Revised Clinical Study Protocol	
Drug Substance	Durvalumab (MEDI4736) and tremelimumab
Study Code	D419CC00002
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A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with advanced Hepatocellular Carcinoma (HIMALAYA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 1.0, 09 August 2017
Initial creation

Version 2.0, 20 December 2017

Synopsis and Section 1.2 - Rationale for study design, doses, and control groups: Removal of "*unresectable*" as a qualifier for hepatocellular carcinoma

Synopsis, Section 2.2.2, Table 12, Section 8.4.1.3, Section 8.5.3.4, and Section 8.5.6.2: Addition of "*disease control rate at 24 weeks (DCR-24w)*"

Synopsis and Section 2.4 - CCI

Synopsis and Section 1.4 – Study design: Introduction of the limit for tumor assessments as being "*until RECIST 1.1-defined radiological progression followed by a subsequent scan if clinically feasible, evaluated by Confirmation of Radiological Progression criteria.*", rather than confirmed PD.

Synopsis, Section 4.3 – Follow-up period:

- Addition of the option for patients discontinuing study treatment to receive the assigned treatment for as long as the patients and their physician feel they are gaining clinical benefit. If continuing treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and undergo monitoring by their Investigators.

- At the time of the final DCO and database closure, patients currently receiving treatment with durvalumab may be transitioned to a rollover or safety extension study, if this type of study is available. Such a study would ensure treatment continuation with visit assessments per its protocol.

Synopsis, **Section 7.2 - Dose and treatment regimens:** Addition of "*after consultation between the Investigator and Study Physician*" for instructions in the event that a patient's weight decreases to ≤30 kg

Section 1.1.1 - Immunotherapies: Addition of text from the new protocol template (Dec 2017) to the immunotherapies section

Section 1.1.2 - Durvalumab

- Addition of text from the new protocol template for the proposed mechanism of durvalumab

- Update of the number of patients who have received 1 or more doses of durvalumab to date

Section 1.1.3 – Tremelimumab: Update of number of patients who have received 1 or more doses of tremelimumab to date

Section 1.1.4 - Durvalumab in combination with tremelimumab: Update of number of patients who have received 1 or more doses of durvalumab in combination with tremelimumab to date.

Section 1.2 - Rationale for study design, doses, and control groups: Clarification of the study stratification factors as follows:

- Subjects will be stratified to the HBV positive cohort if they test positive for HBV, or have a history of HBV infection.

- Subjects will be stratified to the HCV positive cohort if they test positive for HCV, or have a history of HCV infection.

Section 1.2.2.1 - Dose rationale for durvalumab monotherapy CCI Update of the expected half-life with durvalumab doses CCI from CCI

Section 1.2.3.1 - Dose rationale for combination therapy regimen of durvalumab CCI **plus tremelimumab** CCI

- Correction of the data collection date for Study D4190C00022 from 27 April 2017 to 13 January 2017.

- Update of the clinical data for durvalumab in combination with tremelimumab in Study D4190C00022: "*4 (10%) patients*" discontinued treatment due to treatment-related AEs, as opposed to "*3 (7.5%) patients*".

Section 1.3.2 – Overall risks: Updates from new protocol template for the overall risk with durvalumab, tremelimumab, and durvalumab in combination with tremelimumab.

Figure 1 - Study Design: Clarification of dosing arms and removal of endpoints from figure

Section 3.1 - Inclusion criteria:

- Amendment inclusion criteria 10 to indicate HBV DNA detectable level is ≥10 IU/ml rather than >10 IU/ml

- Clarification that only patients with HBV infection (positive HBsAg or detectable HBV DNA), must be treated with antiviral therapy to achieve HBV DNA ≤2000 IU/mL prior to enrollment, and they must remain on it for the study duration and for 6 months after the last dose of study medication. Patients with hepatitis B core antibodies (anti-HBc Ab), but no viral DNA, do not require antiviral treatment.

- Addition from new protocol template of the inclusion criteria "*Must have a life expectancy of at least 12 weeks*"

Section 3.2 – Exclusion criteria

- Amendment to exclusion criteria 12, specifying "*clinically meaningful ascites (defined as ascites requiring non-pharmacologic intervention eg, paracentesis or escalation in pharmacologic intervention to maintain symptomatic control), within 6 months prior to the first scheduled dose*", rather than "*ascites that require ongoing paracentesis, within 6 weeks prior to the first scheduled dose to control symptoms*. In addition, in the amended exclusion criteria "*subjects on stable doses of diuretics for ascites for ≥2 months are eligible*".

- Amendment to HBV DNA detectable level from >10 IU/ml to ≥10 IU/ml for exclusion criteria 18

- Rewording of exclusion criteria 18 and 19 to clarify that they are exclusion criteria

- Qualification for exclusion criteria 22 that a history of, or current, brain metastases will constitute an exclusion criteria.

Section 3.3 – Patient enrollment: Removal of Interactive Voice Response System as only Interactive Web Response System will be used

Section 3.8 – Restrictions: Update from new protocol template to the restrictions that apply to patients' contraception, while receiving study drugs, and for the specified times, before and after study drug administration

Section 3.9 – Discontinuation of study drug(s): Addition from the new protocol template of a supplementary condition under which patients will not receive any further study drugs: "*Clinical progression, ie. Investigator determination that the patient is no longer benefiting from treatment with the investigational product (IP), with or without radiological progression by RECIST 1.1.*"

Section 3.10.2.1: Removal of the condition that survival status for patients who are lost to follow-up or withdraw consent must be "*in the 7 days following data cutoff*"

Tables 2, 3 and 4:

- Addition of table footnote for coagulation stating that "*Either PT or INR can be performed at baseline (screening)*".

- Update of table notes regarding hepatitis stratification factors, and limit for tumor assessments changed to until RECIST 1.1-defined radiological progression rather than confirmed PD

Table 2:

- Removal of ADA sampling post dose

- Addition of the footnote: "*Optional tumor collection upon confirmed PD.*"

Tables 2 and 3:

- Addition of the requirement to assess alcohol use at screening

- For HCV testing assessment, removal of HCV genotype and anti-HCV testing from each treatment visit

- HBV DNA footnote amended to show HBV DNA detectable level is ≥10 IU/ml rather than >10 IU/ml.

Table 3:

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- Addition that alpha-fetoprotein should also be collected at the final visit

- For patients receiving sorafenib CCI without known diagnosis of hepatitis B or C, removal of laboratory assessments from C10 to disease progression

Table 4:

- Clarification of timings of ECOG assessments from "*at 30, 60 and 90 days*" to "*30, 60 after treatment discontinuation, and 90 days*".

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Section 4.1 – Screening/enrollment period: Addition of the necessity to assess alcohol use at screening

Section 5.1 – Efficacy assessments: Rewording of the text on tumor response to align it with the Statistical Analysis Plan and the new protocol template. In addition, the following specific changes were made:

- While RECIST 1.1 assessments will be performed on CT or MRI, with IV contrast of the chest, abdomen, and pelvis, pelvic imaging is only recommended when primary or metastatic disease involvement in the pelvic region is likely.

- During follow-up assessments (Q8W ±1 week for 48 weeks and Q12W ±1 week thereafter until confirmed PD), the imaging schedule must be followed regardless of any delays in dosing.

- The text for confirmation of progression guidelines was removed from this section, as these guidelines are also presented in Appendix B.

Section 5.2.1 – Laboratory safety assessments and 5.2.3 - Electrocardiograms: Provision that additional safety monitoring for patient receiving sorafenib should be carried out as per the label.

Section 5.4.1 – Collection of PK samples: The following collection window was added: Pre-dose (1 hour) and post-dose (10 minutes post-infusion).

Section 5.4.1.3 – Collection of samples to measure for the presence of ADAs: Addition of the following:

- Window for pre-dose sample is 1 hour

- For some countries, these samples may not be collected depending on their local regulatory and ethical requirements.

Section 5.4.1.4 – Storage and destruction of pharmacokinetic/ADA samples: Addition that PK and ADA samples collected in China will be stored and disposed of according to local laws and regulations.

Section 5.5.1 – Collection of patient samples for analysis of PD-L1 expression:

- Inclusion that additional archived tissue not intended for PD-L1 testing, and optional biopsies obtained at the time of progression or part of clinical care will not be collected in China. Additionally, China study sites will not submit tumor tissue blocks and only unstained sections from the tissue block will be submitted for further analysis.

- Retention of sections of tumor (to meet the FDA requirement for approval of a companion diagnostic) can also be kept at the Investigation Use only testing laboratory as well as at Ventana.

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Section 6.3.1 – Time period for collection of adverse events: Update of text with that of the new protocol template, to provide that, if an event starting after the defined safety follow-up period 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.

Section 6.3.2 – Follow-up of unresolved adverse events: Rewording of text in line with the new protocol template.

Section 6.3.10 – New cancers: Clarification that new metastatic lesions will be considered progression of the malignancy under investigation, and should not be reported as a new cancers.

Section 6.3.12 – 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, the following is recommended:

- Patients should continue the scheduled site visits and the 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 after the final DCO and database closure should be recorded in patients' notes. but not reported for the purposes of this study.

- All SAEs that occur after the final DCO and database closure in patients still on durvalumab treatment (or within 90 days following the last dose of durvalumab) must be reported as per Section 6.4 - Reporting of serious adverse events.

Section 6.5 – Adverse events of special interest: Update from new protocol template of the adverse events of special interest observed with durvalumab and/or tremelimumab

Section 6.9.1 – Specific toxicity management and dose modification information - Durvalumab and durvalumab plus tremelimumab

- Update from the new protocol template to introduce the amended Toxicity Management Guidelines.

- Reference to Appendix J which contains a new table to clarify the hepatitis testing stratification factors.

Section 6.9.3 – Management of hepatoxicity

- Replacement of "*irAE*" with "*imAE*"

Section 7.1 – Identity of study drugs:

- Addition from the new protocol template that "*Drug product should be kept in secondary packaging until use to prevent excessive light exposure.*" and "*Preparations are to be carried out in accordance with the study-specific drug handling instructions.*"

- Rewording of weight-based dosing at CCI for patients whose weight decreases to ≤30 kg in accordance with the new protocol.

- Addition of the following provision: "*The standard infusion time is 1 hour (±5 minutes). In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. Other drugs should not be co-administered through the same infusion line.*"

Section 7.2 – Dose and treatment regimens: Redraw of the following for dosing schedules to clarify the rechallenge option

- Durvalumab CCI plus tremelimumab CCI combination therapy (Figure 3)

- Durvalumab CCI plus tremelimumab CCI combination therapy (Figure 4)

Section 8.4.2.3 – Safety assessments: Removal of physical examinations as the only data collected will be the date and the fact that the exam took place.

Section 8.4.3.1 – EORTC QLQ-C30: The following amends were made to Table 13 and Table 15:

- Addition of the definition of ≥+10 as "*increase of at least 10*" and ≥-10 as "*decrease of at least 10*"

- Substitution of other qualification for deterioration to "*Subject too sick to complete the questionnaires (disease under investigation)*" from "*Subject too heavily affected by symptoms of disease under investigation" is answered as the reason for not completing questionnaire at visit*"

Section 8.4.3.1 – EORTC QLQ-C30: For the best response in EORTC QLQ-C30 and EORTC QLQ-HCC18 scores, the following changes to the scoring criteria were made in Table 14:

- Introduction of a "*missing*" response as "*Patient has no evaluable baseline or post-baseline PRO assessment*"

- For the "*improved*" response, the criterion "*Has 1 visit response of improvement with no further assessments, and did not die within 2 PRO assessment visits*" was added

- For the "*no change*" response, the criterion "*Has 1 visit response of no change with no further assessments, and did not die within 2 PRO assessment visits*" was added

Section 8.5.3.3 – Objective response rate: Patients in all arms with confirmed PD who, in the Investigator's opinion, continue to receivebenefit from their assigned treatment and meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment (Section 7.2.1.3). However, patients who develop progression in TLs after a clear response to therapy as defined by RECIST 1.1 will not be permitted to continue therapy.

The following text was added to clarify the differernce between Interim Analysis 1 and the final analysis:

- "*At IA1, only descriptive summaries of ORR including exact 95% CIs will be presented for each treatment arm. The analysis set will include all randomized patients who have had the opportunity for 24 weeks of follow-up at the time of the IA1 data cutoff (ie, randomized ≥24 weeks prior to IA1 DCO).*"

Appendix B – Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria: Update from the new protocol template of the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines for objective tumor response.

Appendix F – Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-related, and Non immune-mediated Reactions: Update from the new protocol template of the Toxicity Management Guidelines.

Appendix J – Hepatitis stratification: Addition that patients will be stratified to the HBV positive cohort if they test positive for HBV or have a history of HBV infection. Similarly, patients will be stratified to the HCV positive cohort if they test positive for HCV or have a history of HCV infection. A table of Hepatitis B Stratification Guidance is included to clarify the threshold for antiviral treatment and stratification for patients that have results of HBV DNA <10 IU/ml and HBV DNA ≥10 IU/ml.

Version 3.0, 23 January 2018

Released to correct errors noted in version 2.0 dated 20 December 2017 and to make administrative updates.

Section 1.2.3.1 – Clinical Data, 3rd paragraph: The data cut off date as been amended to 27 April 2017 as it was incorrect

Section 4.0 -Table 2 :

Corrected assement "Patients with known diagnosis of hepatitis C only".

- Added "HCV genotype, anti-HCV" back into the assessment table and amended the footnotes so they refer to the correct text at screening and on treatment
- Corrected assement "Patients without known diagnosis of hepatitis B or C" by amending the footnotes so they refer to the correct text at screening and on treatment

Added "HCV genotype, anti-HCV" to footnote H to clarify these test are only collected at screening.

Section 4.0 -Table 3 :

Corrected assement "Patients with known diagnosis of hepatitis C only".

- Added "HCV genotype, anti-HCV" back into the assessment table and amended the footnotes so they refer to the correct text at screening and on treatment
- Corrected assement "Patients without known diagnosis of hepatitis B or C" by amending the footnotes so they refer to the correct text at screening and on treatment

Added "HCV genotype, anti-HCV" to footnote I to clarify these test are only collected at screening.

Section 5.2.1 - Laboratory safety assessments: List of other safety tests to be performed was corrected to add in the laboratory assessments HCV RNA and HCV genotype which were absent. In addition, abbreiviation were added for each assessement for consistency.

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Section 5.5.1 – Collection of Patient Samples: added in sentence clarifying the optional collection of samples taken as part of clinical care.

Section 7.2.1.3 - Criteria for treatment through progression and for rechallenge: the exclusion criteria listed as an exception was amended as it was incorrect.

Version 4 (29-Nov-2018)

Following Amendment 4, AstraZeneca will update this study to discontinue enrollment into Arm B (durvalumab in combination with tremelimumab CCI based on results from a pre-planned interim analysis, evaluating tolerability and clinical activity in ongoing Study 22 (D419CC00022). All other arms remain unchanged. All regimens evaluated were tolerable, and no new safety signal was identified. From amendment 4 onwards patients will be randomized in a 1:1:1 ratio to Arm A, Arm C and Arm D. Patients who have been randomized to Arm B prior to this protocol amendment can continue on assigned study treatment (provided investigator and patient agree if it is in the best interest of the patient) until confirmed PD or any other discontinuation criteria is met. For patients assigned to Arm B, if a patient has not completed or started all CCI of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only. With the closure of Arm B (previously included as the Primary Objective – comparing Arm B vs. Arm D for OS), dual Primary Objectives have been incorporated (comparing Arm A vs. Arm D and Arm C vs. Arm D for OS). The sample size (number screened, number randomized) has also been increased to address this change.

Synopsis

Study title updated to patients with advanced HCC vs. unresectable

Added wording the inclusion of a China only extension to this study

Statistical Methods

Revised to include dual primary objectives (A vs. D and C vs. D for OS) and corresponding changes for the number of events, maturity, power and 2-sided significance levels for these analyses.

Independent Data Monitoring Committee

Added clarification of timing for first IDMC

Synopsis, Section 1.2 Rationale for study design, doses, and control groups, Section 1.4 Study Design, Figure 1, Section 3.3 Patient Enrolment and Randomization

Added wording to clarify closure of Arm B recruitment.

Synopsis and Figure 1

Updated to reflect closure of recruitment in Arm B and updated sample size (screened and randomized patients)

Synopsis, Section 1.4 Study design, Section 5.1 Efficacy assessments, Section 7.2.1.2 Re-challenge option for durvalumab and tremelimumab combination therapy arms

Added clarification for patient eligible for re-challenge that have evidence of PD "with or without confirmation according to RECIST 1.1".

Synopsis and Section 2.0 Study Objectives

Revised order of outcome measures for PFS & TTP.

Arm B was initially the primary objective (BvsD) and the dual primary objectives are now (AvsD) and (CvsD) for OS. Arm B will be summarized descriptively but not formally analysed.

Time to deterioration endpoints for key PRO symptoms and functioning specified in the PRO objective. Single-item appetite loss and nausea symptoms from the EORTC QLQ-C30 included to the PRO objective.

Synopsis and Sections 7.2, 8.1, 8.2, 8.5.1, 8.5.2.1, 8.5.3.1, 8.5.3.2, 8.5.3.3, 8.5.6.1, 8.5.6.2 updated Arm 1-4 to Arm A-D.

Added and/or updated the terms Arm A,B,C,D for one or more of the following reasons:

- to replace Arm 1,2,3,4
- to replace the wording that describes the treatment arm
- to indicate the specific immunotherapy arms

Section 1.2 Rationale for study design, doses, and control groups

Stratification factors: Added clarification for stratification for the HBV positive cohort**Section 1.3.3 Overall Benefit/risk**

Updated with safety data from Study 22 (D4190C00022)

Section 1.4 Study design. Section 5.1 Efficacy assessments, Section 7.2.1.2 Re-challenge option for durvalumab and tremelimumab combination therapy arms

Updated to allow patients in Arm B to rechallenge with either tremelimumab CCI OR tremelimumab CCI along with durvalumab.

Section 3.1 Inclusion Criteria

Inclusion criteria #10 – added clarification for HBV DNA limit.

Inclusion criteria #13 – added "Note: INR prolongation due to anticoagulants for prophylaxis (e.g. atrial fibrillation) in patients without liver cirrhosis could be exception".

Section 3.2 Exclusion Criteria

Exclusion criteria #12 – removed "or escalation in pharmacologic intervention".

Exclusion criteria #13 - added clarification for thrombosis - thrombosis (i.e. thrombosis in the main trunk of the portal vein, with or without blood flow) on baseline imaging.

Exclusion criteria #14 – removed "or assessed as high risk for esophageal variceal by the Investigator"

Exclusion criteria #18 – removed "≥10 IU/ml". Clarification added to Appendix I.

Exclusion criteria #19 – added "inferior vena cava thrombosis".

Exclusion criteria #20 – added "Patients with a history of prostate cancer of stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention ".

Section 3.3 Patient Enrolment and Randomization

Clarification added to etiology of liver disease – "confirmed" HBV versus "confirmed "HCV versus others.

Updated randomization ratio

Section 3.9 Discontinuation of Study Drug(s), Section 3.9, Section 5.2.8, Section 6.3.12, Section 6.9.1, Section 6.9.3, Section 7.7

Removal of Appendix F – replaced with reference to Toxicity Management Guidelines website https://tmg.azirae.com. Updated appendices lettering accordingly.

Section 3.10.2.1 Survival status for withdrawn consent and lost to follow-up patients

Clarified that patients are "potentially" lost to follow-up until the end of the study.

Table 2 Schedule of assessments for all immunotherapy arms treatment period

Clarified timeline for C1D1 PRO and tumor collection

Added row for "randomization" to clarify that this must occur prior to C1D1

Added "PT" to Coagulation collection

Updated requirements for virology sample collection and testing

Removed footnotes H and K and aligned all other footnotes accordingly

Clarification added -tremelimumab ADA sample collected at CCI is pre-dose and the tremelimumab ADA sample collected at CCI is 3 months post the last dose of tremelimumab

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Clarification added for "If screening laboratory assessments (including clinical chemistry, hematology, coagulation) are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1"

Clarification added for "If thyroid function, AFP and virology assessment are performed within 14 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. These assessments may be performed more frequently, if clinically indicated".

Footnote added for "HCV genotype will only be collected at baseline or Day 1 C1D1".

Clarified classification and stratification for confirmed HBV and confirmed HCV patients. Clarified that HBV DNA undetectable limit is <10UL/ml or under the limit of detection per local lab standard.

Clarification provided for circumstances where a patient has not completed or started all C of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only. For patients assigned to the tremelimumab CCI combinedwith durvaluamb arm B, who drop tremelimumab should follow the PK/ADA sampling schedule for Arm A.

Table 3 Schedule of assessments for sorafenib CCI therapy treatment period

Removed requirement for EORTC QLQ-C30, QLQ-HCC18, CCI at final visit.

Updated requirements for virology sample collection and testing

Clarified that the additional tumor sample collected is optional

Removed footnote G and realigned all footnotes accordingly

Footnote added for "HCV genotype will only be collected at baseline or Day 1 C1D1".

Footnote added for "If thyroid function, AFP and virology assessment are performed within 14 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. These assessments may be performed more frequently, if clinically indicated".

Table 4 Schedule of assessments for patients who discontinue treatment

Clarification added for collection of PK post discontinuation of IP – in case of a dose delay the PK should be collected 3 months from the last dose.

Removed in appendix I "Either PT or INR can be performed at baseline (screening)".

Section 4.1 Screening/enrolment period

Added clarification for tumor pathology and fibrosis score according to Appendix J

Added requirement to check eligibility at the date of randomization and if the patient does not meet I/E criteria they cannot be randomized.

Section 5.2.1 Laboratory safety assessments

Removed the reference to Table 5 and added quantitative HCV RNA as another safety test to be performed.

Table 6 Hematology

Added total white cell count to hematology with a note for coagulation parameters stating: for coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory haematology assessments are performed within 3 days prior to day 0) and as clinically indicated.

Added a footnote to absolute lymphocyte count that it should be recorded as an absolute count or as a percentage. Percentages will be calculated by DM.

Table 7 Coagulation

Add clarification of PT and INR instead of PT or INR in the Coagulation assessments table and note.

Updated the reference to Appendix E for evaluation of Hy's Law incidents

Section 5.2.7 Child-Pugh Score

Clarified that the use of the Child-Pugh score determines the severity of chronic liver disease, mainly cirrhosis.

