endpoint Definitions: added time to response efficacy endpoint.
17. Section 5.3 Definition of Adverse Events of Special Interest: Changes to AESIs based on updated IBs (Durvalumab edition 12 and Tremelumumab edition 8) and AZ protocol template 2.1
18. Section 5.4.1 Time Period for Collection of Adverse Events: To further specify that AEs to be collected from "the time the patient signs informed consent form" (as opposed to "signature of informed consent"); and added more information on AEs/SAEs that are past the 90 days post dose but due to late onset toxicity to study drug
19. Section 5.4.4 Safety Data to be Collected following the Final DCO of the Study: recommended update based on AZ protocol template 2.1
20. General: revised the protocol to correct the links where error messages appear.
21. Section 3.1.3 Management of Study Medication Related Toxicities and Appendix 2: updated to reflect latest TMG 01Nov2017
22. Appendix 7 Hepatitis B Stratification Guidance: new appendix added to help sites determine infection status

9.5 Protocol Amendment 5

1. Part 3 Arm A Recruitment Closure: Following Amendment 5, AstraZeneca will update Study 22 to evaluate a single durvalumab plus tremelimumab combination arm, based on results from the pre-planned interim analysis (see section 4.8.7 Interim Analysis), evaluating tolerability and clinical activity in Study 22. All other arms remain unchanged. All regimens evaluated were tolerable, and no new safety signal was identified. Following recruitment closure of this arm, if a patient has not completed or started all 4 doses of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only.
2. Part 4 addition (durvalumab + bevacizumab): VEGF has been shown to play a role in the development and spread of HCC (Kaseb et al 2009). Additional evidence suggests that the combination of PD-L1 inhibition with vascular endothelial growth factor (VEGF) inhibition may result in synergistic activity and improved clinical benefit (Barsoum et al 2014, Voron et al 2015, Yasuda et al 2013). Preliminary data from an ongoing Phase Ib study testing atezolizumab (a PD-L1 inhibitor) and bevacizumab therapy as first-line treatment in patients with advanced HCC showed promising clinical activity, with an ORR of 65% (Stein et al 2018). This data indicates further evaluation of durvalumab therapy in combination with VEGF inhibitor therapy in patients with advanced HCC is warranted. Bevacizumab, a mAb targeting VEGF, is approved by the FDA for the treatment of several types of cancer, including colorectal cancer, non-small cell lung cancer, glioblastoma, renal cell carcinoma, cervical cancer, ovarian cancer, fallopian tube cancer, and peritoneal cancer. Bevacizumab has immunomodulatory effects (eg, increased dendritic cell maturation,

enhanced T cell infiltration, and reduced myeloid-derived suppressor cells and Tregs into the tumor) that may enhance the efficacy of durvalumab.

3. Removed China Tail references in this global protocol as there is a China-specific amendment for Chinese sites to follow.
4. Removed Appendix 2: Dose Modification and Toxicity Management Guidelines for Immune mediated, infusion related, and non immune mediated reactions and removed any reference to appendix 2 hyperlinks throughout protocol so that 1) TMGs become a standalone clinical document and 2) cross-program protocol amendments will become unnecessary whenever TMGs are updated in future (i.e. no future protocol amendment required for this change alone).
5. Section 5.6.4 Medication error wording added with instructions for investigators to report medication error events.
6. Change of terms from "unresectable" to "advanced", and from "MEDI4736" to "durvalumab" for medical accuracy and consistency respectively.
7. Table 4.3.3.4-1 wording added to clarify how ascites should be assessed for Child-Pugh classification for ascites.
8. Section 3.1.2.1 wording added to permit crossover for patients in Part 3 Arm A.
9. CCI [redacted]
10. Section 4.5.1.5 Monitoring of dose administration wording changed to allow dose visits recalibration based on actual dosing dates when necessary.
11. Section 4.1.2 Inclusion criterion 4 wording added to sorafenib or other approved VEGFR TKI.
12. Section 10.5 Appendix 5 changes in the identification and report of Potential Hy's Law (PHL) and Hy's Law (HL) cases.

9.6 Protocol Amendment 6

1. Section 10.5 Appendix 5 protocol amendment 5 changes cancelled regarding the identification and report of Potential Hy's Law (PHL) and Hy's Law (HL) cases.
2. Typos throughout the document were corrected.