Table 9 Child-Pugh classification of cirrhosis severity

Added footnote: 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 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.

Added footnote: PT or INR prolongation due to anticoagulants for prophylaxis (e.g. atrial fibrillation) in patients without liver cirrhosis could be recorded as point 1. All evidence, including medical history, pathology, physical examination, laboratory studies and radiographic studies, should be able to consistently support the exclusion of cirrhosis.

Clarified under PT header in the table "seconds prolonged over upper limit of normal" or INR

Section 5.3.3 Administration of the patient-reported outcome questionnaires

Added clarification that information collected is not routinely shared with study staff

Section 5.5.1 Collection of patient samples for analysis of PD-L1 expression

Changed the mandatory additional archived tumour tissue block to optional

Clarified that additional tumour biopsies collected as part of clinical care is optional

Section 5.5.5 Chain of custody of biological samples

Added clarification that the PI at each center will keep documentation of sample shipments

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Section 6.5 Adverse events of special interest

Added clarification that diarrhea/colitis and intestinal perforation is an AESI

Added serum to pancreatitis lipase and amylase increases

Section 6.10.1 Data Monitoring Committee

Added information that the first IDMC safety review can happen 6 months after the first patient is dosed or when approximately 30 patients per arm are randomized (whichever comes first)

Section 7.1.1 Durvalumab

Deleted the words "in line" with regard to the IV administration filter

Removed the sentence "Weight-based dosing language for patients ≤30kg is to be removed if the Investigator's decision is to withdraw patients because their weight falls to <30kg (Section 3.10)."

Updated Appendix reference to F.

Section 7.1.2 Tremelimumab

Added the sentence "Drug product should be kept in secondary packaging until use to prevent excessive light exposure."

Removed the sentence "Weight-based dosing language for patients ≤30kg is to be removed if the Investigator's decision is to withdraw patients because their weight falls to <30kg (Section 3.10). If the patient's weight falls to ≤30 kg, weight-based dosing at CCI

Deleted the words "in line" with regard to the IV administration filter

Updated Appendix reference to G.

Section 7.2 Dose and treatment regimens

Added clarification that crossover of treatment regimen is only allowed for re-challenge of Arm B (Also added to Section 7.2.1)

Added clarification that Following amendment 4 patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment arms: Arm A, Arm C and Arm D.

Section 8.1 Statistical considerations

Added "In the event a dosing arm is discontinued from the study, it is planned that data from this arm will still be presented in the final study reporting as per the SAP."

Clarifies that efficacy data for the Arm B (which was closed for enrollment with Amendment 4) will be summarized descriptively, but will not be formally analyzed (Also added to Section 8.5)

Section 8.2 Sample size estimate

Updated number of patients that will be screened and randomized due to closure of Arm B and change to dual primary objectives. Added text for randomization into China Tail/Cohort.

Indicated the new randomization ration of 1:1:1 into Arm A, Arm C, and Arm D.

Added clarifying text for the sample size calculations: average HRs (0.70 for Arm C vs. D, 0.75 for Arm A vs. D), a statistical weight (2), and follow up and total durations for estimating analysis times. Added that no adjustment has been included for dropouts

Updated the statistical analysis to reflect the new hypotheses given the dropped arm (Arm B) and the update to the primary and secondary objectives.

Section 8.3 Definitions of analysis sets

Table 12 - Added PFS before TTP, added BoR (Best objective Response)

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Section 8.5 Methods for statistical analyses

Added PRO as a secondary endpoint

Changed hypothesis one to a difference between Arm A and Arm D instead of Arm B and Arm D

Removed hypothesis 3

Section 8.5.1 Multiple testing strategy

Indicated that the first interim analysis will be performed after approximately 100 patients per treatment arm have had the "opportunity for 32 weeks" of follow up, instead of 24 weeks.

Added "opportunity" for 32 weeks follow-up to the following sections: Synopsis – statistical methods, 8.5.1 Multiple testing procedure, 8.5.3.3 Objective Response Rate

Updated the multiple testing strategy to reflect the procedure for controlling the type 1 error given the dropped Arm (Arm B), and the update to the dual primary objectives and secondary objectives

Updated Figure 5 to provide an overview of the multiple testing procedure for controlling the type 1 error

Section 8.5.4 Patient-reported outcomes

Sentence stating PROs are not part of the main MTP and will be analysed as supportive endpoints removed.

Section 8.5.4.1 EORTC QLQ-C30

Single-item appetite loss and nausea symptoms specified for MMRM and time to deterioration analysis.

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Section 8.5.6.1 Subgroup analyses for OS

Removed Arm B where it indicates that for each subgroup, the HR and 95% CI will be calculated from a Cox proportional hazards model with treatemtn as the only covariate.

Added at DCR-16 weeks in the following sections: Synopsis – secondary objectives & CCI statistical methods, abbreviation or special term glossary, 1.2 Rationale for study design, doses and control groups, 2.2.2 Other study objectives, CCI 5.1 Efficacy assessments, Table 12, 8.4.1.1 RECIST 1.1-based endpoints, 8.4.1.3 Secondary Endpoints, 8.5.3.4 Disease Control Rate, 8.5.6.2 Subgroup analysis for secondary endpoints, CCI

Section 11. List of References

Added Benson et al 2018.

Added Llover et al 1999.

Appendices

Appendix B - Removed "Only patients with measurable target disease at baseline should be included in the study. A previously irradiated lesion may be selected as a Target Lesion provided it fulfils the criteria for reproducible measurability and is the only lesion available." from target lesions.

Appendix E – added requirement for reporting potential hy's law events as SAEs.

Appendix F - Removed Dose Modification and Toxicity Management Guidelines for Immune mediated, Infusion related, and Non immune-mediated Reactions as an appendix and added the link https://tmg.azirae.com

Updated table 22 to table 21 Hep B Stratification Guidance

Added note to table 21 "If the limit of detection in local lab is higher than 10 IU/ml, sites should follow the local lab standard."

Added Appendix J T, N, M & Fibrosis scoring

Version 5 (17-Dec-2018)

Removed requirement for reporting of potential hy's law events as SAEs from Appendix E that was added in Amendment 4.

Version 6 (20-August-2019)

Table 5 – updated to require both amylase and lipase for serum chemistry

Updated sections: 1.2 study design, 3.1 inclusion criteria, table 2, table 3 - Clarified that HBV DNA undetectable limit is <10UL/ml or under the limit of detection per local or **central** lab standard.

Synopsis and Section 2.0 Study Objectives

Statistical Methods

Revised to change dual primary objectives to hierarchical approach with a single primary objective (Arm C vs. Arm D for superiority) and 2 key secondary objectives (Arm A vs. Arm D for non-inferiority, then Arm A vs. Arm D for superiority) of OS.

Updated number of events, maturity, power and 2-sided significance levels for these analyses.

Added secondary objective to conduct RECIST 1.1 and mRECIST analyses (ORR, BoR, DoR) by BICR for the IA1 set of patients with an opportunity for 32 weeks of follow-up.

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Clarified enrolment must be completed before Interim Analysis 1 can be performed.

Added descriptive text and abbreviation for Final Analysis (FA).

Section 1.2 Rationale for study design

Key Study Endpoints - removed treatment comparisons from text.

Section 8.2 Sample size estimate

Updated the statistical analysis to reflect the new hypotheses given the updates to the primary and secondary objectives and updated follow-up and total durations for estimating analysis times.

Added text for non-inferiority analysis for Arm A vs. Arm D - including margin and approximate events at interim and final analysis.

Section 8.5 Methods for statistical analyses

Changed order of hypotheses for superiority - H1: Arm C vs. Arm D; H3: Arm A vs. Arm D. Added a new hypothesis H2: for non-inferiority Arm A vs. Arm D.

Removed "and secondary endoints (ORR & PRO) from methods for statistical analysis as this will be included in the Statistical Analysis Plan (SAP).

Section 8.5.1 Multiple testing strategy

Updated the multiple testing strategy to reflect the procedure for controlling the type 1 error given the update from dual primary objectives to a hierarchical approach with a single primary objective (Arm C vs. Arm D as superiority) and 2 key secondary objectives (Arm A vs. D as non-inferiority, then Arm A vs. D as superiority) of OS.

Updated Figure 5 to provide an overview of the multiple testing procedure for controlling the type 1 error.

Clarified enrolment must be completed before Interim Analysis 1 can be performed.

Added descriptive text and abbreviation for Final Analysis (FA).

Section 8.5.3.3 Objective Response Rate

Clarified treatment arms as Arm A and Arm C for IA1 analysis.

Clarified ORR will be presented by Investigator assessment (using RECIST1.1) and BICR (using RECIST1.1 and mRECIST) for IA1.

Section 8.5.6.1 Subgroup analyses for OS

Added laboratory units for AFP.

Updated wording BCLC score to BCLC stage.

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Section 11. List of References

Added Cainap et al 2014.

Added Cheng et al 2013.

Added Johnson et al 2013.

Added Kudo et al 2018.

Added FDA Guidance 2016.

Added EMEA Guideline 2005.

Version 7 22-September-2021

Synopsis: Objectives, Statistical Methods – Efficacy Analyses, Section 2.3: Secondary Objectives

Added "OS at 36 months (OS36)" to secondary objectives

Synopsis: Post Final Data Cutoff, Section 4.3: Post Final Analysis Data Cutoff

Updated references to the final "primary analysis" data cutoff (DCO) and removed references to "database closure."

Clarified that patients in all treatment arms, not just durvalumab, may continue to receive treatment following the final primary analysis DCO.

Simplified language for management of patients continuing on treatment post primary analysis DCO.

Added "Long-term follow-up data may be collected in the eCRF post the final primary analysis as outlined in section 9.3."

Clarified the timing of a potential rollover study and that patients currently receiving treatment with durvalumab "(monotherapy or in combination with tremelimumab)" may be transitioned to such a study.

Table of Contents

Added Table 22: Schedule of study assessment and relevant eCRF pages to be completed during Long-term follow-up

List Of Abbreviations And Definition Of Terms

Added OS36.

Section 3.3: Patient Enrolment and Randomization, Table 2: Schedule of Assessments for all Immunotherapy arms treatment period, Table 3: Schedule of Assessments for Sorafenib CCI **therapy period, Section 5.5.1: Collection of patient samples for analysis of PD-L1 expression**

Updated screening tumor biopsy from mandatory to optional for the China cohort.

Section 4.3: Follow-up Period

Clarified reference to the final "primary" analysis.

Added that the study database "may remain open for collection of long term follow-up as presented in Table 22 in section 9.3" and removed "will be closed and only SAEs will be reported, unless there is a medical reason to maintain the database."

Section 5.5: Biomarkers

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Section 6.3.12: Safety Data to be Collected Following the Final DCO of the Study

Clarified that patients in all treatment arms, not just durvalumab, may continue to receive treatment following the final primary analysis DCO.

Simplified language for management of patients continuing on treatment post primary analysis DCO.

Added that "reports of pregnancy" along with Serious Adverse Events will be reported post final DCO and database closure.

Added "If long term survival follow-up is required, all data outlined in section 9.3 will be reported directly in the eCRF."

Section 7.1.2: Tremelimumab

Added the CCI tremelimumab vial presentation.

Updated: "The nominal fill volume is CCI for the CCI vial and CCI for the CCI vial."

Simplified IV administration instructions for the CCI dose by including them in paragraph 1 and removing paragraph 3.

Section 7.8: Post Study Access to Study Drug(s)

Clarified that after the final analysis, AstraZeneca will continue to supply open-label drug to patients "per their assigned study treatment."

Table 12: Summary of outcome variables and analysis populations

Added OS36

Section 8.4.1.3: Secondary endpoints

Added: "Proportion of patients alive at 36 months after randomization (OS36). The OS36 will be defined as the KM estimate of OS at 36 months after randomization."

Table 16: Pre-planned statistical and sensitivity analyses to be conducted

Added "Proportion of patients alive at 36 months, Hazard ratio using the KM estimates of OS at 36 months (following method described in Section 8.5.3)"

Section 8.5.2.1: Overall survival

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Section 8.5.3.6: OS18, OS24 and OS36

Added OS36

Section 9.3: Study timetable and end of study

Clarified that Q4 2021 refers to estimated "final primary analysis."

Added: "Long-term follow-up data may be collected in eCRFs post final primary analysis for approximately 3 years, as outlined in Table 22."

Added: "Long-term follow-up: Subjects continuing treatment should be followed for below assessments Q4W (+/-1 week). Subjects who have discontinued from treatment should be followed for below assessments Q8W (+/-1week). All SAEs and reports of pregnancy experienced by patients whilst receiving treatment or within 90 days of treatment discontinuing must continue to be reported to the Sponsor within the usual timelines (ie, immediately, or no later than 24 hours of when the site become aware of the SAE) directly in the EDC."

Added "If long-term follow-up is collected post final primary analysis, then the end of study is defined as the last visit of the last patient in the study".

Table 22: Schedule of study assessment and relevant eCRF pages to be completed during Long-term follow-up.

Added Table 22 to specify data collection post final primary DCO.

Section 9.4: Data management by AstraZeneca

Added "Limited data collection may continue after the final primary analysis database lock per section 9.3."

Appendix G: Tremelimumab Weight-based Dose Calculation

Added "OR Number of vials = Dose (mL) / CCI ▮▮▮▮▮ to allow for use of the CCI ▮ tremelimumab vial presentation.

In the Example, added "OR Number of vials = CCI ▮▮▮▮▮▮▮ = 2 vials" for the CC ▮ tremelimumab vial presentation.

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

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PROTOCOL SYNOPSIS

A Randomized, Open-label, Multi-center Phase III Study of Durvalumab and Tremelimumab as First-line Treatment in Patients with advanced Hepatocellular Carcinoma (HIMALAYA)

International co-ordinating Investigators

PPD

Memorial Sloan Kettering Cancer Center

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Study site(s) and number of patients planned

This study will screen approximately 1650 patients, with no prior systemic therapy for hepatocellular carcinoma (HCC) and not eligible for locoregional therapy, in order to randomize approximately 1310 patients. (This includes 1155 patients randomized to Arms A, C, D with 385 per arm; and approximately 155 patients in Arm B, randomized prior to the closure of this arm). Once global enrolment has completed, recruitment into an expansion cohort will continue in China until a total of 180 Chinese patients have been randomized. Details will be outlined in the China specific protocol amendment.

Study duration		Phase of development
Estimated date of first patient enrolled	Q4 2017	III
Estimated date of last patient completed	Q4 2021	III

Study design

This is a randomized, open-label, multi-center, global, Phase III study to assess the efficacy and safety of durvalumab monotherapy and durvalumab plus tremelimumab combination therapy versus sorafenib in the treatment of patients with no prior systemic therapy for HCC. The patients cannot be eligible for locoregional therapy.

Patients will be randomized in a 1:1:1:1 ratio to durvalumab CCI monotherapy (Arm A), combination therapy with durvalumab CCI plus tremelimumab CCI (Arm B),

combination therapy with durvalumab CCI plus tremelimumab CCI (Arm C), and sorafenib CCI (Arm D). Patients will be stratified according to macrovascular invasion (yes versus no), etiology of liver disease (hepatitis B virus [confirmed HBV] versus hepatitis C virus [confirmed HCV] versus others), and performance status (Eastern Cooperative Oncology Group [ECOG] 0 versus 1). Protocol amendment 4 will close enrollment to the combination therapy with durvalumab CCI plus tremelimumab CCI (Arm B). Patients will be randomized in a 1:1:1 ratio to durvalumab CCI monotherapy (Arm A), combination therapy with durvalumab CCI plus tremelimumab CCI (Arm C), and sorafenib CCI (Arm D). Patients who have been randomized to Arm B prior to this protocol amendment can continue on assigned study treatment (provided investigator and patient agree if it is in the best interest of the patient) until confirmed PD or any other discontinuation criteria is met. For patients allocated to Arm B, if a patient has not completed or started all CCI of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only.

Objectives

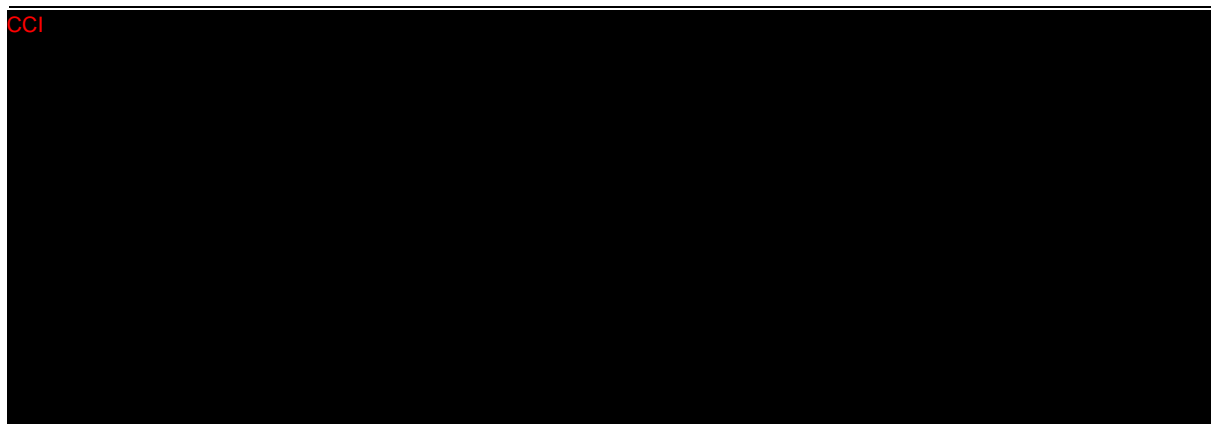All patients will be evaluated for all endpoints unless otherwise indicated.

Primary objective:	Outcome measure:
To assess the efficacy of Arm C vs. Arm D (for superiority)	Overall survival (OS)

Key Secondary objectives:	Outcome measure:
To assess the efficacy of Arm A vs. Arm D (for non-inferiority)	OS
To assess the efficacy of Arm A vs. Arm D (for superiority)	OS

Secondary objectives:	Outcome measures:
To assess the efficacy of Arm A vs. Arm D and Arm C vs. Arm D	• OS at 18 months (OS18), OS at 24 months (OS24) and OS at 36 months (OS36) • Progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), disease control rate (DCR), disease control rate at 16 weeks (DCR-16w), disease control rate at 24 weeks (DCR-24w) and duration of response (DoR), according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) using Investigator assessments

Secondary objectives:	Outcome measures:
To assess the efficacy of Arm A and Arm C in patients with an opportunity for 32 weeks of follow-up.	• ORR, BoR, and DoR according to RECIST1.1 and mRECIST by Blinded Independent Central Review (BICR)
To assess the efficacy of Arm A vs. Arm D and Arm C vs. Arm D by PD-L1 expression	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DoR according to RECIST 1.1 using Investigator assessments
To assess disease-related symptoms, impacts, and health-related quality of life (HRQoL) in Arm A vs. Arm D and Arm C vs. Arm D	• European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30): Time to deterioration in global health status/QoL, functioning (physical), multi-term symptom (fatigue), single-item symptoms (appetite loss, nausea) • EORTC 18-item hepatocellular cancer health-related quality of life questionnaire (QLQ-HCC18): Time to deterioration in single-item symptoms (shoulder pain, abdominal pain, abdominal swelling)
To investigate the immunogenicity of Arm A and Arm C	Presence of anti-drug antibody (ADA) for durvalumab and tremelimumab
To evaluate the population pharmacokinetics (PK) and pharmacodynamics of Arm A and Arm C	Durvalumab and tremelimumab concentrations and PK parameters in individual arms

Safety objective:	Outcome measures:
To assess the safety and tolerability profile across all treatment arms	Adverse events and laboratory findings.

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Target patient population

The study population includes patients 18 years of age or older with advanced HCC, Barcelona Clinic Liver Cancer stage B (not eligible for locoregional therapy) or stage C, and Child-Pugh A classification liver disease. Patients must not have received any prior systemic therapy for HCC.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

Duration of treatment

Patients in all treatment arms, should, wherever possible, continue to receive their initially assigned treatment to disease progression.

At the Investigator's discretion, patients in all treatment arms may continue receiving treatment until progressive disease (PD) by RECIST 1.1 is confirmed on a follow-up scan as per Confirmation of Radiological Progression criteria (Section 7.2.1.3). The follow up scan should preferably occur at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD. Refer to Appendix B for the criteria for confirmation of progression.

Patients in all arms with confirmed PD who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment. However, patients who develop progression in target lesions (TLs) after a clear response to therapy as defined by RECIST 1.1 will not be permitted to continue therapy.

Rechallenge option for patients in the durvalumab plus tremelimumab combination therapy arms

Patients in the durvalumab plus tremelimumab combination therapy arms who complete the assigned dosing cycle(s) of durvalumab plus tremelimumab, and are benefiting from study drug(s) in the Investigator's opinion, and subsequently have evidence of PD with or without confirmation according to RECIST 1.1 during the durvalumab monotherapy portion of their regimen can be rechallenged with tremelimumab, provided they meet eligibility criteria for rechallenge, as described in Section 7.2.1.3. Patients in Arm B can be rechallenged in their assigned treatment arm, or, with tremelimumab CCI along with durvalumab with prior approval from the AstraZeneca Study Physician. Patients in Arm C may only be rechallenged with tremelimumab CCI along with durvalumab if eligible for rechallenge.

Patients who rechallenge with tremelimumab after PD must have a rechallenge baseline tumor assessment within 28 days of restarting treatment with tremelimumab plus durvalumab combination therapy. Using regular RECIST 1.1 baseline guidelines, the rechallenge baseline may have TLs and non-target lesions different from those at the original baseline (including pre-existing new lesions). Rechallenge follow-up scans should occur Q8W (±1 week) for the first 48 weeks (relative to the date of first rechallenge treatment) then Q12W thereafter until confirmed disease progression.

Tumor assessments

Tumor assessments, based on RECIST 1.1, will be performed every 8 weeks (±1 week) for the first 48 weeks relative to the date of randomization and then every 12 weeks (±1 week) thereafter until RECIST 1.1-defined radiological progression is confirmed by a follow-up scan, if clinically feasible, as per Confirmation of Radiological Progression criteria (Appendix B). Patients who continue treatment beyond radiological progression should continue with tumor assessments on their regular imaging schedule for the duration of their treatment.

Post final data cutoff

Patients who continue to receive benefit from their assigned treatment at the final primary analysis data cutoff (DCO) 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 treatment following the final primary analysis DCO, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results during treatment in order to manage adverse events (AEs). Long-term follow-up data may be collected in the eCRF post the final primary analysis as outlined in section 9.3.

In the event that a rollover or safety extension study is available following the final primary analysis DCO, patients currently receiving treatment with durvalumab (monotherapy or in combination with tremelimumab) may be transitioned to such a study, and the current study would reach its end. The rollover 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.

Investigational product, dosage, and mode of administration

Durvalumab and tremelimumab will be administered via intravenous (IV) infusion CCI Sorafenib will be administered orally CCI

Durvalumab CCI monotherapy (Arm A)

- Durvalumab CCI via IV infusion CCI starting at CCI until confirmed PD, unacceptable toxicity, or any discontinuation criterion are met. (Note: If a patient's weight decreases to ≤30 kg, the patient should receive weight-based dosing of durvalumab CCI after consultation between the Investigator and the

Study physician, until the weight increases to >30 kg, at which point the patient should receive the fixed dose of durvalumab [CCI]

Durvalumab [CCI] plus tremelimumab [CCI] combination therapy (Arm B).

- Durvalumab [CCI] plus tremelimumab [CCI] starting at [CCI] followed by durvalumab [CCI] monotherapy [CCI] starting [CCI] after the final infusion of the combination therapy until confirmed PD, unacceptable toxicity, or any discontinuation criteria are met. (Note: If a patient's weight decreases to 30 kg or below (≤30 kg), the patient should receive weight-based dosing of durvalumab [CCI] and tremelimumab [CCI] after consultation beween The Investigator and the Study physician, until the weight increases to >30 kg, at which point the patient should receive the original assigned fixed dose of durvalumab [CCI] with or without tremelimumab [CCI] Following protocol amendment 4, enrollment into Arm B will be closed therefore patients will be randomized in a 1:1:1 ratio to Arm A, Arm C and Arm D. Patients who have been randomized to Arm B prior to protocol amendment 4 can continue on assigned study treatment (provided investigator and patient agree if it is in the best interest of the patient) until confirmed PD or any other discontinuation criteria is met. For patients assigned to Arm B, if a patient has not completed or started all [CCI] of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only.

Durvalumab [CCI] plus tremelimumab [CCI] combination therapy (Arm C)

- Durvalumab [CCI] plus tremelimumab [CCI] starting at [CCI] followed by durvalumab [CCI] monotherapy [CCI] starting [CCI] after the first and final infusion of the combination therapy until confirmed PD, unacceptable toxicity, or any discontinuation criteria are met. (Note: If a patient's weight decreases to 30 kg or below (≤30 kg), the patient should receive weight-based dosing of durvalumab [CCI] and tremelimumab [CCI] after consultation between the Investigator and Study Physician until the weight increases to above 30 kg (>30 kg), at which point the patient should receive the original fixed dose of durvalumab [CCI] with or without tremelimumab [CCI]

Sorafenib [CCI] therapy (Arm D)

- Sorafenib [CCI] orally [CCI] until confirmed PD at the Investigator's discretion, unacceptable toxicity, or any discontinuation criteria are met. Note: Suspected sorafenib-related toxicities should be managed based on the approved product label for each country.)

Statistical methods

Efficacy analyses

The primary endpoint of this study is OS. The secondary endpoints are ORR, DCR, DCR-16w, DCR-24w, DoR, PFS, TTP, OS18, OS24 and OS36. CCI ██████████████ ██ ██ ███████ All tumor-assessment-related endpoints will be analyzed using Investigator assessments according to RECIST 1.1.

Efficacy data will be summarized and analyzed on an intent-to-treat (ITT) basis, and the treatment arms will be compared on the basis of randomized treatment, regardless of the treatment actually received. Patients who are randomized but do not subsequently go on to receive study drug(s) are included in the ITT population.

Two interim analyses and a final analysis are planned as described below:

Interim Analysis 1 (IA1): The first interim analysis will be performed after approximately 100 patients per treatment arm have had the opportunity for 32 weeks of follow-up. The objective is to evaluate the efficacy of Arm A and Arm C in terms of ORR and DoR. The efficacy analysis set will include all randomized patients who have had the opportunity for at least 32 weeks of follow-up at the time of the IA1 data cutoff (ie, randomized ≥ 32 weeks prior to IA1 DCO). Descriptive summaries of ORR including exact 95% confidence intervals (CIs) will be presented. Kaplan-Meier plots of DoR and median DoR derived from the KM curves will also be provided. No formal comparison between arms will be performed in this interim analysis.

Interim Analysis 2 (IA2): The second interim analysis will be performed when approximately 404 OS events have occurred in Arm C and Arm D combined (~52% maturity) approximately 30 months after the first patient is randomized. The goal is to evaluate the efficacy of Arm C vs. Arm D in terms of OS (for the primary objective of superiority) and Arm A vs. Arm D in terms of OS (for the key secondary objectives – first for non-inferiority and then for superiority). OS will be analyzed using a stratified log-rank test (stratified for macro-vascular invasion, etiology of liver disease, and ECOG performance status). The treatment effect will be estimated by the hazard ratio (HR) together with its corresponding 95% confidence interval (CI) and p-value for each comparison.

Enrollment must be completed before Interim Analysis 1 can be performed.

Final Analysis (FA): The final analysis is expected to be performed when approximately 515 OS events have occurred in Arm C and Arm D combined (~67% maturity) approximately 37.5 months after the first patient is randomized. The primary objective is to assess the efficacy of Arm C vs. Arm D in terms of OS (for superiority). The key secondary objectives are to assess the efficacy of Arm A vs. Arm D in terms of OS (first for non-inferiority and then for superiority). OS will be analyzed as described in IA2. Efficacy data for Arm B (which was

closed for enrollment following Amendment 4) will be summarized descriptively, but will not be formally analyzed.

ORR will also be analyzed using logistic regression models adjusting for the same factors as OS. The results of the analysis will be presented in terms of an odds ratio together with its associated 95% CI and p-values.

The primary objective of OS will be tested as H1: Arm C versus Arm D for superiority. The key secondary objectives of OS will be tested as H2: Arm A versus Arm D for non-inferiority and then as H3: Arm A vs. Arm D for superiority. Overall strong control of the type I error will be applied testing endpoints as outlined in the MTP (Figure 5, further details in the SAP).

Sample size estimate

The study is sized to characterize the OS benefit of Arm C vs. Arm D. The sample size estimation assumes an exponentially distributed OS and a 2-month delay in separation of the OS curves for Arm C vs. Arm D. A non-uniform accrual of patients with a duration of 22 months is assumed when estimating the analysis times.

For the efficacy comparisons, the median OS for sorafenib (Arm D) is assumed to be 11.5 months, with an 18-month OS rate of 33.8%.

Durvalumab CCI *plus tremelimumab* CCI *(Arm C) versus sorafenib* CCI *(Arm D) [OS in FAS ITT]*

The assumed OS treatment effect is an average HR of 0.70 for Arm C versus Arm D. This translates to an increase in median OS from 11.5 months to 16.5 months, and in the 18-month OS rate from 33.8% to 46.8% in Arm C versus Arm D.

Final analysis of OS will be performed when approximately 515 events in Arm C and Arm D combined (~67% maturity) have occurred. This number of OS events will provide 97% power to demonstrate a statistically significant difference in OS at a 2-sided 4.25% significance level. The smallest treatment difference that could be observed as statistically significant at the final analysis is an average HR of 0.84 (an increase in median OS from 11.5 months to 13.7 months in Arm C versus Arm D).

Durvalumab CCI *monotherapy (Arm A) versus sorafenib* CCI *(Arm D) [OS in FAS ITT]*

It is estimated that approximately 453 and 560 events can be observed at the time of the interim and final analysis respectively. The power of the NI test at margin of 1.08 is approximately 84% at final analysis.

Safety analysis

Safety data will be summarized descriptively and will not be formally analyzed.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study, to ensure the integrity of the study, and to oversee the 2 planned interim analyses. The first IDMC safety review will occur when approximately 30 patients per arm are randomized or 6 months after the first patient is dosed (whichever comes first), and will occur approximately every 6 months thereafter; the frequency of IDMC review may be adjusted by the IDMC as needed. The IDMC will be composed of individuals external to AstraZeneca. An IDMC charter will be developed which will specify the Committee's responsibilities, authorities, and procedures along with details of the interim analysis planning, decision-making guidance, and dissemination of the results as well as the recommendations and decisions after the interim analyses. Formal implementation and communication of IDMC recommendations will be managed by the AstraZeneca Executive Committee, which will be unrelated to the HIMALAYA project team.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{ss}	Area under the serum drug concentration-time curve at steady state
BCLC	Barcelona Clinic Liver Cancer
BICR	Blinded Independent Central Review
BID	Twice daily
BoR	Best objective response
BP	Blood pressure
BUN	Blood urea nitrogen
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximum serum concentration at steady state
CR	Complete response
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CCI	
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4

Abbreviation or special term	Explanation
C$_{trough,ss}$	Trough concentration at steady state
DCO	Data cutoff
DCR	Disease control rate
DCR-16w	Disease control rate at 16 weeks
DCR-24w	Disease control rate at 24 weeks
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic Patient-reported Outcome
CCI	
EU	European Union
FAS	Full analysis set
FDG-PET	F-Fluoro-deoxyglucose positron emission tomography
FWER	Familywise error rate
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBc	Hepatitis B core
HBeAg	Hepatitis B e antigen
HBs	Hepatitis B surface
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma

Abbreviation or special term	Explanation
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	Human immunodeficiency virus
HL	Hy's law
CCI	
HR	Hazard ratio
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
IA1	Interim Analysis 1
IA2	Interim Analysis 2
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemical
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
CCI	
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
KM	Kaplan-Meier
LFT	Liver function test
LIMS	Laboratory Information Management System

Abbreviation or special term	Explanation
LLN	Lower limit of normal
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
CCI	
MMRM	Mixed effect model repeat measurement
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
CCI	
MTP	Multiple testing procedure
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
OS18	Overall survival at 18 months
OS24	Overall survival at 24 months
OS36	Overall survival at 36 months
PCP	Pneumocystis carinii pneumonia
PD	Progressive disease/Progression of disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
CCI	
PHL	Potential Hy's Law
CCI	

Abbreviation or special term	Explanation
CCI	
PK	Pharmacokinetic(s)
PO	By mouth
PR	Partial response
PRO	Patient-reported outcome
CCI	
PS	Performance status
Q12W	Every 12 weeks
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QLQ-C30	30-item core quality of life questionnaire
QLQ-HCC18	18-item hepatocellular cancer health-related quality of life questionnaire
QoL	Quality of life
QTcF	QT interval corrected for using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RFA	radiofrequency ablation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TACE	transarterial chemoablation
TB	Tuberculosis
TBL	Total bilirubin
TC	Tumor cells
TL	Target lesion
TNF	Tumor necrosis factor
Treg	Regulatory T-cell

Abbreviation or special term	Explanation
TSH	Thyroid stimulating hormone
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
US	United States
CCI	
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Revised Clinical Study Protocol
Drug Substance Durvalumab (MEDI4736) and tremelimumab
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49 (251)

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Hepatocellular carcinoma (HCC) is the third most common cause of cancer death worldwide and the second most common cause of cancer death in males (Altekruse et al 2009, Parkin et al 2005, Torre et al 2015). The incidence and prognosis of HCC vary geographically largely due to variations in etiological factors such as hepatitis B (HBV) and hepatitis C virus (HCV) infection and alcohol use. While the incidence rate of HCC has historically remained very high in HBV endemic regions of eastern Asia, the rates have recently been gradually increasing in many other parts of the world including North America, Latin America, and Europe (Bosetti et al 2008, Golden-Mason et al 2007, Hashim et al 2016, Ryerson et al 2016), possibly related to the higher incidence of cirrhosis due to chronic HCV infection and alcoholic/non-alcoholic fatty liver disease (Davila et al 2004, Dunn et al 2004, El-Serag et al 2003).

Patients with early-stage and localized HCC with well-preserved liver function can be treated with potentially curative options such as surgical resection, liver transplantation, and/or radiofrequency ablation (RFA). Only about 30% of the HCC patients are eligible for curative treatments (Llovet 2005), while the rest present with intermediate/advanced stage disease, which is usually treated with palliative intent. Advanced unresectable HCC for which liver-directed therapy is not appropriate is usually managed with systemic treatment approaches with palliative intent. However, HCC expresses high levels of multi-drug resistance proteins and is inherently chemotherapy resistant (Johnson et al 2013

Johnson PJ, Qin S, Park JW, Poon R, Raoul JL, Philip PA, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013; 31:3517-3524.

Kato et al 2001, Zhu 2006). Cytotoxic chemotherapy has limited clinical value as first-line systemic regimen because of the limited survival benefit and tolerability issues in patients with underlying hepatic dysfunction (Zhu 2006).

Sorafenib is currently accepted as the reference standard systemic therapy for advanced HCC based on the demonstrated overall survival (OS) superiority over placebo. The median survival of sorafenib-treated advanced HCC patients is between 6.5 and 10.7 months (Cheng et al 2009, Llovet et al 2008). While sorafenib overall demonstrated a manageable tolerability profile in advanced HCC patients, certain adverse events (AEs) such as diarrhea, hand-foot skin reaction, and fatigue occurred significantly more in sorafenib-treated patients (Cheng et al 2009, Lencioni et al 2014, Llovet et al 2008). AEs such as hand-foot skin reaction and rash, while not life-threatening, are often associated with superimposed complications such as infections and pain and can severely limit the activities and the quality of life (QoL) of the patients.

In summary, the currently available therapies have had a positive impact on the survival of HCC patients; however, the overall prognosis and QoL remain poor. HCC, therefore,

represents a significant unmet medical need. Hence, novel therapies are needed for patients with HCC not eligible for locoregional therapy.

1.1.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004).

Programmed cell death ligand 1 (PD-L1) is a member of the B7 family of ligands that inhibit T-cell activity through binding to the programmed cell death (PD-1) receptor (Keir et al 2008) and to cluster of differentiation (CD)80 (Butte et al 2007). PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T-cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1, CD274) and programmed cell death ligand 2 (PD-L2), (B7-DC, CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T-cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment(Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T-cells. These deactivated T-cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T-cells and upregulated on activated T-cells. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (eg, interferon gamma [IFNγ]) and can be found on both tumor cells (TC) and tumor-infiltrating IC. The binding of PD-L1 to PD-1 on activated T-cells delivers an inhibitory signal to the T-cells, preventing them from killing target TC and protecting the tumor from immune elimination (Zou and Chen 2008). PD-L1 may also inhibit T-cells through binding to CD80, although the exact mechanism is still not elucidated (Butte et al 2007, Paterson et al 2011).

PD-L1 is expressed with a high frequency in a broad range of cancers, up to 88% in some types of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of nonclinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting

the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance anti-tumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Huz et al 2012, Iwai et al 2002, Okazaki and Honjo 2007

Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19(7):813-824.

Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008), with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Qin et al 2016

Qin A, Coffey DG, Warren EH, Ramnath N. Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. Cancer Med 2016;9:2567–2578.

Rizvi et al 2015, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma) (Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

In contrast to PD-L1, CTLA-4 is constitutively expressed by regulatory T-cells and upregulated on activated T-cells. CTLA-4 delivers a negative regulatory signal to T-cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (FDA Guidance for Industry (issued November 2016). Non-Inferiority Clinical Trials to Establish Effectiveness. Available from: URL: https://www.fda.gov/media/78504/download.

Fife and Bluestone 2008). In addition, blockade of CTLA-4 binding to CD80 and CD86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

Nonclinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as CTLA-4 and PD-L1 has promising clinical activity. There are data from agents in the anti-PD-1/PD-L1 anti-CTLA-4 class showing clinical activity in a wide range of tumor types including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck, and urothelial carcinoma.

1.1.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin (Ig) G1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T-cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.)

The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T-cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, across the entire clinical development program, an estimated 6000 patients have been exposed to 1 or more doses of durvalumab in AstraZeneca- or MedImmune-sponsored studies, either as monotherapy or in combination, including 2878 patients in open-label trials, and 2347 patients as an estimate based on the randomization scheme in studies where the treatment arm is blinded. Additionally, more than 1700 patients have been exposed to 1 or more doses of durvalumab in externally sponsored/Investigator-initiated clinical trials (ESR/IITs). Of the 2878 patients exposed to durvalumab in ongoing AstraZeneca- or MedImmune-sponsored open-label studies, 1744 received durvalumab monotherapy, 808 received durvalumab in combination with tremelimumab, 140 received durvalumab in combination with other investigational products, and 186 received durvalumab in combination with approved products. No study has been terminated prematurely due to toxicity. Details on the safety profile of durvalumab CCI monotherapy is summarized in Section 1.3.2.1. Refer to the current durvalumab Investigator's Brochure (IB) for a complete summary of nonclinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

1.1.3 Tremelimumab

Tremelimumab is a human IgG2 mAb that is directed against CTLA-4 (CD152), a cell surface receptor that is expressed primarily on activated T-cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin-2 and IFNγ) from human T-cells, peripheral blood mononuclear cells, and whole blood (Tarhini and Kirkwood 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date, 1500 patients received tremelimumab in completed monotherapy studies and 380 patients in ongoing, Phase IIb monotherapy studies. An ongoing rollover study provides continued access to treatment for 37 patients treated in prior completed studies. In a third ongoing monotherapy study, 104 patients have been treated as of the data cutoff (DCO) date. In addition, approximately 80 patients have been treated with tremelimumab in monotherapy arms of combination studies. Five studies of tremelimumab in combination with other anticancer agents have been completed, and 18 studies are ongoing. In total, approximately 250 patients with a variety of tumor types have been treated. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.2. Refer to the current

tremelimumab IB for a complete summary of nonclinical and clinical information including safety, efficacy, and PK.

1.1.4 Durvalumab in combination with tremelimumab

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant, targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012); therefore, in addition to evaluating both agents in the monotherapy setting in a number of cancer indications, AstraZeneca is also investigating the use of durvalumab plus tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab plus tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab CCI   combined with tremelimumab CCI

 The study is ongoing and continues to accrue patients. In addition, other clinical studies have since started looking at the drug combination in both NSCLC and other oncology indications.

To date, across the entire clinical development program, 3000 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab plus tremelimumab combination therapy are summarized in Section 1.3.2.3. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of nonclinical and clinical information including safety, PK, and efficacy.

1.1.5 Sorafenib

Sorafenib is an orally active multi-kinase inhibitor that can inhibit both cell surface tyrosine kinase receptors (vascular endothelial growth factor receptors, platelet-derived growth factor receptor-b) and downstream intracellular kinases (C-Raf, B-Raf, and mutant B-Raf), which are thought to be involved in tumor cell proliferation, angiogenesis, and apoptosis (Adnane et al 2006, Keating and Santoro 2009, Wilhelm et al 2006). In early studies utilizing animal models, sorafenib was shown to inhibit tumor proliferation and angiogenesis of multiple human tumor xenograft including HCC and renal cell carcinoma (Adnane et al 2006, Butte et al 2007, Cainap et al 2014

Cainap C, Qin S, Huang W, Chung Ik, Pan H, Cheng Y, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2014; 33:172-179.

Chang et al 2007, Keating and Santoro 2009, Liu et al 2006). Since then, several Phase II and Phase III studies have been conducted, and their results have supported the approval in several countries of sorafenib as a treatment option for unresectable HCC, advanced renal cell carcinoma, and refractory advanced differentiated thyroid carcinoma (Abou-Alfa et al 2006,

Brose et al 2014, Ellis et al 2008, EMEA Guideline (issued July 2005). Guideline on the choice of the non-inferiority margin. Doc. Ref. EMEA/CPMP/EWP/2158/99.

Escudier et al 2009, Llovet et al 2008).

Two Phase III studies, the European SHARP study and the Asia-Pac Sorafenib study, have compared the OS of patients with advanced HCC on sorafenib versus placebo (Llovet et al 2008, Cheng et al 2009). In the SHARP study, the patients receiving sorafenib demonstrated a significantly better median OS (10.7 versus 7.9 months, hazard ratio [HR]: 0.69, p-value: <0.0001) (Llovet et al 2008). In the Asia-Pac study, while the magnitude of benefit was less than the SHARP study, the patients receiving sorafenib demonstrated a significantly better median OS (6.5 versus 4.2 months, HR: 0.68, p-value: 0.014) (Cheng et al 2009). The most common sorafenib-related Grade 3 or 4 AEs noticed in these studies include hand-foot skin reaction (8% in SHARP and 10.7% in Asia-Pac), diarrhea (8% in SHARP and 6% in Asia-Pac), fatigue (4% in SHARP and 3.4% in Asia-Pac), and hypertension (2% in SHARP and 3% in Asia-Pac). Based on these results, sorafenib has been widely accepted as the reference standard systemic therapy for unresectable HCC in several countries.

1.1.6   Rationale for durvalumab and tremelimumab as treatment options for HCC

The liver has a unique immunobiology whereby multiple regulatory mechanisms are in place to maintain an immunosuppressive environment. Normal liver is inherently tolerogenic to environmental auto-antigens and toxins in order to prevent aberrant immunity to pathogens exposed through arterial circulation and from the gut (Pardee and Butterfield 2012). Clinical and nonclinical data in HCC show increased expression of immunosuppressive cell populations such as regulatory T-cells (Treg) and myeloid-derived suppressor cells, along with the upregulation of inhibitory signaling molecules, including CTLA-4 and PD-1 (Gao et al 2009, Hato et al 2014, Pardee and Butterfield 2012). HBV and HCV infection has also been associated with the upregulation of Treg and PD-L1/PD-1 expression, thereby suggesting a role for this pathway in HBV and HCV-mediated hepatocarcinogenesis (Miroux et al 2010, Pardee and Butterfield 2012, (Golden-Mason et al 2007, Peng et al 2008).

Overexpression of PD-L1 has been shown to also be associated with tumor aggressiveness, progressive disease (PD), and high mortality in HCC patients (Klein et al 2007, Gao et al 2009). Therefore, therapeutic agents that are capable of blocking PD-L1 and CTLA-4 may potentially improve clinical outcomes by reversing the immunosuppressive nature of the HCC tumors and stimulating host immunity against HCC.

Currently, there are early and encouraging clinical data that suggest that anti-CTLA-4 and anti-PD-L1/PD-1 agents may be active in HCC and may provide better response rates and survival.