10 APPENDICES

10.1 Appendix 1 Signatures

Sponsor Signature(s)

A Study of Safety, Tolerability, and Clinical Activity of Durvalumab and Tremelimumab Administered as Monotherapy, or Durvalumab in Combination with Tremelimumab or Bevacizumab in Subjects with Advanced Hepatocellular Carcinoma

I agree to the terms of this protocol.

Signature and date: Electronic signature is appended

PPD

PPD Gaithersburg MD, 20878, USA

Telephone number: PPD

Signature of Principal Investigator

A Study of Safety, Tolerability, and Clinical Activity of Durvalumab and Tremelimumab Administered as Monotherapy, or Durvalumab in Combination with Tremelimumab or Bevacizumab in Subjects with Advanced Hepatocellular Carcinoma

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available):_____

10.2 CCI

CCI

CCI

[redacted]

10.3 Appendix 3 Additional Safety Guidance

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03 as provided below. The determination of severity for all other events not listed in the NCI CTCAE v4.03 should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

10.4 Appendix 4 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

The NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al, 2006). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING:
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

References

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report -- second National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

10.5 Appendix 5 Actions Required in Cases of Increases in Liver Biochemistry and Evaluations of Hy's Law

Introduction
This Appendix describes the process to be followed to identify and appropriately report cases of Hy's law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

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

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law

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

Hy's Law

AST or ALT ≥3 × ULN together with TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, for example, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of potential Hy's Law cases

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

- ALT ≥3 × ULN
- AST ≥3 × ULN
- TBL ≥2 × ULN

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met; where this is the case, the Investigator will do the following:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results, the Investigator will, without delay, do the following:

- Determine whether the patient meets PHL criteria (see definitions within this Appendix) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

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

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see definitions within this Appendix) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law criteria not met

If the patient does not meet PHL criteria, the Investigator will do the following:

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

Potential Hy's Law criteria met

If the patient does meet PHL criteria, the Investigator will do the following:

- Determine whether PHL criteria were met at any study visit prior to starting study drug(s) (see Section 6)
- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance as well as discuss and agree on an approach for the study patient's follow-up and the continuous review of data. Subsequent to this contact, the Investigator will do the following:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used.
- Complete the 3 Liver eCRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and assessment of Potential Hy's Law cases

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

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

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

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

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

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP,

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

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

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

Actions required for repeat episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study drug(s) and has already met PHL criteria at a previous on-study treatment visit.

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

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

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, for example, chronic or progressing malignant disease or severe infection or liver disease, or did the patient meet PHL criteria prior to starting study drug(s)and at his or her first on-study treatment visit as described in Section 6?

If no, follow the process described in the Potential Hy's Law criteria of this Appendix.

If yes, determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in Section 4.2 of this Appendix

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

References

FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: Premarketing clinical evaluation. Available from: URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

10.6 Appendix 6 Hepatitis B Stratification Guidance

Test	Result	Interpretation	Action	Stratified to Hepatitis B?
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible	None	No
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection or chronic infection without antigenemia	Test HBV DNA load: • If <10 IU/ml, (or below the limit of detection per local lab), no antiviral treatment required. Continue testing monthly to ensure levels do not exceed 10 IU/ml. • If ≥10 IU/ml, start anti-viral treatment and maintain treatment until 6 months post last dose study drug. • If subject on anti-viral therapy for HBV with undetectable HBV DNA (<10 IU/ml or under the limit of detection per local lab) patient will be stratified to HBV+ cohort.	If HBV DNA load ≥10 IU/ml (or above limit of detection per local lab): Yes If HBV DNA load <10 IU/ml (or below the limit of detection per local lab): No
HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination	None	No
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acute Infection	Start anti-viral treatment and maintain treatment until 6 months post last dose study drug	Yes
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronic Infection	Start anti-viral therapy and maintain treatment until 6 months post last dose study drug	Yes
HBsAg anti-HBc anti-HBs	Negative Positive Negative	4 potential interpretations: • Resolved infection (most common) • False-positive anti-HBc: susceptible • Low-level chronic infection • Resolving acute infection	Test HBV DNA load: • If <10 IU/ml, no treatment required. Continue testing monthly to ensure levels do not exceed 10 IU/ml. • If ≥10 IU/ml, start anti-viral treatment and maintain treatment until 6 months post last dose study drug	If HBV DNA load ≥10 IU/ml (or above limit of detection per local lab): Yes If HBV DNA load <10 IU/ml (or below the limit of detection per local lab): No

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