Tremelimumab at a dose of CCI intravenously (IV) CCI has been administered to 20 subjects with HCV-associated 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 unresectable HCC (Child-Pugh class A/B7) patients were treated with tremelimumab at 2 dose levels CCI IV CCI in combination with subtotal ablation (RFA/ transarterial chemoablation [TACE]) during CCI of treatment (Duffy et al 2017). Safety evaluation showed no clear trend in AEs across the cohorts utilizing different doses of tremelimumab. No dose-limiting toxicity (DLT) was encountered on the study. The most common Grade 3 or Grade 4 toxicities were aspartate aminotransferase (AST) elevation (21%), alanine aminotransferase (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).

The safety and efficacy of durvalumab monotherapy (anti-PD-L1 antibody) has been studied in 40 patients with HCC in a Phase I/II study (CD-ON-MEDI4736-1108), the objective response rate (ORR) was 10.3% and the median OS was 13.2 months. Additional detail on the safety and efficacy data from this study are presented in Section 1.2.2.1. Similar results have also been noted with another PD-1 receptor antagonist, which has shown an ORR of 18.6% and median OS of 13.2 months in patients with advanced HCC patients (Melero et al 2017).

The data from the above mentioned studies, although exploratory, are suggestive that both durvalumab and tremelimumab monotherapies have anti-tumor activity against HCC.

Durvalumab plus tremelimumab combination therapy for patients with unresectable HCC is being evaluated in an ongoing Phase I/II study (Study D4190C00022). In this study, immunotherapy-naive patients with unresectable HCC were treated with durvalumab plus tremelimumab combination therapy CCI followed by durvalumab monotherapy CCI The study demonstrated an ORR of 18% based on the interim data from 40 patients with ≥16 weeks follow-up. Overall, durvalumab plus tremelimumab combination therapy was well tolerated in this unresectable HCC population. Additional detail on the safety and efficacy data from this study is presented in Section 1.2.3.1.

The overall clinical evidence suggests that while both durvalumab and tremelimumab have clinical activity in patients with HCC as monotherapies, the combination of these two agents may provide an even better anti-tumor effect in this population. Hence, a global, randomized, Phase III study is warranted to evaluate the safety and efficacy of both agents in patients with unresectable HCC and not eligible for locoregional therapy.

1.2 Rationale for study design, doses, and control groups

Study design:

This randomized Phase III study will assess the efficacy and safety of durvalumab with or without tremelimumab compared to sorafenib in the treatment of patients with no prior systemic therapy for HCC that is not eligible for locoregional therapy. This will be a multi-center global study enrolling patients from different regions including North America, South America, Asia and Europe. Therefore, the study population is expected to be representative of the demographic variation and the global distribution of HCC. Patients will be randomized in a 1:1:1:1 ratio to durvalumab CCI monotherapy (Arm A), durvalumab CCI plus tremelimumab CCI combination therapy (Arm B), durvalumab CCI plus tremelimumab CCI combination therapy (Arm C), and sorafenib CCI Arm D). Following protocol amendment 4 enrollment into Arm B will be closed therefore patients will be randomized in a 1:1:1 ratio to Arm A, Arm C and Arm D. Patients who have been randomized to arm B prior to protocol amendment 4 can continue on assigned study treatment (provided investigator and patient agree if it is in the best interest of the patient) until confirmed PD, or any other discontinuation criteria is met. For patients assigned to Arm B, if a patient has not completed or started all CCI of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only.

The rationale for the selection of the dose regimens is provided later in this section. This study will use an open-label design because blinding of the treatment assignment is challenging owing to the unique safety profile differences between durvalumab and tremelimumab compared with sorafenib, and the different routes of administration causing undue burden to patients.

Stratification factors:

Some of the key prognostic factors for HCC include Eastern Cooperative Oncology Group (ECOG) performance status, macrovascular invasion, geographic region, etiology of liver disease, extra-hepatic disease, Child-Pugh status, and baseline AFP (Llovet et al 2008a, Bruix et al 2012, Cheng et al 2012). The 3 important factors selected for stratification were macrovascular invasion (yes versus no), etiology of liver disease (Confirmed HBV versus confirmed HCV versus others), and ECOG performance status (0 versus 1). Three factors, resulting in 12 different combinations, ensure sufficient events in each of the combinations to allow for precise estimation of treatment effects and adequate power for analysis. Geographical region was not selected because etiology of liver disease accounts for some of the different prognosis observed in the different geographic regions. Similarly, macrovascular invasion and extra-hepatic disease both represent the impact of tumor burden. The selection of patients with Child-Pugh class A removed the need to include Child-Pugh status. Hence, the proposed stratification factors are considered appropriate for the proposed Phase III study.

Subjects will be stratified to the HBV positive cohort if subjects:

- Test positive for HBV (test positive for hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibodies (anti-HBcAb) with detectable HBV DNA (≥10 IU/ml or above the limit of detection per local or central lab) (Appendix I). Subjects must be treated with antiviral therapy, as per institutional practice, to ensure adequate viral suppression (**HBV DNA ≤2000 IU/mL**) prior to enrolment.

Subjects will be stratified to the HCV positive cohort if subjects

- Subjects will be stratified to the HCV positive cohort if they test positive for HCV or have a history of HCV infection (Refer to Appendix I).

Key study endpoints:

OS is considered the most appropriate endpoint in randomized controlled oncology clinical studies for registration. In the pivotal study, OS is the primary endpoint for the efficacy evaluation. Supportive efficacy endpoints based on tumor progression, such as ORR, progression-free survival (PFS), time to progression (TTP), duration of response (DoR), disease control rate (DCR), DCR at 16 weeks (DCR-16w), DCR at 24 weeks (DCR-24w) will be evaluated as secondary endpoints.

1.2.1 Sorafenib dose and treatment regimen justification.

Sorafenib CCI orally CCI taken until disease progression is the regulatory approved regimen for treatment of patients with unresectable HCC and not eligible for locoregional therapy; the data supporting this dose and schedule are described in Section 1.1.5.

1.2.2 Durvalumab monotherapy dose and treatment justification

1.2.2.1 Dose rationale for durvalumab monotherapy CCI

A durvalumab dose of CCI (equivalent to CCI CCI is supported by in vitro data, nonclinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

Pharmacokinetics/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study CD-ON-MEDI4736-1108 with doses ranging from CCI durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity for doses CCI suggesting near complete target saturation of membrane-bound PD-L1 and soluble PD-L1 (sPD-L1) and further shows that the durvalumab dosing frequency can be adapted to a particular regimen, given the linearity seen at doses higher than CCI Based on population PK modelling, the estimated half-life of durvalumab is approximately 17 days following CCI dose. Consequently, the expected half-life with doses CCI is also approximately 17 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range

studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. For further information on immunogenicity, please see the current IB.

Data from Study D4190C00006 (a Phase Ib study in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of ▮CCI▮ durvalumab ▮CCI▮ For further information on PK observations in Study 006, please see the current IB.

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th, 50th, and 95th percentiles) for a ▮CCI▮ regimen.

A population PK model was developed using the data from Study CD-ON-MEDI4736-1108 (doses of ▮CCI▮ (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both ▮CCI▮ regimens, as represented by area under the serum drug concentration-time curve at steady state ([AUC_{ss}] 4 weeks). Median maximum serum concentration at steady state ($C_{max,ss}$) is expected to be higher with ▮CCI▮ (approximately 1.5-fold), and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with ▮CCI▮ (approximately 1.25-fold). Clinical activity with the ▮CCI▮ dosing regimen is anticipated to be consistent with ▮CCI▮ with the proposed similar dose of ▮CCI▮ ▮CCI▮ expected to (a) achieve complete target saturation in the majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of anti-drug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal anti-tumor activity in animal models.

Given the similar area under the serum drug concentration-time curve and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the ▮CCI▮ regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of ▮CCI▮

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK of the ▮CCI▮ regimen.

The safety and preliminary efficacy of durvalumab ▮CCI▮ monotherapy in unresectable HCC population was evaluated in Study CD-ON-MEDI4736-1108. As of 24 October 2016, 40 HCC patients have received durvalumab monotherapy with a median 23.9 months follow-up. Most common treatment-related AEs were fatigue (27.5%), pruritus (25.0%), and elevated AST (22.5%). Grade ≥3 related AEs were reported in 8 (20%) patients. The most common Grade ≥3 related AE was elevated AST (7.5%) and elevated ALT (5.0%). Seven (17.5%) patients completed the initial 12-month treatment and 7 (17.5%) patients

discontinued treatment because of an AE (none related to treatment). There were no deaths due to treatment-related AEs. Of the 39 patients evaluable for response, 4 (10.3%) showed confirmed partial response. The median OS was 13.2 months.

Overall, this regimen of durvalumab monotherapy demonstrated promising anti-tumor activity with an acceptable safety profile in unresectable HCC population. Therefore, this regimen was included in the current study.

1.2.2.2   Rationale for fixed-dose regimen of durvalumab

A fixed-dose regimen of CCI (equivalent to CCI of durvalumab will be used in this study. Refer to Section 1.2.3.3 for the rationale for using the fixed-dose regimen.

1.2.3   Durvalumab plus tremelimumab dose and treatment regimen justification

The combination dose regimens selected for this study are to permit examination of the drug, dose, and schedule that may demonstrate sustained target suppression, promising efficacy, and an acceptable safety profile in patients with unresectable HCC.

1.2.3.1   Dose rationale for combination therapy regimen of durvalumab CCI plus tremelimumab CCI

A summary of the existing PK, pharmacodynamics, and clinical data (presented below) has been utilized to guide the dose regimen selection for the combination of durvalumab CCI plus tremelimumab CCI in this study.

Pharmacokinetics/pharmacodynamics data

Study D4190C00006 included dose cohorts with both a CCI and a CCI schedule of durvalumab in combination with a CCI schedule of tremelimumab. The CCI schedule was included to align with the CCI dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar AUC_{ss} at 4 weeks was expected following both CCI dosing with durvalumab. The durvalumab PK data from Study D4190C00006 were in line with the predicted monotherapy PK data developed nonclinically and in line with that seen in the first-time-in-human, single-agent study (Study CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure following durvalumab CCI dosing, with no alterations in PK when durvalumab and tremelimumab (doses ranging from CCI are dosed together. While the median $C_{max,ss}$ is expected to be higher with CCI (approximately 1.5-fold) and median $C_{trough,}$CCI (approximately 1.25-fold), this is not expected to impact the overall safety and efficacy profile, based on existing nonclinical and clinical data.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented pharmacodynamic activity relative to

durvalumab monotherapy, with combination doses containing CCI tremelimumab including both the CCI durvalumab plus CCI tremelimumab combinations.

Clinical data

In Study D4190C00006, various dose combinations durvalumab and tremelimumab have been explored, with doses of tremelimumab ranging from CCI and doses of durvalumab ranging from CCI (Antonio et al 2016). Tremelimumab was given on a CCI schedule for CCI and CCI for CCI for a total of CCI whilst durvalumab was explored in both a CCI and CCI schedule until PD, with the goal of identifying the dose combination that best optimizes the risk-benefit profile in an acceptable range of PK and pharmacodynamic values. Of all treatment cohorts, the cohort of patients treated in the CCI durvalumab plus CCI tremelimumab CCI cohort had a tolerable safety profile, but still showed strong evidence of clinical activity. No DLTs were reported in this cohort. Additionally, this cohort demonstrated a lower rate of all AEs, discontinuation due to AEs, SAEs, and severe AEs compared to cohorts treated with durvalumab plus tremelimumab above CCI Efficacy data in this NSCLC cohort suggest that the CC CCI durvalumab plus CCI tremelimumab CCI dose cohort may demonstrate equivalent clinical activity to other dose combinations evaluated on the study. Based on this data, the combination dose of CCI durvalumab plus CCI tremelimumab CCI was selected for further development.

Refer to the current durvalumab IB for a complete summary of nonclinical and clinical information on this combination therapy regimen.

Combination therapy of durvalumab CCI plus tremelimumab CCI is being evaluated in unresectable HCC population in an ongoing Phase I/II study (Study D4190C00022). As of the 27 April 2017, 40 patients with HCC were evaluable for response at ≥16 weeks follow-up. Most common (≥15%) treatment-related AEs were fatigue (27.5%), pruritus (22.5%), increased ALT (20.0%), increased AST (17.5%), decreased appetite (15.0%), and increased lipase (15.0%). Grade ≥3 or serious treatment-related AEs were reported in 10 (25.0%) of the patients. Most common Grade ≥3 or serious treatment-related AEs were increased AST (10.0%) and increased lipase (10.0%). Four (10.0%) patients discontinued treatment due to treatment-related AEs. Of the 40 patients evaluable for response with ≥16 weeks follow-up, 7 (18.0%) showed partial response; this includes confirmed responses only. The disease control rate was 60.0%. Overall, this regimen of durvalumab and tremelimumab showed a tolerable safety profile in this unresectable HCC population, while demonstrating encouraging early responses. Enrollment to the Phase II expansion portion of this study is ongoing.

Rationale for CCI of combination therapy followed by durvalumab monotherapy

Long-term follow-up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed CCI for CCI and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately

22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow-up (Sangro et al 2013).

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies. Nivolumab (anti-PD-1) was dosed CCI for up to 96 weeks in a large Phase I dose-escalation and expansion study and showed responses were maintained for a median of 22.94 months for melanoma (doses CCI 17 months for NSCLC (doses CCI and 12.9 months for renal cell carcinoma patients (doses CCI at the time of data analysis (Brahmer et al 2012, Drake et al 2013, Hodi et al 2014). In MPDL3280a (anti-PD-L1) studies, and studies of the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period, it has been reported that responses were maintained beyond treatment discontinuation (Gandhi et al 2014, Wilhelm et al 2006).

Similar long-term results may be expected with use of other immune-mediated cancer therapeutics such as tremelimumab, durvalumab, or the combination of the 2 agents. Therefore, durvalumab plus tremelimumab combination therapy for this regimen will be administered for CCI followed by durvalumab monotherapy CCI until PD, unacceptable toxicity, or any discontinuation criteria are met.

Rationale for fixed-dose regimen of durvalumab and tremelimumab

A fixed-dose regimen of CCI (equivalent to CCI of durvalumab plus CCI (equivalent to CCI of tremelimumab will be used in this study.

Refer to Section 1.2.3.3 for the rationale for using the fixed-dose regimen.

1.2.3.2 Dose rationale for combination regimen of durvalumab CCI plus tremelimumab CCI

A summary of the existing PK and pharmacodynamic data has been utilized to guide the regimen selection for the combination of durvalumab CCI plus single dose of tremelimumab CCI

Pharmacokinetics/pharmacodynamics data

The supporting data for this regimen are based on PK and pharmacodyamic data from regimens that used tremelimumab doses of greater than CCI from Study D4190C00006. An approximate dose-proportional increases in PK exposure (maximum serum concentration and area under the serum drug concentration-time curve from time 0 to Day 28 post-dose) was observed with increasing doses of tremelimumab CCI An exploratory pharmacodynamic analysis bioanalytically evaluated the effects of tremelimumab on proliferating T-cells from NSCLC patients who received tremelimumab CCI and durvalumab CCI combination treatment. Monotonic increases in pharmacodynamic activity with the combination (increased activation/ proliferation markers on CD4 and CD8 T-cells in periphery) were observed with increasing doses of tremelimumab CCI The peak increase (%) from baseline of CD4+Ki67+ T-cells was observed

8 days post administration, and the peak level was significantly increased (p ≤ 0.05) as increasing dose of tremelimumab in the range of CCI Study data also suggested that higher peak exposure (maximum serum concentration [C_{max}]) of tremelimumab is related to a higher maximum pharmacodynamic effect in the NSCLC patient population. Overall, the PK/pharmacodynamic data suggest that tremelimumab of dose greater than CCI with a higher peak exposure may be associated with a higher pharmacodynamic effect.

Additionally, based on simulation data, the C_{max} (78 µg/mL) post single dose administration of tremelimumab CCI is approximately 4-fold higher than the predicted C_{max} (19 µg/mL) post the first dose of tremelimumab CCI and is 3-fold higher than the predicted C_{max} (25 µg/mL) post the fourth dose of tremelimumab CCI in a CCI setting.

Clinical data

The safety and preliminary efficacy of combination of durvalumab CCI plus single dose of tremelimumab CCI in unresectable HCC population is being evaluated in the ongoing Phase I/II study (Study D4190C00022).

In summary, a single dose of tremelimumab CCI while maintaining a similar overall exposure, has a 3- to 4-fold higher C_{max} compared to the CCI of tremelimumab CCI Therefore, this single administration of the higher dose of tremelimumab may have the potential for better anti-tumor activity while potentially avoiding any cumulative toxicity associated with repeated dosing of the CCI tremelimumab. Therefore, the regimen of durvalumab CCI plus tremelimumab CCI is being evaluated in the current study.

Rationale for fixed-dose of durvalumab and tremelimumab

A fixed-dose regimen of CCI (equivalent to CCI of durvalumab plus CCI (equivalent to CCI of tremelimumab will be used in this study. Refer to Section 1.2.3.3 for the rationale for using the fixed-dose regimen.

1.2.3.3 Rationale for utilizing a fixed-dose regimen for durvalumab and tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (Study CD-ON-MEDI4736-1108; N=292; CCI solid tumors). Similarly, a population PK model was developed for tremelimumab using data from Phase I through Phase III (N=654; CCI 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-dose (based on median weight of approximately 75 kg) regimens of both durvalumab and tremelimumab were compared using predicted PK concentrations (5th, 50th, and 95th percentiles) using a population PK model. A total of 1000 patients were simulated using weight distribution of

40 kg to 120 kg. Simulation results demonstrate that 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 (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Wolchok et al 2013, Zhang et al 2008). 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 (Wolchok et al 2013, Zhang et al 2008). 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/pharmacodynamics parameters (Wolchok et al 2013).

A fixed-dose 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-dose regimens. Based on the average body weight of 75 kg, a fixed dose of CCI durvalumab (equivalent to CCI and a fixed dose of CCI tremelimumab (equivalent to CCI are selected for the current study. Therefore, the selected regimen of the durvalumab and/or tremelimumab arms are:

- Durvalumab monotherapy of CCI (Arm A)

- Durvalumab CCI plus tremelimumab CCI followed by durvalumab monotherapy CCI and (Arm B)

- Durvalumab CCI plus tremelimumab CCI followed by durvalumab monotherapy CCI (Arm C)

1.3 Benefit/risk and ethical assessment

1.3.1 Potential benefits

1.3.1.1 Durvalumab monotherapy

Information on the potential benefit of durvalumab CCI monotherapy or equivalent in patients with HCC are based on Study CD-ON-MEDI4736-1108 and are presented in Section 1.1.6. For other tumor types, see the most current durvalumab IB.

1.3.1.2 Durvalumab plus tremelimumab combination therapy

The potential benefits of adding tremelimumab to durvalumab is presented in Section 1.1.6. Information on the data supporting the selected combination regimen of durvalumab plus tremelimumab in patients with HCC are presented in Section 1.2.3. For other tumor types, see the most current durvalumab and tremelimumab IBs.

1.3.2 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed

against TC. By stimulating the immune system, however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal (GI) AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations; skin events such as rash and dermatitis, and endocrinopathies including hypo- and hyperthyroidism.

1.3.2.1   Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea, colitis, intestinal perforation pneumonitis/ILD, endocrinopathies (hypo- and hyperthyroidism, diabetes mellitus type I, hypophysitis, and adrenal insufficiency), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis, increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

For information on all identified and potential risks with durvalmab, always refer to the current version of the durvalumab IB.

In monotherapy clinical studies of durvalumab, AEs (all grades) reported very commonly (≥10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab, and approximately 6% of patients experienced an SAE that was considered to be related to durvalumab by the Investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see 6.9.1).

The safety profile of the HCC cohort in Study CD-ON-MEDI4736-1108 is consistent with the overall safety profile of durvalumab in other indications. In addition to the above mentioned AEs, the study showed a higher percentage of AST/ALT elevation, which would be expected in a HCC patient population. Refer to Section 1.2.1 for additional details.

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.3.2.2   Tremelimumab

Risks with tremelimumab monotherapy comprise, but are not limited to, GI effects (colitis, diarrhea, enterocolitis, and intestinal perforation), endocrine disorders (hypo- and hyperthyroidism, hypophysitis, and adrenal insufficiency), skin effects (rash and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other GI events (eg, ulcerative colitis, dehydration, nausea, and vomiting); hepatic events including hepatitis and liver enzyme elevations; pneumonitis and ILD, nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre, and proximal muscle weakness; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis, and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome, and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia.

For information on all identified and potential risks with tremelimumab, always refer to the current version of the tremelimumab IB.

Using pooled data from monotherapy clinical studies, AEs (all grades) reported very commonly (≥10% of patients) were diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab, and approximately 45% of patients experienced an SAE.

A summary of tremelimumab monotherapy AE data in patients with HCC is provided in Section 1.1.6. A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.

1.3.2.3   Durvalumab and tremelimumab

The safety of durvalumab plus tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study D4190C00006 in patients with NSCLC and is being studied in a number of other ongoing clinical trials, in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab plus tremelimumab (based on an equivalent durvalumab dose of CCI and a tremelimumab dose of CCI are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from Study D4190C00006 and other studies evaluating the combination and combinations of other agents in the same drug class for patients with advanced HCC indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with durvalumab in combination with tremelimumab, always refer to the current version of the durvalumab IB.

In durvalumab plus tremelimumab combination studies at the dose of durvalumab CCI and tremelimumab CCI AEs (all grades) reported very commonly (≥ 10% of patients) were fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, edema peripheral, weight decreased, hyponatremia, and rash.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug(s), and approximately 15% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study Investigator.

The safety of the weight-based equivalent regimen of durvalumab CCI plus tremelimumab CCI in unresectable HCC population has been demonstrated in Study D4190C00022, and the safety summary is presented in Section 1.2.3. Safety data of durvalumab CCI plus tremelimumab CCI combination therapy is being evaluated as a part of the expansion of the ongoing Phase I/II Study D4190C00022.

A detailed summary of durvalumab plus tremelimumab combination therapy AE data can be found in the current version of the durvalumab IB.

1.3.3   Overall benefit risk

Durvalumab and tremelimumab have shown encouraging anti-tumor activity as single agents in advanced HCC population. The summary of this efficacy data is presented in Section 1.1.6 and Section 1.2.1. The combination regimen of these two agents shows a higher response rate in HCC population compared to either of the monotherapies. Thus, durvalumab plus tremelimumab combination therapy may potentially offer benefit to this patient population. Both durvalumab monotherapy and durvalumab plus tremelimumab combination therapy was tolerable in advanced HCC. The current study design aims to minimize potential risks by providing for early and intensive safety monitoring for any unexpected safety signals and for managing those risks deemed to be most likely based on prior experience with durvalumab, tremelimumab, and sorafenib. Two combination dose regimens of durvaluamb plus tremelimumab combination therapy were selected for this study with the aim to select the regimen with the most benefit for patients with advanced HCC. The safety and efficacy of these 2 dose regimens are being evaluated in the ongoing Phase I/II study (Study D4190C00022). Safety data showed that both dose regimens were tolerable and no new safety signals were identified. While efficacy for durvalumab in combination with tremelimumab at the CCI was not meaningfully better than durvalumab monotherapy, efficacy data supports continued evaluation of durvalumab in combination with tremelimumab at the CCI Therefore, the study will continue evaluating durvalumab in combination with tremelimumab CCI only following implementation of protocol amendment 5.

Patients with unresectable HCC have very limited systemic therapeutic options and a poor life expectancy and health-related quality of life (HRQoL) based on the currently available treatments. HCC, therefore, represents a significant unmet medical need and underlines the need for novel therapies for this patient population. The durvalumab monotherapy and

durvalumab plus tremelimumab combination therapy options proposed in this study may demonstrate a meaningful clinical benefit and a manageable safety profile compared with sorafenib. The overall benefit-risk profile of durvalumab and tremelimumab is expected to be favorable, therefore supporting the current study design.

1.4 Study design

This is a randomized, open-label, multi-center, Phase III study to assess the efficacy and safety of durvalumumab monotherapy and durvalumab plus tremelimumab combination therapy versus sorafenib in the treatment of patients with unresectable HCC not eligible for locoregional therapy.

Patients will be randomized in a 1:1:1:1 ratio to durvalumab CCI monotherapy (Arm A), durvalumab CCI plus tremelimumab CCI combination therapy (Arm B), durvalumab CCI plus tremelimumab CCI combination therapy (Arm C), or sorafenib CCI (Arm D). Following amendment 4 enrollment into Arm B will be closed therefore patients will be randomized in a 1:1:1 ratio to Arm A, Arm C and Arm D. Patients will be stratified according to macro-vascular invasion (yes versus no), etiology of liver disease (confirmed HBV versus confirmed HCV versus others), and performance status ([ECOG] 0 versus 1).

Patients in all treatment arms may continue receiving their originally assigned treatment, at the Investigator's discretion, until clinical progression with or without Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)-defined radiological PD (confirmed PD; see Section 7.2.1.3). A subsequent scan is required following the assessment of PD by RECIST 1.1, preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD, and this subsequent scan is evaluated according to the criteria for Confirmation of Radiological Progression (Appendix B).

Additionally, patients in all arms with confirmed PD who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment

Patients in the durvalumab plus tremelimumab combination therapy arms who complete the assigned dosing cycle(s) of durvalumab plus tremelimumab, and are benefiting from study drug(s) in the Investigator's opinion, and subsequently have evidence of PD with or without confirmation according to RECIST 1.1 during the durvalumab monotherapy portion of their regimen can be rechallenged with tremelimumab, provided they meet eligibility criteria for rechallenge, as described in Section 7.2.1.3. Patients in Arm B can be rechallenged in their assigned treatment arm, or, with tremelimumab CCI along with durvalumab with prior approval from the AstraZeneca Study Physician. Patients in Arm C may only be rechallenged with tremelimumab CCI along with durvalumab if eligible for rechallenge. Crossover within the study will not be permitted for any of the treatment arms with the exception of rechallenge in Arm B as per section 7.2.1.2 .

Tumor assessments, based on RECIST 1.1, will be performed every 8 weeks (Q8W) (±1 week) for the first 48 weeks from the date of randomization and then Q12W (±1 week) thereafter until RECIST 1.1-defined radiological progression followed by a subsequent scan if clinically feasible, evaluated by Confirmation of Radiological Progression criteria (Appendix B). Patients who permanently discontinue study drug(s) for reasons other than PD should continue to have radiographic scans performed per their original schedule until confirmed PD

Figure 1 Study design
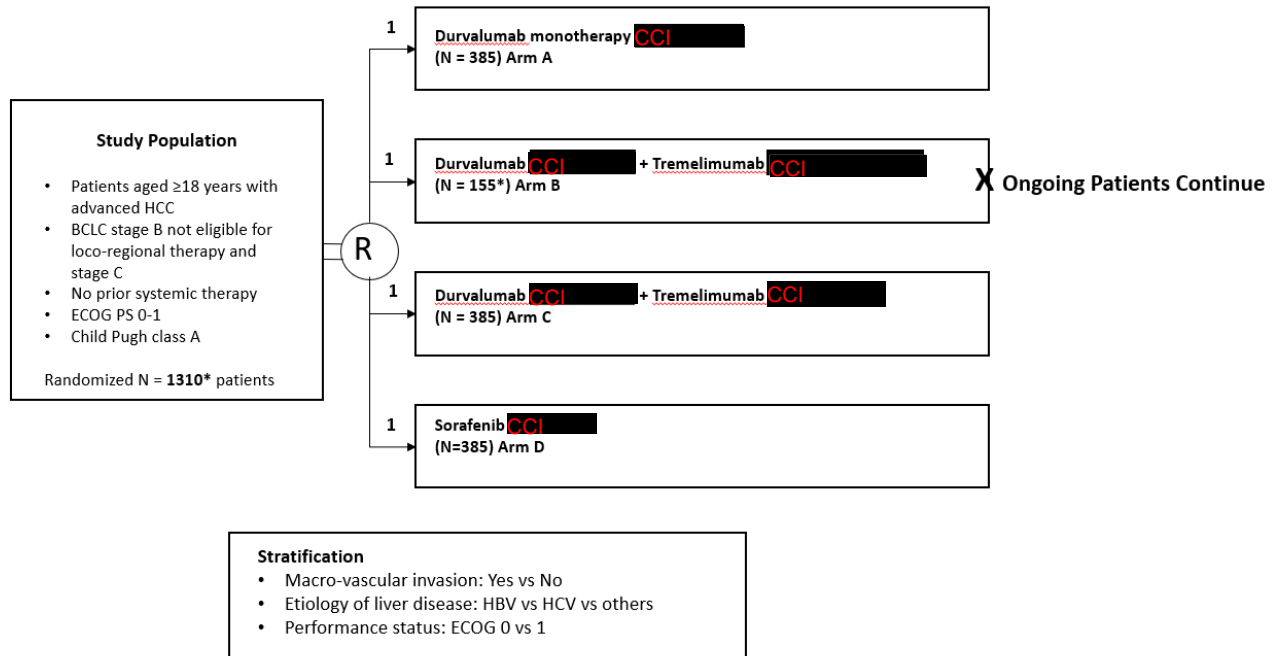
*approximately
BCLC Barcelona Clinic Liver Cancer; CCI ECOG Eastern Cooperative Oncology Group;
HBV hepatitis B virus; HCC hepatocellular carcinoma; HCV hepatitis C virus; PS performance status; CCI

2. STUDY OBJECTIVES

All patients will be evaluated for all endpoints unless otherwise indicated.

2.1 Primary objectives

Primary objective:	Outcome measure:
To assess the efficacy of Arm C vs. Arm D (for superiority)	OS

2.2 Key Secondary objectives

Key Secondary objectives:	Outcome measure:
To assess the efficacy of Arm A vs. Arm D (for non-inferiority)	OS
To assess the efficacy of Arm A vs. Arm D (for superiority)	OS

2.3 Secondary objectives

Secondary objectives:	Outcome measures:
To assess the efficacy of Arm A vs. Arm D and Arm C vs. Arm D	• OS at 18 months (OS18),OS at 24 months (OS24) and OS at 36 months (OS36) • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DoR, according to RECIST 1.1 using Investigator assessments
To assess the efficacy of Arm A and Arm C in patients with an opportunity for 32 weeks of follow-up.	• ORR, BoR, and DoR according to RECIST1.1 and mRECIST by Blinded Independent Central Review (BICR)
To assess the efficacy of Arm A vs. Arm D and Arm C vs. Arm D by PD-L1 expression	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DoR according to RECIST 1.1 using Investigator assessments

Secondary objectives:	Outcome measures:
To assess disease-related symptoms, impacts, and HRQoL in Arm A vs. Arm D and Arm C vs. Arm D	• European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30): Time to deterioration in global health status/QoL, functioning (physical), multi-term symptom (fatigue), single-item symptoms (appetite loss, nausea) • EORTC 18-item hepatocellular cancer health-related quality of life questionnaire (QLQ-HCC18): Time to deterioration in single-item symptoms (shoulder pain, abdominal pain, abdominal swelling)
To investigate the immunogenicity of Arm A and Arm C	Presence of ADA for durvalumab and tremelimumab
To evaluate the population PK and pharmacodynamics in Arm A and Arm C	Durvalumab and tremelimumab concentrations and PK parameters in individual arms

2.4   Safety objectives

Safety objective:	Outcome measures:
To assess the safety and tolerability profile across all treatment arms	Adverse events and laboratory findings.

2.5   CCI

CCI

Revised Clinical Study Protocol
Drug Substance Durvalumab (MEDI4736) and tremelimumab
Study Code D419CC00002
Version 7.0
Date 22-September-2021

CCI

73 (251)

CCI

3. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Age ≥18 years at the time of screening

2. Body weight >30 kg.

3. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

4. Confirmed HCC based on histopathological findings from tumor tissues.

5. Must not have received prior systemic therapy for HCC.

6. Must not be eligible for locoregional therapy for unresectable HCC. For patients who progressed after locoregional therapy for HCC, locoregional therapy must have been completed ≥28 days prior to the baseline scan for the current study.

7. Barcelona Clinic Liver Cancer (BCLC) stage B (that is not eligible for locoregional therapy) or stage C. (refer to appendix J)

8. Child-Pugh Score class A. (refer to table 9)

9. ECOG performance status of 0 or 1 at enrollment. (refer to section 5.2.6)

10. Patients with HBV infection, characterized by positive hepatitis B surface antigen (HBsAg) and/or hepatitis B core antibodies (anti-HBcAb) with detectable HBV DNA (≥10 IU/ml or above the limit of detection per local or central lab standard), 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 anti-hepatitis B core (HBc) with undetectable HBV DNA (<10 IU/ml or under the limit of detection per local or central lab standard) 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 or above the limit of detection per local or central lab standard). 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.

11. 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).

12. At least 1 measurable 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 computerized tomography (CT) or magnetic resonance imaging (MRI), and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines. A lesion which progressed after previous ablation or TACE could be measurable if it meets these criteria.

13. 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 ≥1000/μL
   c. Platelet count ≥75000/μL
   d. Total bilirubin (TBL) ≤2.0× upper limit of normal (ULN)
   e. AST and ALT ≤5×ULN
   f. Albumin ≥2.8 g/dL
   g. International normalized ratio (INR) ≤1.6. Note: INR prolongation due to anticoagulants for prophylaxis (e.g. atrial fibrillation) in patients without liver cirrhosis could be exception.
   h. Calculated creatinine clearance ≥50 mL/minute as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine creatinine clearance

14. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal as described in Section 3.8.

15. Must have a life expectancy of at least 12 weeks

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

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

2. Previous study drug(s) assignment in the present study.

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

4. Have received an investigational product within 28 days prior to the first dose of study drug(s).

5. Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:

    –   Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

    –   Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.

6. Any concurrent chemotherapy, study drug, or biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

7. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

8. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 28 days of the first dose of study drug(s).

9. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study drug(s). Note: Local surgery of isolated lesions for palliative intent is acceptable.

10. History of allogeneic organ transplantation (eg, liver transplant).

11. 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).

12. Clinically meaningful ascites, defined as any 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.

13. Patients with main portal vein thrombosis (i.e. thrombosis in the main trunk of the portal vein, with or without blood flow) on baseline imaging.

14. Active or prior documented 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.)

15. Patient currently exhibits symptomatic or uncontrolled hypertension defined as diastolic blood pressure >90 mmHg or systolic blood pressure >140 mmHg.

16. Any condition interfering with swallowing pills, uncontrolled diarrhea, or other contraindication to oral therapy.

17. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). Patients without active disease in the last 5 years are excluded unless discussed with the Study Physician and considered appropriate for study participation.

The following are exceptions to this criterion:

– Patients with vitiligo or alopecia

– Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement

– Any chronic skin condition that does not require systemic therapy

– Patients with celiac disease controlled by diet alone

18. Patients co-infected with HBV and HCV, or co-infected with HBV and hepatitis D virus (HDV). HBV positive (presence of HBsAg and/or anti-HBcAb with detectable HBV DNA); HCV positive (presence of anti-HCV antibodies); HDV positive (presence of anti-HDV antibodies).

19. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable

angina pectoris, cardiac arrhythmia, ILD, serious chronic GI conditions associated with diarrhea, inferior vena cava thrombosis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase the risk of incurring AEs, or compromise the ability of the patient to give written informed consent.

20.   History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug(s) and of low potential risk for recurrence

- Patients with a history of prostate cancer of stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention .

- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

- Adequately treated carcinoma in situ without evidence of disease

21.   History of leptomeningeal carcinomatosis.

22.   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.

23.   Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.

24.   History of active primary immunodeficiency.

25.   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 immunodeficiency virus [HIV] 1/2 antibodies).

26.   Current or prior use of immunosuppressive medication within 14 days before the first dose of study drug(s). The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

     –   Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

27.   Receipt of live attenuated vaccine within 30 days prior to the first dose of study drug(s). Note: Patients, if enrolled, should not receive live vaccine while receiving study drug(s) and up to 30 days after the last dose of study drug(s).

28.   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 monotherapy or 180 days after the last dose of durvalumab plus tremelimumab 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.

29.   Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

30.   Patients who have received anti-PD-1, anti PD-L1, or anti CTLA-4 prior to the first dose of study drug(s)

For procedures for withdrawal of incorrectly enrolled patients, see Section 3.4.

3.3   Patient enrollment and randomization

Investigators should keep a record (ie, the patient screening log) of patients who entered screening.

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

- Obtain signed informed consent before any study-specific procedures are performed, including optional consent for genetic research study. 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. For patients with a single target lesion (TL), if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired. Informed consent of study procedures may be obtained prior to the 28-day screening window in order to permit tumor biopsy sample acquisition. Note: tumor biopsy is optional for China Cohort.

- Obtain a unique PPD enrollment number, through the Interactive Web Response System (IWRS) in the following format PPD

    This number is the patient's unique identifier and is used to identify the patient on the electronic Case Report Forms (eCRFs).

- Information on macro-vascular invasion (yes versus no), etiology of liver disease (confirmed HBV versus confirmed HCV versus confirmed others (HBV - and HCV -), and performance status (ECOG 0 versus 1) must be available in the IWRS in order for the patient to be randomized, as these are stratification factors. Patients will be randomized in a 1:1:1:1 ratio to (Arm A), (Arm B), (Arm C), or (Arm D) in a stratified manner accordingly. Following protocol amendment 4 enrollment into Arm B will be closed therefore patients will be randomized in a 1:1:1 ratio to Arm A, Arm C and Arm D. Patients who have been randomized to Arm B prior to protocol amendment 4 can continue on assigned study treatment (provided investigator and patient agree if it is in the best interest of the patient) until confirmed PD or any other discontinuation criteria is met. For patients assigned to Arm B, if a patient has not completed or started all CCI of tremelimumab, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only.

- Obtain tumor sample. This may be an archived tumor sample (taken ≤3 years) or a fresh tumor biopsy if archived tissue is not available. Patients must be able to undergo a fresh tumor biopsy during screening or to provide an available tumor sample taken ≤3 years prior to screening. Tumor lesions used for fresh biopsies should not be TLs, unless there are no other lesions suitable for biopsy. Fine needle aspirate specimens are not acceptable. Note: tumor biopsy is optional for China cohort.

- Determine patient eligibility (see Sections 3.1 and 3.2)

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

- Record the presence or absence of macro-vascular invasion as a stratification factor in the IWRS (yes versus no).

- Record the etiology of liver disease (Confirmed HBV versus confirmed HCV versus others) as a stratification factor in the IWRS.

- Record performance status (ECOG 0 versus 1) as a stratification factor in the IWRS.

- Obtain a unique randomization number via the IWRS. Numbers will start at PPD and will be assigned strictly sequentially by IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the treatment arms.

If the patient is ineligible and not randomized, the IWRS should be contacted to terminate the patient in the system.

Patients will begin treatment on Day 1. Treatment should start no more than 3 working days after being randomized. Patients must not be randomized and treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

3.4   Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study drug(s). There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria, must not be randomized or initiated on treatment and must 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. In situations where an agreement cannot be reached, the patient should have their study therapy stopped and be withdrawn from the study.

3.5   Methods for assigning treatment groups

The actual treatment given to patients will be determined by the randomization scheme in the IWRS. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. A randomization list will be produced for each of the randomization stratum. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment arm.

Patients will be identified to the IWRS per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The IWRS will provide the kit identification number accordingly to the assigned treatment arm).

3.6   Methods for ensuring blinding

This is an open-label study. To maintain the integrity of the study, AstraZeneca personnel directly involved in the study conduct will refrain from accessing treatment records whenever possible and under no circumstances will they view data aggregated by treatment arm during the course of the study.

The study includes 2 interim analyses (by treatment arm), which will be performed by an Independent Data Monitoring Committee (IDMC). Details will be given in the IDMC charter.

3.7   Methods for unblinding

Not applicable as this is an open-label study.

3.8   Restrictions

The following restrictions apply while the patient is receiving study drug(s) and for the specified times before and after study drug(s) administration:

1.   Female patients of childbearing potential

–   Females patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 1) from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, as well as the rhythm and withdrawal methods, are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

2.   Male patients with a female partner of childbearing potential

–   Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). However, occasional abstinence, as well as the rhythm and withdrawal methods, are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

–   Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1).

Note: Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

•   Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, <1% per year) when used consistently and correctly are described in Table 1. 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.

Patients in the sorafenib CCI arm must follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the sorafenib CCI treatment.

Table 1   Highly effective methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: etonogestrel-releasing implants (eg, Implanon®, Norplan®) • Intravaginal devices: ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: medroxyprogesterone injection (eg, Depo-Provera®) • Combined pill: normal and low-dose combined oral contraceptive pill • Patch: norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: progesterone-based oral contraceptive pill using desogestrel (Cerazette® is currently the only highly effective progesterone-based pill)

[a]   This is also considered a hormonal method.

All patients

– Patients should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of the durvalumab plus tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy or until alternate anticancer therapy is started.

Restrictions relating to concomitant medications are described in Section 7.7.

3.9   Discontinuation of study drug(s)

An individual patient will not receive any further study drug(s) if any of the following occur in the patient in question:

• Withdrawal of consent from further treatment with study drug(s). The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 3.10.2).

• An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.

- Any AE that meets criteria for discontinuation as defined in Toxicity Management Guidelines or as defined in the local prescribing information for sorafenib CCI

- Pregnancy or intent to become pregnant

- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with study drug(s) (eg, refusal to adhere to scheduled visits)

- Initiation of alternative anticancer therapy, including another investigational agent.

- Clinical progression, ie, Investigator determination that the patient is no longer benefitting from treatment with the investigational product (IP), with or without radiological progression by RECIST 1.1

3.9.1 Procedures for discontinuation of a patient from study drug(s)

At any time, patients are free to discontinue study drug(s) without prejudice to further treatment. A patient who decides to discontinue study drug(s) will be asked about the reason(s) for discontinuation and the presence of any AE. If possible, they will be seen and assessed by an Investigator. AEs will be followed up (see Section 6.3). The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Patients who are permanently discontinued from further receipt of study drug(s), regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up.

Patients who permanently discontinue study drug(s) for reasons other than objective confirmed RECIST 1.1 PD should continue to have RECIST 1.1 assessments performed Q8W (±1 week) for the first 48 weeks relative to the date of randomization and then Q12W (±1 week) thereafter until confirmed PD as defined in Table 2 and Table 4.

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in Table 4 as an alternative.

Patients who have permanently discontinued from further receipt of study drug(s) will need to be discontinued from the IWRS.

If a patient is withdrawn from study, see Section 3.10.

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3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients can be re-screened a single time, but they cannot be re-randomized.

If a screen failed patient is re-screened, a new E-code must be assigned. Patients will reconfirm their consent to participate in the study by resigning and dating their original consent form(s), next to their initial signature and date.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (study drug[s] and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further study drug(s) or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow-up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study, including any further follow-up (eg, survival contact telephone calls)

- Use of their study generated data

- Use of any samples (see Section 5.5.6)

3.10.2.1 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 9.3), 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.

At the time of OS analyses, the survival status of all patients in the full analysis set (FAS) and the safety analysis sets should be re-checked as follows (this includes survival status of patients who withdrew consent or are classified as "potentially lost to follow-up):"

- Potentially 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. (The applicable electronic Case Report Form [eCRF] modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of his or her 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. (The applicable eCRF modules will be updated.)

3.11 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings. In addition, the study may be stopped based on the findings of the interim safety analysis conducted by the IDMC (see Section 6.10.1).

Regardless of the reason for termination, all data available for the patients at the time of discontinuation of follow-up must be recorded in the eCRFs. All reasons for discontinuation of treatment must be documented.In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the patients interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and treatment periods in this study are presented in Table 2 and Table 3, and the procedures for the follow-up period are presented in Table 4. Patients who continue beyond Cycle 5 (C5) will continue with all C5 assessments until termination of treatment (Table 2).

For all treatment arms:

- Patient-reported outcome (PRO) and tumor efficacy (RECIST 1.1) assessment dates will not be affected by dose delays, rechallenge and will remain as originally scheduled.

- All other scheduled assessments must be performed relative to the start of the dosing cycle, such that all laboratory procedures, etc required for dosing should be performed within 3 days prior to dosing.

For all immunotherapy arms:

- Patients may delay dosing under the following circumstances:

    - Dosing may be delayed per Toxicity Management Guidelines due to either an immune or a non-immune-related AE.

    - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.

    - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST 1.1) and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab and tremelimumab (see current IBs for durvalumab and tremelimumab).

For sorafenib CCI arm:

- Patients may delay and subsequently resume dosing per local standard clinical practice and as follows:

    - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.

    - Any dose adjustments for suspected sorafenib-related toxicities should be managed based on the approved product label for each country.

Table 2   **Schedule of assessments for all immunotherapy arms treatment period**

	Screening	Treatment period					Final visit	Source
Durvalumab cycle	Week -4 to -1	C1	C2	C3	C4	C5 to PD[a]	At time of confirmed PD	
Day	-28 to -1	1						
Window (days)	NA	(+3 days, tumor assessments)	(±3 days, tumor assessments and e-PRO assessments ±7 days)					
Informed consent								
Informed consent: study procedures[b]	X							4.1, 10.4
CCI								
Study procedures								
Full physical exam (including height)	X							5.2.2
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	5.2.2
Vital signs (including weight)[c]	X	X	X	X	X	X	X	5.2.4
ECG[d]	X	As clinically indicated						5.2.3
Concomitant medications	<------------------------------------ All visits ------------------------------------>							7.7
Demography, incl baseline characteristics, tobacco and alcohol use, and medical/surgical history	X							4.1
Assessment of Child-Pugh score	X	X	X	X	X	X	X	5.2.7
Eligibility criteria	X	X						3.1, 3.2
Randomization		X						
Laboratory assessments								
Serum chemistry (see Table 5 for a full list of tests)[e]	X	X[e]	X	X	X	X	X	5.2.1
Hematology (see Table 6 for a full list of tests)[e]	X	X[e]	X	X	X	X	X	5.2.1
Coagulation (aPTT, PT and INR)[e]	X	X[e]	X	X	X	X	X	Table 7
AFP	X	X[g]	X	X	X	X	X	5.5.2
Thyroid function (TSH, free T3[f], free T4[f])	X	X[g]	X	X	X	X	X	5.2.1
Virology assessment for all screened patients [h] Qualitative HBsAg, anti-HBc, quantitative HBV DNA, anti-HCV and anti-HDV, qualitative HBeAg, anti-HBs, anti-Hbe, HCV RNA	X							
Patients with confirmed HBV only Quantitative HBV DNA		X[g]	X	X	X	X	X	5.2.1

Table 2   Schedule of assessments for all immunotherapy arms treatment period

	Screening	Treatment period					Final visit	Source
Durvalumab cycle	Week -4 to -1	C1	C2	C3	C4	C5 to PD[a]	At time of confirmed PD	
Day	-28 to -1	1						
Window (days)	NA	(+3 days, tumor assessments)	(±3 days, tumor assessments and e-PRO assessments ±7 days)					
Patients with confirmed HCV only Quantitative HCV RNA [i], HCV genotype (C1D1 only) [j], HBV DNA[h] (only required for patients with positive anti-HBc and undetectable HBV DNA at screening)		X[g]	X	X	X	X	X	5.2.1
Patients without HBV/HCV (other) HBV DNA[h] (only required for patients with positive anti-HBc and undetectable HBV DNA at screening)		X[g]	X	X	X	X	X	5.2.1
HIV	X							5.2.1
Urinalysis	X	As clinically indicated						Table 8
Pregnancy test[k]	X	X	X	X	X	X	X	5.2.1
Pharmacokinetic sampling (serum)								
Durvalumab CCI monotherapy								
Durvalumab PK sample (pre-dose) [l]		CCI						
Durvalumab PK sample (post-dose)[m]								
Durvalumab CCI plus tremelimumab CCI combination therapy[Y]								
Durvalumab PK sample (pre-dose) [l]		CCI						
Durvalumab PK sample (post-dose)[m]								
Tremelimumab PK sample (pre-dose) [l]								
Tremelimumab PK sample (post-dose)[m]								
Durvalumab CCI plus tremelimumab CCI combination therapy								
Durvalumab PK sample (pre-dose) [l]		CCI						
Durvalumab PK sample (post-dose) [m]								
Tremelimumab PK sample (pre-dose) [l]								
Tremelimumab PK sample (post-dose) [m]								
Monitoring								

Table 2   Schedule of assessments for all immunotherapy arms treatment period

	Screening	Treatment period					Final visit	Source
Durvalumab cycle	Week -4 to -1	C1	C2	C3	C4	C5 to PD[a]	At time of confirmed PD	
Day	-28 to -1	1						
Window (days)	NA	(+3 days, tumor assessments)	(±3 days, tumor assessments and e-PRO assessments ±7 days)					
ECOG performance status	X	X	X	X	X	X	X	5.2.6
AE/SAE assessment[n]	<-------------------------------------All visits-->							6.3
Patient follow-up contact/Patient review for safety		On D14 of C1, 2, 3						5.2.5
Study drug(s) administration								
Durvalumab CCI monotherapy								
Durvalumab CCI		CCI ■■■						
Durvalumab CCI plus tremelimumab CCI ■ combination therapy								
Durvalumab CCI [o,p,q]		CCI ■■■						
Tremelimumab CCI ■ [o,p,q]		■■■						
Durvalumab CCI plus tremelimumab CCI ■ combination therapy								
Durvalumab CCI [o,p,q]		CCI ■■■						
Tremelimumab CCI ■■■ [o,p,q]		■■■						
ADA sampling								
Durvalumab CCI monotherapy								
Durvalumab ADA sample (pre-dose)		CCI ■■■						
Durvalumab CCI plus tremelimumab CCI ■ combination therapy[y]								
Durvalumab ADA sample (pre-dose)		CCI ■■■						
Tremelimumab ADA sample (pre-dose)		■■■						
Durvalumab CCI plus tremelimumab CCI ■ combination therapy								
Durvalumab ADA sample (pre-dose)		CCI ■■■						
Tremelimumab ADA sample[w]		■■■						
Other assessments and assays								
CCI ■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■■								
Vitamin D assessment (serum)		X						5.2.1

Table 2   Schedule of assessments for all immunotherapy arms treatment period

	Screening	Treatment period					Final visit	Source
Durvalumab cycle	Week -4 to -1	C1	C2	C3	C4	C5 to PD[a]	At time of	
Day	-28 to -1	1					confirmed PD	
Window (days)	NA	(+3 days, tumor assessments)	(±3 days, tumor assessments and e-PRO assessments ±7 days)					
PRO assessmentsr [r,v]								
EORTC QLQ-C30, QLQ-HCC18, CCI		X	Q8W (±7 days relative to Cycle 1 Dose 1 date) for the first 48 weeks and then Q12W±7 days thereafter until treatment discontinuation. Note: All confirmed PD patients should complete additional assessments up to 3 months after treatment discontinuation). The schedule of Q8W±7 days for the first 48 weeks and then Q12W ±7 days thereafter MUST be followed regardless of any delays in dosing.						5.3.1
CCI								
Tumor biopsy (newly acquired or archival ≤3 years old) for PD-L1 status (mandatory). Note: tumor biopsy is optional for China cohort.	X							5.5.1

Table 2   Schedule of assessments for all immunotherapy arms treatment period

	Screening	Treatment period					Final visit	Source
Durvalumab cycle	**Week -4 to -1**	**C1**	**C2**	**C3**	**C4**	**C5 to PD[a]**	**At time of confirmed PD**	
Day	**-28 to -1**	**1**						
Window (days)	**NA**	**(+3 days, tumor assessments)**	**(±3 days, tumor assessments and e-PRO assessments ±7 days)**					
Archived tumor sample (optional)	X							5.5.1
Fresh tumor biopsy (optional)							X[t]	5.5.1
Tumor and disease assessments								
Disease assessment by RECIST 1.1 (CT or MRI)[u]	X	Q8W ±1 week for the first 48 weeks (relative to the date of randomization) and then Q12W±1 week thereafter until RECIST 1.1-defined radiological progression followed by a subsequent scan if clinically feasible. The schedule of Q8W±1 week for first 48 weeks and then Q12W±1 week thereafter MUST be followed regardless of any delays in dosing.						5.1

a   Visits continue every 4 weeks.

b   Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary. If laboratory, imaging, or pathology 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. Note: tumor biopsy is optional for China cohort.

c   For the first infusion, BP and pulse will be collected from patients prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes), at 30 minutes during the infusion (halfway through infusion), and the end of the infusion (approximately 60 minutes ±5 minutes). These collection times should be followed for each of the durvalumab and the tremelimumab infusions. For subsequent infusions, BP and pulse should be collected during and post-infusion as per institution standard and as clinically indicated.

d   Any clinically significant abnormalities detected require triplicate ECG results.

e   If screening laboratory assessments (including clinical chemistry, hematology, coagulation) are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

f   Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

g   If thyroid function, AFP and virology assessment are performed within 14 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. These assessments may be performed more frequently, if clinically indicated.

h   Patients who are anti-HBc positive and HBV DNA undetectable (<10UL/ml or under the limit of detection per local or central lab standard) at screening are considered as HBV negative. If these patients are stratified to HCV positive or others, they still must be tested for HBV DNA viral load every cycle. In case of HBV reactivation (HBV DNA ≥10 IU/ml or above the limit of detection per local or central lab standard), patients 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.

i   HCV RNA will be assessed during treatment only if HCV RNA is positive at baseline or Day 1.

j   HCV genotype will only be collected at baseline or Day 1 C1D1.

k   For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug(s) and then every 4 weeks. Pregnancy test may be performed within 3 days prior to Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

l   Durvalumab PK pre-dose samples should be collected within 1hour before the beginning of durvalumab infusion. Durvalumab and tremelimumab PK pre-dose samples should be collected within 1 hour before the beginning of both durvalumab and tremelimumab infusions (when applicable).

m   Durvalumab post-dose samples should be collected within 10 minutes after the end of durvalumab infusion. Tremelimumab post-dose samples should be collected within 10 minutes after the end of tremelimumab infusion.

n   For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed. Any AEs/SAEs detected on non-study-related visits should be reported.

o   Results for LFTs, electrolytes, full blood count, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

p   During the combination portion of treatment, tremelimumab will be administered first; the durvalumab infusion will start immediately after tremelimumab infusion. If there are no clinically significant infusion reactions within the first cycle, and at the discretion of the Investigator, for all other cycles, durvalumab can be given immediately after the tremelimumab infusion has finished.

q   Patients in the durvalumab plus tremelimumab combination therapy arms who have completed the durvalumab plus tremelimumab (with clinical benefit per Investigator judgement) dosing, but subsequently have PD while receiving durvalumab CCI monotherapy may rechallenge with as per their original randomized treatment assignment (provided they meet eligibility criteria for rechallenge). Patients assigned to Arm B may receive rechallenge with either CCI Tremelimumab or CCI Tremelimumab along with Durvalumab as per section 7.2.1.2 with prior approval from the AstraZeneca Study Physician.

r   For patients who are rechallenged with tremelimumab CCI or treated through disease progression, the schedule of assessments should be followed as per the initial treatment period.

s   CCI

t   Optional tumor collection upon confirmed PD.

u   RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands), and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to and prior to the start of study drug(s). Tumor assessments should continue on schedule until RECIST 1.1-defined radiological progression followed by a subsequent scan if clinically feasible, evaluated by Confirmation of Radiological Progression criteria (Appendix B). The subsequent scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

v   In the event patient discontinued treatment after first PD, first PD should be used as disease progression to trigger a patient for follow-up ePRO assessments.

w   Pre-dose at CCI 3 month post last cycle of tremelimumab at CCI

x   Samples for patients enrolled in China will be collected according to local laws and regulations

Y   If a patient has not completed or started all CCI of tremelimumab in Arm B, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only. For patients assigned to the tremelimumab CCI combined with durvaluamb arm, who drop tremelimumab should follow the PK/ADA sampling schedule for Arm A.

Note: For patients who are rechallenged with tremelimumab CCI ███████████████████ the schedule of assessments should be followed as per the initial treatment period (except PK, ADA, CCI ██████████████████ tumor biopsies, and CCI ███████████ assessments, which do not need to be repeated).

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

ADA Anti-drug assay; AE Adverse event; AFP Alpha-fetoprotein; aPTT Activated partial thromboplastin time; BP Blood pressure; C Cycle; CCI ████████ CT Computerized tomography; DNA Deoxyribonucleic acid; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; ePRO Electronic patient-reported outcome; CCI ████████████ HBc Hepatitis B core; HBe Hepatitis B e: HBeAg Hepatitis B e antigen; HBs Hepatitis B surface; HBsAg Hepatitis B surface antigen; HBV Hepatitis B virus; HCV Hepatitis C virus; HDV Hepatitis D virus; HIV Human immunodeficiency virus; CCI ██████████████ INR International normalized ratio; IV Intravenous; LFT Liver function test; CCI ██████████ MRI Magnetic resonance imaging; CCI ██████████ NA Not available; PD progression of disease; PD-L1 Programmed cell death-ligand 1; CCI ███████████████ PK Pharmacokinetic; PRO Patient-reported outcome; CCI ██████████████████████ PT Prothrombin time; CCI ████████ Q8W Every 8 weeks; Q12W Every 12 weeks; QLQ-C30 30-item core quality of life questionnaire; QLQ-HCC18 18-item hepatocellular cancer health-related quality of life questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; RNA Ribonucleic acid; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

Table 3   Schedule of assessments for sorafenib CCI therapy treatment period

Cycles	Screening Week -4 to -1	C1[a]	C2	C3	C4	C5	C6	C7	C8	C9	C10 to PD[b]	Final visit	Source
Day	-28 to -1	1	29	57	85	113	141	169	197	225	253 to PD		
Window (days)	NA	(±3 days, tumor assessments and e-PRO assessments ±7 days)											
Informed consent													
Informed consent: study procedures[c]	X												4.1, 10.4
CCI													
Study procedures													
Full physical (including height)	X												5.2.2
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	X	X	X	X	X	5.2.2
Vital signs (including weight)[d]	X	X	X	X	X	X	X	X	X	X	X	X	5.2.4
ECG[e]	X	As clinically indicated											5.2.3
Concomitant medications	<--------------------------------------All visits-->												7.7
Demography, incl baseline characteristics, tobacco and alcohol use, and medical/surgical history	X												4.1
Assessment of Child-Pugh score	X	X	X	X	X	X	X	X	X	X	X	X	5.2.7
Eligibility criteria	X	X											3.1,3.2
Laboratory assessments													
Serum chemistry (see Table 5 for a full list of tests)[f]	X	X[f]	X	X	X	X	X	X	X	X	X	X	5.2.1
Hematology (see Table 6 for a full list of tests)[f]	X	X[f]	X	X	X	X	X	X	X	X	X	X	5.2.1
Coagulation (aPTT, PT and INR)[f]	X	X[f]	X	X	X	X	X	X	X	X	X	X	Table 7
AFP	X	X[r]	X	X	X	X	X	X	X	X	X	X	5.5.2
Thyroid function (TSH, free T3[g], free T4 [g])	X	X[r]	X	X	X	X	X	X	X	X	X	X	5.2.1
Virology assessment for all screened patients [h] Qualitative HBsAg, anti-HBc, quantitative HBV DNA, anti-HCV and anti-HDV, qualitative HBeAg, anti-HBs, anti-Hbe, HCV RNA	X												5.2.1
Patients with confirmed HBV only Quantitative HBV DNA		X	X	X	X	X	X	X	X	X	X	X	5.2.1

Table 3   Schedule of assessments for sorafenib CCI therapy treatment period

Cycles	Screening Week -4 to -1	C1[a]	C2	C3	C4	C5	C6	C7	C8	C9	C10 to PD[b]	Final visit	Source
Day	-28 to -1	1	29	57	85	113	141	169	197	225	253 to PD		
Window (days)	NA	(±3 days, tumor assessments and e-PRO assessments ±7 days)											
Patients with confirmed HCV only[h] Quantitative HCV RNA [i], HCV genotype (C1D1) [j], HBV DNA (required for patients with positive anti-HBc and undetectable HBV DNA at screening)		X[j]	X	X	X	X	X	X	X	X	X	X	5.21.1
Patients without HBV/HCV (other) [h] HBV DNA (required for patients with positive anti-HBc and undetectable HBV DNA at screening)		X	X	X	X	X	X	X	X	X	X	X	5.2.1
HIV	X												5.2.1
Urinalysis	X	As clinically indicated											Table 8
Pregnancy test[k]	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Monitoring													
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	5.2.6
AE/SAE assessment[l]	<--All visits-->												6.3
Sorafenib administration													
Sorafenib CCI	CCI												
Other assessments and assays													
CCI													
PRO Assessments[m,n]													
EORTC QLQ-C30, QLQ-HCC18, CCI		X	Q8W (±7 days relative to Cycle 1 Dose 1 date) for the first 48 weeks and then Q12W±7 days thereafter until treatment discontinuation. (Note: All confirmed PD patients should complete additional assessments up to 3 months after treatment discontinuation.) The schedule of Q8W ±7 days for the first 48 weeks and then Q12W±7 days week thereafter MUST be followed regardless of any delays in dosing.										5.3.1

Table 3 **Schedule of assessments for sorafenib** CCI **therapy treatment period**

Cycles	Screening Week -4 to -1	C1[a]	C2	C3	C4	C5	C6	C7	C8	C9	C10 to PD[b]	Final visit	Source
Day	-28 to -1	1	29	57	85	113	141	169	197	225	253 to PD		
Window (days)	NA			(±3 days, tumor assessments and e-PRO assessments ±7 days)									
CCI													
Vitamin D assessment (serum)		X											5.2.1
CCI													
Tumor biopsy (newly acquired or archival ≤3 years old) for PD-L1 status. (Note: tumor biopsy is optional for China Cohort).	X												5.5.1
Archived tumor sample (optional)	X												5.5.1
Fresh tumor biopsy (optional)											X[p]		5.5.1
Tumor and disease assessments													
Disease assessment by RECIST 1.1 (CT or MRI)[q]	X	Q8W±1 week for the first 48 weeks (relative to the date of randomization) and then Q12W±1 week thereafter until RECIST 1.1-defined radiological progression followed by a subsequent scan if clinically feasible. The schedule of Q8W±1 week for first 48 weeks and then Q12W±1 week thereafter MUST be followed regardless of any delays in dosing.											5.1

[a]   Cycles are 28 days long such that patients receive uninterrupted sorafenib CCI treatment.

[b]   Visits continue every 4 weeks.

[c]   Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition prior to randomization. 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. Note: tumor biopsy is optional for the China cohort.

d   Vital signs should be collected at each visit.

e   Any clinically significant abnormalities detected require triplicate ECG results.

f   If screening laboratory assessments are performed within 3 days prior to Day 1, they do not need to be repeated at Day 1.

g   Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

h   Patients who are anti-HBc positive and HBV DNA undetectable (<10UL/ml or under the limit of detection per local or central lab standard) at screening are considered as HBV negative. If these patients are stratified to HCV positive or others, they still must be tested for HBV DNA viral load every cycle. In case of HBV reactivation (HBV DNA ≥10 IU/ml or above the limit of detection per local or central lab standard), patients 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.

i   HCV RNA will be assessed during treatment only if HCV RNA is positive at baseline or Day 1.

j   HCV genotype will only be collected at baseline or Day 1 C1D1.

k   For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug(s) and then every 4 weeks. Pregnancy test may be performed within 3 days prior to Day 1, but results must be available and reviewed by the treating physician or Investigator prior to receiving drug.

l   For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed. Any AEs/SAEs detected on non-study-related visits should be reported.

m   In the event patient discontinued treatment after first PD, first PD should be used as disease progression to trigger a patient for follow-up ePRO assessments.

n   For patients who are treated through disease progression, the schedule of assessments should be followed as per the initial treatment period.

o   CCI

p   Optional tumor collection upon confirmed PD.

q   RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands), and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to and prior to the start of study drug(s). Tumor assessments should continue on schedule until RECIST 1.1-defined radiological progression followed by a subsequent scan if clinically feasible, evaluated by Confirmation of Radiological Progression criteria (Appendix B). The subsequent scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

r   If thyroid function, AFP and virology assessment are performed within 14 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. These assessments may be performed more frequently, if clinically indicated.

s   Samples for patients enrolled in China will be collected according to local laws and regulations

Note: All assessments on treatment days are to be performed prior to administration, unless otherwise indicated.

AE Adverse event; AFP Alpha-fetoprotein;; aPTT Activated partial thromboplastin time; CCI C Cycle; CT Computed tomography; CCI ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; ePRO Electronic Patient-reported Outcome; CCI HBc Hepatitis B core; HBe Hepatitis B e; HBeAG Hepatitis B e antigen; HBs Hepatitis B surface; HBsAg Hepatitis B surface antigen; HBV Hepatitis B virus; HCV Hepatitis C virus; HDV Hepatitis D virus; HIV Human immunodeficiency virus; CCI INR International normalized ratio; IV intravenous; CCI MRI Magnetic resonance imaging; NA Not applicable; PD Progression of disease; PD-L1 Programmed cell death ligand 1; CCI PRO Patient-reported outcome; CCI

PT Prothrombin time; CCI Q8W Every 8 weeks; Q12W Every 12 weeks; QLQ-C30 30-item core quality of life questionnaire; QLQ-HCC18 18-item hepatocellular cancer health-related quality of life questionnaire; RECIST 1.1 Response evaluation criteria in solid tumors version 1.1; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

Table 4   Schedule of assessments for patients who discontinue treatment

Evaluation	Day (±3)	Months (±1 week)							12 months and every 2 months (±1 week)	Source
	30	2	3	4	6	8	10			
Study procedures										
Full physical exam	X									5.2.2
Vital signs	X									5.2.4
Weight	X	X	X							5.2.4
Pregnancy test[a]	X	X	X							5.2.1
Concomitant medications	X	X	X							7.7
ADA sampling										
Durvalumab ADA sample			X[b]							5.4
Tremelimumab ADA sample			X[c]							5.4
Other assessments and assays										
EORTC QLQ-C30, EORTC QLQ-HCC18, CCI	Q8W (±7 days relative to Cycle 1 Dose 1 date) for the first 48 weeks and then Q12W ±7 days thereafter until disease progression[k] and up to 3 months after disease progression[k]. (Note: Patients who have PD at treatment discontinuation should complete additional assessments up to 3 months after the treatment discontinuation.)									5.3.1
CCI										
Monitoring										
ECOG performance status	At timepoints consistent with tumor assessments: 30, 60, and 90 days (after treatment discontinuation), and then at initiation of subsequent anticancer therapy[e]									5.2.6
AE/SAE assessment	X	X	X							6.3
Subsequent anticancer therapy[f,g]	<-->									NA
Survival status[h]		X	X	X	X	X	X	X		5.1
Hematology	X	X	X							Table 6

Table 4   Schedule of assessments for patients who discontinue treatment

Evaluation	Day (±3)	Months (±1 week)							12 months and every 2 months (±1 week)	Source
	30	2	3	4	6	8	10			
AFP	X	X	X							5.5.2
Coagulation (aPTT, PT and INR)	X	X	X							Table 7
Serum chemistry	X	X	X							Table 5
Thyroid function (TSH, free T3[i], free T4[i])	X	X	X							Table 5
Pharmacokinetic sampling (serum)										
Durvalumab CCI monotherapy										
Durvalumab PK sample			X[b]							5.4
Durvalumab CCI plus tremelimumab CCI combination therapy										
Durvalumab PK sample			X[b]							5.4
Tremelimumab PK sample			X[c]							5.4
Durvalumab CCI plus tremelimumab CCI combination therapy										
Durvalumab PK sample			X[b]							5.4
Tremelimumab PK sample			X[c]							5.4
Tumor and disease assessments										
Disease assessment by RECIST 1.1 (CT or MRI)[j]	Q8W ±1 week for the first 48 weeks (relative to the date of randomization) and then Q12W ±1 week thereafter until confirmed PD. Additional scans post confirmed PD to be completed per standard clinical practice.									5.1

[a]   For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[b]   Sample to be taken 3 months after discontinuation of durvalumab.   Sample to be taken 3 months after discontinuation of durvalumab. Note: if a patient is on a dose delay > 3 months PK/ADA sample should be collected 3 months post last administration of IP

[c]   Sample to be taken 3 months after discontinuation of tremelimumab. Note: if a patient is on a dose delay > 3 months PK/ADA sample should be collected 3 months post last administration of IP

[d]   CCI

[e]   ECOG performance status should also be collected at other site visits that the patient attends; if appropriate, site staff are available to collect such information. In addition, ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.

[f]   Details of any treatment for HCC (including surgery) after the last dose of study drug(s) must be recorded in the eCRF. At minimum, the start date and description of the subsequent anticancer therapy should be collected.

[g]   For patients who discontinue their assigned study drug(s) following confirmed progression, available readings of CT/MRI from local practice will be collected from patients' medical charts while information on subsequent anticancer treatment is collected.

[h]   Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for HCC (including surgery) after the last dose of study drug(s) must be recorded in the eCRF.

i   Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

j   Only for patients yet to progress, RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands), and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients. Tumor assessments should continue on schedule until RECIST 1.1-defined radiological progression followed by a subsequent scan if clinically feasible, evaluated by Confirmation of Radiological Progression criteria (Appendix B). The subsequent scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the initial assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (relative to the date of randomization).

k   Disease progression is the first scan of progressive disease.

l   Samples for patients enrolled in China will be collected according to local laws and regulations

ADA Anti-drug antibody; AE Adverse event; AFP Alpha-fetoprotein; aPTT activated partial thromboplastin time; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC European Organisation for Research and Treatment of Cancer; CCI ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ HCC hepatocellular cancer; CCI ▮▮▮▮▮▮▮▮▮▮▮▮▮▮ INR International normalized ratio; IV Intravenous; MRI Magnetic resonance imaging; NA Not applicable; PD Progression of disease; PD-L1 Programmed cell death-ligand 1; PFS Progression-free survival; CCI ▮▮▮▮▮▮▮▮▮▮▮▮ PK Pharmacokinetic; CCI ▮▮▮▮▮▮▮▮▮▮ PT Prothrombin time; Q8W Every 8 weeks; Q12W Every 12 weeks; QLQ-C30 30-item core quality of life questionnaire; QLQ-HCC18 18-item hepatocellular cancer health-related quality of life questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

4.1 Screening/enrollment period

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. 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. All patients will be required to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent is included in the main patient informed consent form (ICF).

All screening and enrollment procedures will be performed according to the schedule of assessments in Table 2 and Table 3. Demographic data and other characteristics will be recorded, including date of birth or age, sex, smoking and alcohol use, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained. Tumor pathology (including fibrosis score) and tumor stage (Llovet et al 1999 and Benson et al 2018) should be collected per Appendix J. all screening laboratory and imaging results must have been obtained within 28 days of randomization.

Screening/baseline evaluations may be performed over more than 1 visit.

All eligibility criteria must be checked on the date of randomization. If a patient meets eligibility criteria during screening, but subsequently becomes ineligible at randomization, the patient cannot be randomized. If there are multiple tests for a lab parameter, the one which is most recent should be used for the eligibility check.

4.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule (see Table 2 and Table 3).

Whenever ECG, vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, then vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Table 2 and Table 3.

4.3 Follow-up period

Patients who are permanently discontinued from further receipt of study drug(s), regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (Table 4).

Patients who permanently discontinue drug for reasons other than objective RECIST 1.1 disease progression should continue to have RECIST 1.1 scans performed Q8W (±1 week) for the first 48 weeks relative to the date of randomization and then Q12W (±1 week) thereafter until confirmed PD as defined in Table 4.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Table 4.

All patients will be followed for survival until the end of the study. Following the final primary analysis, which will include all study endpoints, the study database may remain open for collection of long term follow-up as presented in Table 22 in section 9.3.

Post final data cutoff

Patients who continue to receive benefit from their assigned treatment at the final primary analysis DCO 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 treatment following the final primary analysis DCO, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results during treatment in order to manage AEs the Long-term follow-up data may be collected post the final primary analysis DCO as outlined in section 9.3.

In the event that a rollover or safety extension study is available following the final primary analysis DCO, patients currently receiving treatment with durvalumab (monotherapy or in combination with tremelimumab) may be transitioned to such a study, and the current study would reach its end. The rollover or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient that would be proposed to move to such study would be given a new Informed Consent.

5. STUDY ASSESSMENTS

A Web-Based Data Capture (WBDC) 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 will ensure 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.

The Investigator will record data on the observations, tests, and assessments specified in the protocol on the eCRFs provided by AstraZeneca. The eCRF will be accompanied with "Instructions for the Investigator," which should be followed. These instructions provide guidance for the recording of study data in the eCRF, including how to change data incorrectly recorded.

5.1 Efficacy assessments

This study will evaluate the primary endpoint of OS. Efficacy assessments of PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DoR will be derived (by AstraZeneca) according to RECIST 1.1.

For all patients, the RECIST tumor response data will be used to determine each patient's visit response according to RECIST version 1.1 (Appendix B). It will also be used to determine if, and when, a patient has progressed in accordance with RECIST 1.1 and their best objective response to study treatment. RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands), and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up.

Baseline radiological tumor assessments are to be performed no more than 28 days before the date of randomization and, ideally, as close as possible to randomization (Table 2 and Table 3). Follow-up assessments will be performed Q8W (±1 week) for the first 48 weeks following randomization, and then Q12W (±1 week) thereafter until confirmed PD. The imaging schedule must be followed regardless of any delays in dosing.

If an unscheduled imaging assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments as per the standard imaging schedule. If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) after the initial assessment of progression, the patient should continue to be followed with scheduled imaging until confirmed objective disease progression.

At each visit, using the information from TLs, non-target lesions (NTLs), and new lesions, patients will be programmatically assigned a RECIST 1.1 visit response of complete response (CR), PR, stable disease (SD), PD, or not evaluable (NE) depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to randomization. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE, unless there is objective disease progression according to RECIST 1.1 in which case the response will be assigned as PD). Confirmation of progression guidelines are set for the reasons shown in Appendix B.

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

Following confirmed progression, patients should continue to be followed up for survival as outlined in the follow-up schedules of assessments (Table 4). In addition, all patients will be contacted in the week following data cutoff to confirm survival status.

Patients in the durvalumab plus tremelimumab combination therapy arms who complete the assigned dosing cycle(s) of durvalumab plus tremelimumab, and are benefiting from study drug(s) in the Investigator's opinion, and subsequently have evidence of PD with or without confirmation according to RECIST 1.1 during the durvalumab monotherapy portion of their regimen can be rechallenged with tremelimumab, provided they meet eligibility criteria for rechallenge, as described in Section 7.2.1.3. Patients in Arm B can be rechallenged in their assigned treatment arm, or, with tremelimumab CCI along with durvalumab with prior approval from the AstraZeneca Study Physician. Patients in Arm C may only be rechallenged with tremelimumab CCI along with durvalumab if eligible for rechallenge.

Patients who rechallenge with tremelimumab after PD must have a rechallenge baseline tumor assessment within 28 days of and prior to restarting treatment with tremelimumab plus durvalumab combination therapy. Using regular RECIST 1.1 baseline guidelines, the rechallenge baseline may have TLs and NTLs different from those at the original baseline (including pre-existing New Lesions). Rechallenge follow-up scans should occur Q8W (±1 week) for the first 48 weeks (relative to the date of first rechallenge treatment), then Q12W thereafter until confirmed disease progression.

5.1.1 Central collection of scans

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 retained for a potential future BICR. The management of patients will be based in part on the results of the RECIST 1.1 assessments conducted by the Investigator.

5.1.2 Survival assessments

Assessments for survival must be made following treatment discontinuation as outlined in the follow-up schedule of assessments (Table 4).

Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the data cutoff for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the data cutoff.

5.2   Safety assessments

5.2.1   Laboratory safety assessments

Blood and urine samples for determination of serum chemistry, hematology, and urinalysis will be taken at the times indicated in the schedule of assessments and as clinically indicated (see Table 2 through Table 8). Additional safety monitoring for patients receiving sorafenib should be carried out as per the label. If a patient has completed any safety laboratory tests within 3 days before Day 1, they do not need to be repeated at Day 1.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

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

The laboratory variables to be measured are presented in Table 5 (serum chemistry), Table 6 (hematology), Table 7 (coagulation), and Table 8 (urinalysis).

Serum samples will be obtained prior to first dose and will be analyzed for vitamin D values; correction may occur as clinically indicated.

Other safety tests to be performed include :

- Qualitative hepatitis B surface antigen (HBsAg), qualitative hepatitis B e antigen (HBeAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs), hepatitis B e antibody (anti-HBe), hepatitis C antibody (anti-HCV), hepatitis D antibody (anti-HDV), and quantitative HBV DNA, quantitative HCV RNA and HCV genotype.

- HIV antibodies (as per local standards)

Note: HBV positive patients must remain on antiviral therapy for the study duration and must continue therapy for 6 months after the last dose of study medication.

Table 5   Serum chemistry

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH
Chloride[c]	Free T3[d] (reflex)
Creatinine clearance[c]	Free T4[d] (reflex)
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[c]	
Glucose	
Lactate dehydrogenase	

[a]   Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2×upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.

[b]   It is preferable that both amylase and lipase parameters are assessed.

[c]   Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium tests will be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated.

[d]   Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.
ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid-stimulating hormone; T3 Triiodothyronine; T4 Thyroxine.

Table 6   Hematology

Absolute neutrophil count	Absolute lymphocyte count[a]
Hemoglobin	Platelet count
Total white cell count	

Note: for coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory haematology assessments are performed within 3 days prior to day 0) and as clinically indicated.

[a] Can be recorded as absolute counties or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

Table 7   Coagulation

PT and INR	aPTT

aPTT Activated partial thromboplastin time; INR international normalized ratio; PT prothrombin time

Table 8   Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis should be done at baseline (screening) and then as clinically indicated.
Note: Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells.

If a patient shows an AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN, refer to Appendix E for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week), and 3 months (±1 week) after permanent discontinuation of study drug(s) (see Table 4).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 6.3.7.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study drug(s) must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

5.2.2 Physical examination

Physical examinations will be performed according to the schedule of assessments (see Table 2, Table 3, and Table 4). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 6.3.6.

5.2.3 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study (see Table 2 and Table 3). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. Additional safety monitoring for patient receiving sorafenib should be carried out as per the label

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation.

Situations in which ECG results should be reported as AEs are described in Section 6.3.7.

5.2.4   Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the schedule of assessments (see Table 2, Table 3, and Table 4). Body weight will also be recorded at each visit along with vital signs.

Vital signs for patients in the sorafenib CCI arm will be collected per visit and as clinically indicated.

First infusion of immunotherapy

BP and pulse will be collected from patients in all immunotherapy arms before, during, and after infusions at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes ie, the beginning of the infusion)

- At 30 minutes during the infusion (**halfway** through infusion)

- At the end of the infusion (approximately 60 minutes ±5 minutes)

For patients randomized to the combination arms, the above collections should be performed for each of the durvalumab and the tremelimumab infusions.

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab. For subsequent doses, this observation period will not be required unless a patient experiences an infusion-related reaction.

Subsequent infusions

BP, pulse, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of the infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and after infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled Vital Signs eCRF page.

Situations in which vital signs results should be reported as AEs are described in Section 6.3.7. For any AEs of infusion reactions, vital signs should be recorded in the eCRF.

5.2.5 Early patient review for safety

It is strongly recommended that patients are contacted 2 weeks after receiving the first 3 cycles of any immunotherapy (Cycle 1 Day 14, Cycle 2 Day 14, and Cycle 3 Day 14) to ensure early identification and management of toxicities

5.2.6 ECOG performance status

Performance status as determined by the ECOG Scale will be recorded in the eCRF as per the schedules in Table 2, Table 3, and Table 4), based on the following:

0=Fully active; able to carry out all usual activities without restrictions

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

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

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

4=Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5=Dead

5.2.7 Child-Pugh score

The severity of chronic liver disease, mainly cirrhosis, as determined by the Child-Pugh score (Pugh et al 1973), will be recorded in the eCRF as specified in the assessment schedules (see Table 2, Table 3, and Table 4).

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 is shown in Table 9. 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 9   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 prolonged over ULN, OR	<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. ULN upper limit of normal

* 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.

** PT or INR prolongation due to anticoagulants for prophylaxis (e.g. atrial fibrillation) in patients without liver cirrhosis could be recorded as point 1. All evidence, including medical history, pathology, physical examination, laboratory studies and radiographic studies, should be able to consistently support the exclusion of cirrhosis.

5.2.8   Other safety assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in Toxicity Management Guidelines will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis/ILD should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

5.3   Other assessments

5.3.1   Clinical Outcome Assessments

PRO, a clinical outcome assessment, is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical studies. In addition to assessing OS and other clinical endpoints in oncology clinical trials, it is important to assess the treatment impact on disease-related symptoms, physical function and other HRQoL of the patient and thereby aid understanding of how clinical benefit relates to patient wellbeing, and for making a comprehensive risk-benefit assessment. Moreover, patient reported outcomes assist in the documentation of what specific symptoms and impacts are most important to patients and how these relate to clinical outcomes. The EORTC QLQ-C30 and QLQ-HCC18 were selected as the primary PROs for the study because they have good coverage of the conceptual model of HCC symptom and impact concepts. HRQoL is important in hepatocellular cancer because most patients are symptomatic when diagnosed and the disease is usually incurable. Patients may continue to suffer from symptomatic, nutritional or functional problems. Even when treatment improves overall or PFS this benefit can be counterbalanced by the burden of treatment and or its potential effect on patients' HRQoL (Gandhi et al 2014). CCI

The PRO instruments will be completed by the patients at study sites using a handheld electronic patient-reported outcome (ePRO) tablet device. All questionnaires should be completed according to the assessment schedules (see Table 2, Table 3, and Table 4) and must be completed before any other study procedures or meeting with study nurse or physician to discuss cancer-related issues

or health status. It takes approximately 30 to 40 minutes for patients to complete all questionnaires; therefore, the burden to the patient is moderate.

For patients rechallenged with tremelimumab after confirmed PD (patients assigned to durvalumab plus tremelimumab combination therapy arms only), or treated through disease progression (all treatment arms), questionnaires should be completed according to the initial assessment schedule (Table 2 or Table 3 as applicable).

For patients who discontinue study drug(s), assessments should be performed as per the assessment schedule in Table 4.

5.3.1.1   EORTC QLQ-C30

The key analysis of EORTC QLQ-C30 will be focused on the following scales/domains: global health status/QoL, physical function and fatigue. The EORTC QLQ-C30 was developed to assess HRQoL in cancer clinical trials (Aaronson et al 1993). It has undergone extensive testing and validation as well as detailed cross-cultural testing and validation (Aaronson et al 1993) and has been used extensively in HCC studies (Gandhi et al 2014). The EORTC QLQ-C30 is a 30-item self-administered questionnaire (Appendix H). There are 9 multiple item scales: 5 scales that assess aspects of functioning (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and a global measure of health status/QoL scale. There are 5 single-item measures assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and a single item concerning the perceived financial impact of the disease. All but 2 questions have 4-point scales: "Not at all," "A little," "Quite a bit," and "Very much." The 2 questions concerning global health status and QoL have 7-point scales with ratings ranging from "Very poor" to "Excellent." For each of the 15 domains (9 multiple-item scales and 6 single-item scales), final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms (Aaronson et al 1993).

5.3.1.2   EORTC QLQ-HCC18

The EORTC QLQ-HCC18 will be used to assess disease-related symptoms such as abdominal pain and abdominal swelling. The EORTC QLQ-HCC18 module is an 18-item self-administered questionnaire (Appendix H) developed and validated specifically for HCC (Blazeby et al 2004, Cheng et al 2013

Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013; 31:4067-4075.

Chie et al 2012). There are 5 multiple-item symptom scales (fatigue [3 items], jaundice [2 items], nutrition [5 items], pain [2 items], and fever [2 items]); 2 single-item symptom scales (abdominal swelling and sexual interest); and 1 multiple-item functional scale (body image [2 items]). All questions have a 4-point scale: "Not at all," "A little," "Quite a bit," and "Very much." For each of the 8 domains (6 multiple-item scales and 2 single-item scales), final scores are transformed such that they range from 0 to 100, where higher scores indicate greater level of symptoms (Cheng et al 2013

Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013; 31:4067-4075.

Chie et al 2012). All item response scores are converted into 0 to 100 scores; for all scales, a higher score means a worse symptom or a poorer HRQoL.

5.3.1.3 CCI

CCI

5.3.1.4   CCI

CCI

5.3.1.5   CCI

CCI

5.3.2   CCI

CCI

5.3.3 Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments by using a tablet ePRO device.

Each center must allocate the responsibility for the administration of the ePRO devices to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover for that individual if he or she is absent. The PRO questionnaires must be completed per the schedule of assessments (see Table 2, Table 3, and Table 4).

The following best practice guidelines should be followed when collecting PRO data using the tablet ePRO device:

- The research nurse or appointed site staff must explain the value and relevance of participation to patients and inform them that these questions are being asked in order to find out from them directly how they feel. This can help motivate patients to comply with data collection. The research nurse or appointed site staff should also stress that the information is not routinely shared with study staff.. Therefore, if the patient has any medical problems, he or she should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided by the ePRO vendor and provide guidance on whom to call if there are problems with the device.

- The PRO questionnaires should be completed in the following order: EORTC QLQ-C30, EORTC QLQ-HCC18, CCI

- Questionnaires must be completed in private and prior to any other study procedures (following informed consent) and before discussion of disease progress to avoid biasing the patient's responses to the questions.

- If the patient cannot complete the questionnaire, the reason for this should be provided in the ePRO device.

- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and must avoid introducing bias by not clarifying items. The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.

- Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient should be exempted from completing PRO questionnaires but may still participate in the study. It should be documented that the patient exempted in this regard.

- The study nurse or appointed site staff must administer questionnaires available in the language that the patient speaks and understands. Questions should not be read in an available language and translated into another language for the patient.

- The research nurse or appointed site staff must monitor compliance; minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early.

5.4   Pharmacokinetics

5.4.1   Collection of samples

Blood samples for determination of durvalumab and tremelimumab concentration in serum will be obtained according to the assessment schedules (see Table 2 and Table 4). The following collection windows are applied: Pre-dose (1 hour) and post-dose (10 minutes post-infusion).

Samples for determination of durvalumab and tremelimumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

5.4.1.1   Durvalumab PK samples

Samples should be taken:

- Pre-dose at CCI

- Post-dose at CCI

- 3 months after the last dose of durvalumab.

5.4.1.2 Tremelimumab PK samples

Durvalumab plus tremelimumab CCI

Samples should be taken:

- Pre-dose at CCI

- CCI

- 3 months after the last dose of tremelimumab.

- If a patient has not completed or started all CCI of tremelimumab in Arm B, the patient may either continue to complete the full schedule, or continue with durvalumab monotherapy only. For patients assigned to the tremelimumab CCI combined with durvaluamb arm, who drop tremelimumab should follow the PK/ADA sampling schedule for Arm A.

Durvalumab plus tremelimumab CCI

Samples should be taken:

- Pre-dose at CCI

- Post-dose at CCI

- 3 months after the last dose of tremelimumab.

5.4.1.3 Collection of samples to measure for the presence of ADAs

The presence of ADA will be assessed in serum samples taken according to the assessment schedules (see Table 2 and Table 4).

Pre-dose (1 hour window) samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for both durvalumab and tremelimumab using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naïve validation samples will

be used. For some countries however, these samples may not be collected depending on their local regulatory and ethical requirements.

5.4.1.4   Storage and destruction of pharmacokinetic/ADA samples

PK and ADA samples will be disposed of after a maximum of 15 years from the end of the study.

PK and ADA samples may be disposed of or destroyed and anonymized by pooling. CCI

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Validation Report.

CCI

PK and ADA samples collected in China will be stored and disposed of according to local laws and regulations.

5.5   Biomarkers

By participating in this study, the patient consents to the mandatory collection and use of donated biological samples as described in this section. Tissue samples will be obtained from all screened patients.

Pretreatment tumor PD-L1 expression will be evaluated in all randomized patients. Data will be compared between arms to determine if baseline PD-L1 expression is prognostic and/or predictive of outcomes associated with combination immunotherapy compared with durvalumab CCI monotherapy or sorafenib CCI Baseline tumor requirements are briefly described in Section 5.5.1.

CCI

Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

CCI

5.5.1 Collection of patient samples for analysis of PD-L1 expression

Patients should be strongly encouraged to provide a fresh tissue biopsy for the purpose of PD-L1 expression analyses at screening. The tumor specimen submitted to the central laboratory for PD-L1 expression analysis should be of sufficient quantity and quality (with pathology quality control) to allow for PD-L1 immunohistochemical (IHC) analyses (see the Laboratory Manual). Newly acquired or archived specimens with limited tumor content and fine needle aspirates are not acceptable for defining tumor PD-L1 expression.

- MANDATORY: Provision of a tumor biopsy, formalin fixed and embedded in paraffin, for the purpose of PD-L1 expression analyses CCI A newly acquired tumor biopsy (<3 months) is strongly preferred; however, if not feasible with an acceptable clinical risk, an archival sample taken ≤3 years prior to screening can be submitted. Note: the tumor biopsy is optional for the China cohort.

- Samples should be collected via an image-guided core needle (at least 18 gauge) or an excisional archival tumor biopsy sample. Where institutional practice, in this setting, uses a smaller gauge needle, samples should be submitted with tissue adequate to ensure that a valid result can be achieved (ie, total tissue quantity submitted should be similar to core needle or excisional biopsy requirements described briefly here and outlined in the Laboratory Manual).

- When fresh tissue is obtained, 2 cores should be placed in formalin and processed to a single paraffin-embedded block, as described in the Laboratory Manual. As a guidance, it is anticipated that 4 passes of an 18 gauge core needle will provide sufficient tissue for both PD-L1 analyses CCI Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy, and in this instance, only core needle (not excisional/incisional) biopsy is allowed. For patients with a single TL, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.

- OPTIONAL: Additional archived tumor tissue block (formalin fixed and paraffin embedded), where such samples exist in a quantity sufficient to allow for analysis. Tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. Please consult the Laboratory Manual for specific instructions and guidelines regarding sections.

- OPTIONAL: Tumor biopsy at the time of progression is requested

OPTIONAL: Additional tumor biopsies collected as part of clinical care (eg, for mixed responses or upon PD) can be submitted for further analysis.

Additional archived tissue not intended for PD-L1 testing, and optional biopsies obtained at the time of progression or part of clinical care will not be collected in China. Additionally, China study sites will not submit tumor tissue blocks and only unstained sections from the tissue block will be submitted for analysis.

The Laboratory Manual provides further details of requirements including sample quality control and shipping.

CCI

The Ventana SP263 IHC assay will be used to determine PD-L1 expression in all available specimens. To meet the requirement of the United States Food and Drug Administration for approval of a companion diagnostic, sections of the tumor will be retained at Ventana and/or at the Investigation Use only testing laboratory for potential additional studies to support potential test approval.

5.5.2   CCI

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CCI

5.5.3 Storage, re-use, and destruction of biological samples

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. CCI

5.5.4 Labeling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), (Appendix C).

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

5.5.5 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of sample shipments.

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

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers. Samples retained for further use will be stored in the AstraZeneca-assigned biobank and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

5.5.6   Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed, and the action will be documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of the study.

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of patients' withdrawal of informed consent to the use of donated samples

- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of, or destroyed, and the action is documented

- Ensure that the organization(s) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, and the action is documented

- Ensure that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca will ensure that the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or destroyed, and the action is documented.

5.6   CCI

CCI

5.6.1 CCI

5.6.2 CCI

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea and chest pain), signs (eg, tachycardia and enlarged liver), or the abnormal results of an investigation (eg, laboratory findings and electrocardiogram). In

clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study drug(s) has/have been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death

- Is immediately life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Further guidance on the definition of a SAE is provided in Appendix A.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab±tremelimumab or sorafenib). If an event that starts after 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.

6.3.2   Follow-up of unresolved adverse events

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study will be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3   Variables

The following variables will be collected for each AE:

- AE (verbatim)

- Date when the AE started and stopped

- Maximum CTCAE grade reported

- Changes in CTCAE grade

- Whether the AE is serious or not

- Investigator causality rating against the study drug(s) (yes or no)

- Action taken with regard to study drug(s)

- Administration of treatment for the AE

- Outcome

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

- Date the AE met criteria for SAE

- Date the Investigator became aware of the SAE

- Seriousness criteria

- Date of hospitalization

- Date of discharge

- Probable cause of death

- Date of death

- Whether an autopsy was performed

- Causality assessment in relation to study procedure(s)

- Causality assessment in relation to other medication, as explained in Section 6.3.4

- Description of the SAE

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the NCI CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but it is not an SAE unless it meets the criteria shown in Section 6.2. In

addition, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would only be considered an SAE if it satisfies the criteria shown in Section 6.2.

6.3.4 Causality collection

The Investigator will assess causal relationship between the study drug(s) and each AE and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

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

A guide to the interpretation of the causality question is found in Appendix A.

6.3.5 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment-emergent (ie, SAEs that occur prior to the administration of study drug[s]) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection). 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 or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.

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

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.7 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the CSR. Deteriorations as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study drug(s).

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.3.8 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq$3×ULN together with total bilirubin $\geq$2×ULN may need to be reported as SAEs. Appendix E provides further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

6.3.9 Disease progression

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

6.3.10 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for study inclusion and have been identified after the patient's enrollment in this study. New metastatic lesions will be considered progression of the malignancy under investigation and should not be reported as a new cancer.

6.3.11 Deaths

All deaths that occur during the treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A postmortem may be helpful in the assessment of the cause of death. If performed, a copy of the postmortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

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

6.3.12 Safety data to be collected following the final DCO of the study

For patients continuing to receive treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits, and the Investigators should continue to monitor the patient's safety laboratory results during treatment in

order to manage AEs. All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of Serious Adverse Events and reports of pregnancy, will not otherwise be reported for the purposes of this study. If long term survival follow-up is required, all data outlined in section 9.3 will be reported directly in the eCRF.

All SAEs and pregnancy (but not overdose) that occur in patients still receiving study 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 below.

6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then Investigators or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, that is, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day, that is, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate that an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative. If the WBDC system is not available, then the Investigator or other study site personnel must report an SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such.**

6.5   Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the study drug(s) and may require close monitoring and rapid communication by the Investigator to AstraZeneca. An AESI may be serious or non-serious. The rapid reporting of AESIs will allow ongoing surveillance of these events in order to characterize and understand them in association with the use of this study drug(s)

AESIs for durvalumab and 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 immune-mediated adverse event (imAE) is defined as an AESI 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 imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regard to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab and/or tremelimumab include the following:

- Diarrhea/colitis, and intestinal perforation

- Pneumonitis/ILD

- Hepatitis/transaminase increases

- Endocrinopathies (ie, events of hypophysitis, hypopituitarism adrenal insufficiency, hyper- and hypothyroidism, and type I diabetes mellitus)

- Rash/dermatitis

- Nephritis/blood creatinine increases

- Pancreatitis/serum lipase and amylase increases

- Myocarditis

- Myositis/polymyositis

- Neuropathy/neuromuscular toxicity (eg., Guillain-Barré syndrome, myasthenia gravis)

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

- In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab IBs. More specific guidelines for their evaluation and treatment are described in detail in Section 6.9.1. These guidelines have been prepared by AstraZeneca to assist the Investigator in the exercise of his or her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

6.6 Overdose

6.6.1 Durvalumab and tremelimumab

The use of durvalumab or tremelimumab in doses in excess of that specified in the protocol is considered to be an overdose. Currently, there is no specific treatment in the event of overdose of durvalumab or tremelimumab, and possible symptoms of overdose are not yet established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.

- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

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

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

For overdoses associated with an SAE, the standard reporting timelines apply (see Section 6.4). For other overdoses, reporting must occur within 30 days.

6.6.2 Sorafenib

For patients randomized to the sorafenib CCI arm, please refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, please record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for any pregnancy discovered before the study patient has received any study drugs

6.7.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study drug(s) should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. 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 patient was discontinued from the study.

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

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.7.2   Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab CCI plus tremelimumab CCI combination therapy or durvalumab CCI plus tremelimumab CCI combination therapy or 90 days after the last dose of durvalumab CCI monotherapy, whichever is the longer time period. Please follow the local prescribing information relating to contraception and the time limit for such precautions for sorafenib.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab CCI plus tremelimumab CCI combination therapy or durvalumab CCI plus tremelimumab CCI combination therapy or 90 days after the last dose of durvalumab CCI monotherapy, whichever is the longer time period, should, if possible, be followed up and documented.

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

6.8   Medication Error

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

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 patient.

Medication error includes situations where an error:

- occurred

- was identified and intercepted before the patient 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 eg, medication prepared incorrectly, even if it was not actually given to the patient

- Drug not administered as indicated, for example, wrong route or wrong site of administration

- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet

- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature

- Wrong patient received the medication (excluding IWRS errors)

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

- Errors related to or resulting from IWRS, including those which lead to one of the above listed events that would otherwise have been a medication error

- Patient accidentally missed drug dose(s) eg, forgot to take medication

- Accidental overdose (will be captured as an overdose)

- Patient 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 AstraZeneca product

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

If a medication error occurs in the course of the study, then the Investigator or other site personnel inform the appropriate AstraZeneca representatives within 1 day ie, immediately and **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 (see Section 6.4) and within 30 days for all other medication errors.

6.9 Management of investigational product-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 study drug(s) 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 NCI CTCAE version 4.03.

6.9.1 Specific toxicity management and dose modification information - Durvalumab and durvalumab plus tremelimumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy and durvalumab in combination with tremelimumab 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 the clincal study associate on how to gain access to this website.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 3.9 and Toxicity Management Guidelines).

Following the first dose of study drug(s), subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in toxicity Management Guidelines. These guidelines have been prepared by AstraZeneca to assist the Investigator in the exercise of his or her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab plus tremelimumab regimen by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

6.9.2 Specific toxicity management and dose modification information - sorafenib CCI

Investigators should follow local standard clinical practice regarding dose modifications for agents used in the sorafenib CCI arm. For specific information regarding the individual agent used in this study, please refer to the local prescribing information for the relevant agent.

6.9.3 Management of Hepatotoxicity

Management of hepatotoxicity should take into consideration the viral status of the patient 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 patients treated with tremelimumab monotherapy (Sangro et al 2013), should be considered to be of a different risk-benefit profile from increases in ALT associated with other signs of hepatotoxicity.

General guiding principles for select patient populations are as follows:

1. Uninfected HCC: Interpretation of hepatic laboratory results not confounded by underlying viral infection. Management should focus on ruling out non-imAEs 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 the following:

   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-imAEs unrelated to HCV or HBV

   d. imAEs 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 imAEs 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 imAEs 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, TBL, direct bilirubin, albumin, alkaline phosphatase (ALP), gamma glutamyltransferase, and INR. Patients should be monitored/evaluated for etiologies (eg, viral hepatitis, disease progression, concomitant medications, herbals, over-the-counter medications, and supplements) other than immune-related hepatotoxicity before the initiation of dose modifications and immunosuppression.

Treatment modification and management guidelines for hepatotoxicity are presented in the Toxicity Management Guidelines.

6.10 Study governance and oversight

6.10.1 Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study, to ensure the integrity of the study, and to oversee the 2 planned interim analyses. The first IDMC safety review will occur when approximately 30 patients per arm are randomized or 6 months after the first patient is dosed (whichever occurs first) and will occur approximately every 6 months thereafter; the frequency of IDMC review may be adjusted by the IDMC as needed. The IDMC will be composed of individuals external to AstraZeneca. An IDMC charter will be developed which will specify the Committee's responsibilities, authorities, and procedures along with details of the interim analysis planning, decision-making guidance, and dissemination of the results as well as the recommendations and decisions after the interim analyses. Formal implementation and communication of IDMC recommendations will be managed by the AstraZeneca Executive Committee, which will be unrelated to the study project team.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

7. STUDY DRUGS AND OTHER TREATMENTS

7.1 Identity of study drugs

AstraZeneca will supply durvalumab and tremelimumab. Sorafenib will be supplied locally. Additional details are provided below.

Investigational product	Dosage form and strength
Durvalumab	CCI solution for infusion after dilution
Tremelimumab	CCI solution for infusion after dilution
Sorafenib[a]	CCI orally CCI

CCI

[a]   Under certain circumstances when local sourcing is not feasible, sorafenib treatment may be supplied centrally through AstraZeneca.

7.1.1 Durvalumab

Durvalumab will be supplied by AstraZeneca as a CCI vial solution for infusion after dilution. The solution contains CCI

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 the following:

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

- 4 hours at room temperature

The infusion solution must be allowed to equilibrate to room temperature prior to administration.

A dose of CCI (for patients weighing >30 kg) will be administered using an IV bag containing CCI with a final durvalumab concentration ranging from CCI and will be delivered through an IV administration set with a CCI CCI will be added to the IV bag. The IV bag size should be selected such that the final concentration is between CCI The bag will be mixed by gently inverting to ensure homogeneity of the dose in the bag.

If the patient's weight falls to ≤30 kg, weight-based dosing at CCI will be administered using an IV bag containing CCI with a final durvalumab concentration ranging from CCI and will be delivered through an IV administration set with a CCI Appendix F includes an example of a weight-based dose calculation.

The standard infusion time is 1 hour (±5 minutes). In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. Other drugs should not be co-administered 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 the infusion will be completed according to institutional policy to ensure the full dose is administered. It will be documented 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. CCI and any unused portion must be discarded.

Preparations are to be carried out in accordance with the study-specific drug handling instructions.

7.1.2 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a CCI vial solution for infusion after dilution. The solution contains CCI The nominal fill volume is CCI for the CCI vial and CCI for the CCI vial.

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 tremelimumab doses 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 the start of administration should not exceed the following:

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

- 4 hours at room temperature

The infusion solution must be allowed to equilibrate to room temperature prior to administration.

A dose of CCI (for participants >30 kg in weight) will be administered using an IV bag containing CCI with a final tremelimumab concentration ranging from CCI and delivered through an IV administration set with a CCI Add CCI dose volume rounded to nearest tenth mL) or CCI of tremelimumab to the IV bag. The IV bag size should be selected such that the final concentration is within CCI Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If the patient's weight falls to ≤30 kg, weight-based dosing of either CCI group) or CCI group) will be administered using an IV bag containing CCI with a final tremelimumab concentration ranging from CCI and will be delivered through an IV administration set with a CCI

Appendix G includes an example of a weight-based dose calculation. The standard infusion time is 1 hour (± 5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. Other drugs should not be co-administered 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 the infusion will be completed according to institutional policy to ensure the full dose is administered. It will be documented 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. Preparations are to be in accordance with the study-specific drug handling instructions.

7.1.3   Sorafenib

Sorafenib will either be locally sourced or centrally supplied by AstraZeneca and will be administered according to prescribing information or treatment guidance in general use by the investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug, and the drug will be labeled with text translated into local language in accordance with regulatory guidelines.

7.2 Dose and treatment regimens

Patients will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment arms:

- Arm A: durvalumab CCI monotherapy,

- Arm B: durvalumab CCI plus tremelimumab CCI combination therapy,

- Arm C: durvalumab CCI plus tremelimumab CCI combination therapy, or

- Arm D: sorafenib CCI

Crossover within the study will not be permitted for any of the treatment arms, except for rechallenge in Arm B. Following amendment 4 patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment arms: Arm A, Arm C and Arm D.

Durvalumab monotherapy (Arm A)

Patients in Arm A will receive CCI durvalumab via IV infusion CCI starting on CCI until confirmed PD, unacceptable toxicity, or any discontinuation criterion are met (Figure 2). (Note: If a patient's weight decreases to ≤30 kg, the patient should receive weight-based dosing of durvalumab CCI after consultation between the Investigator and the Study physician, until the weight increases to >30 kg, at which point the patient should receive the fixed dose of durvalumab CCI

Standard infusion time is 1 hour (±5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Figure 2   Durvalumab monotherapy dosing schedule
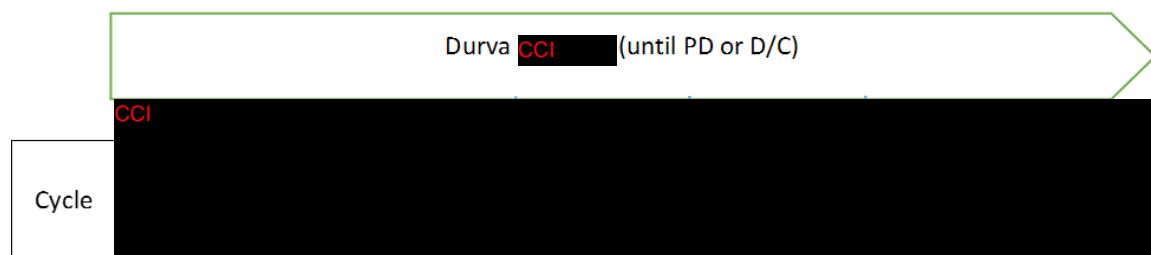
Durva Durvalumab; D/C Discontinuation; PD Progressive disease.

Durvalumab CCI plus tremelimumab CCI combination therapy (Arm B)

Patients in Arm B will receive durvalumab CCI plus tremelimumab CCI starting at CCI followed by durvalumab CCI monotherapy CCI starting CCI after the final infusion of the combination therapy until confirmed PD, unacceptable toxicity, or any discontinuation criteria are met (Figure 3). (Note: If a patient's weight decreases to 30 kg or below (≤30 kg), the patient should receive weight-based dosing of durvalumab CCI and tremelimumab CCI after consultation beween The Investigator and the Study physician, until the weight increases to >30 kg, at which point the patient should receive the original assigned fixed dose of durvalumab CCI with or without tremelimumab CCI

Tremelimumab will be administered first; the durvalumab infusion will start immediately after the end of the tremelimumab infusion. The standard infusion time is 1 hour (±5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. If there are clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of durvalumab can be given up to 1 hour after the tremelimumab infusion has finished.

Figure 3   Durvalumab CCI **plus tremelimumab** CCI **combination therapy dosing schedule (Arm B)**
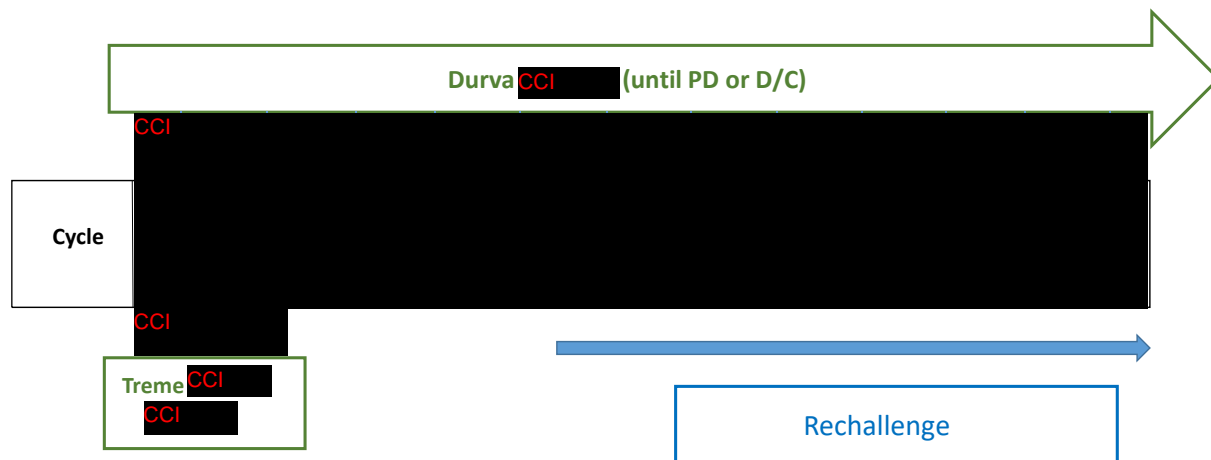
Durva Durvalumab; D/C Discontinuation; PD Progressive disease; Treme Tremelimumab.

Durvalumab CCI **plus tremelimumab** CCI **combination therapy (Arm C)**

Patients in Arm C will receive durvalumab CCI plus tremelimumab CCI at CCI followed by durvalumab CCI monotherapy CCI starting CCI after the first and final infusion of the combination therapy until confirmed PD, unacceptable toxicity, or any discontinuation criteria are met (Figure 4). (Note: If a patient's weight decreases to 30kg or below (≤30 kg), the patient should receive weight-based dosing of durvalumab CCI and tremelimumab CCI after consultation between investigator and study physician, until the weight increases to >30 kg, at which point the patient should receive the original assigned fixed dose of durvalumab CCI with or without tremelimumab CCI

Tremelimumab will be administered first; the durvalumab infusion will start immediately after the end of the tremelimumab infusion. Standard infusion time is 1 hour (±5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. If there are clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of durvalumab can be given up to 1 hour after the tremelimumab infusion has finished.

Figure 4 **Durvalumab** CCI **plus tremelimumab** CCI **combination therapy dosing schedule**
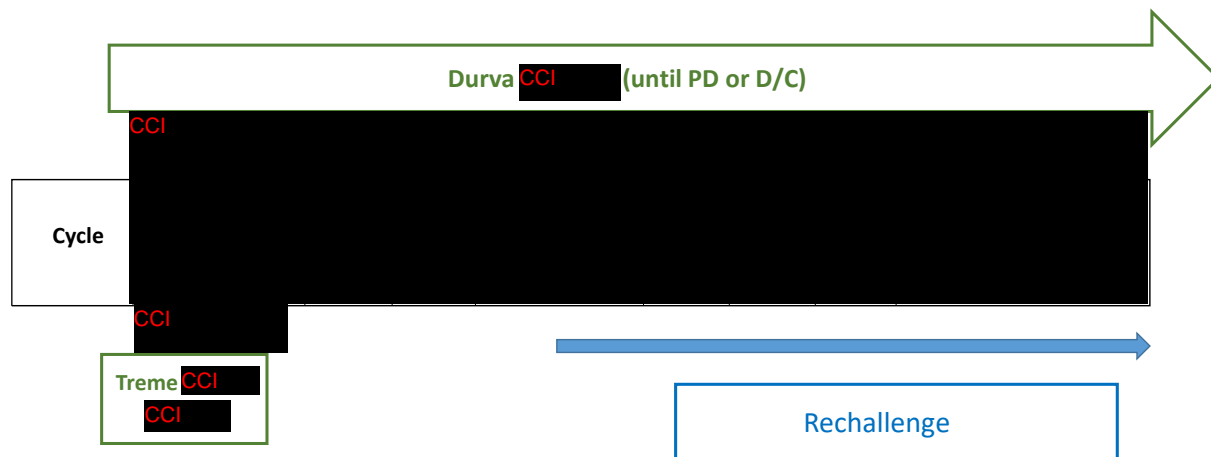
Durva Durvalumab; D/C Discontinuation; PD Progressive disease; Treme Tremelimumab.

Sorafenib CCI **(Arm D)**

Patients in the sorafenib arm will receive CCI orally CCI until PD, unacceptable toxicity, or any discontinuation criteria are met.

Dose reductions for the management of adverse drug reactions will be based on the locally approved product label for sorafenib. In countries where sorafenib is not approved, the following modification will be followed: sorafenib dose may be reduced to CCI orally CCI If additional dose reduction is required, the sorafenib dose may be reduced to a single CCI orally CCI

7.2.1 Duration of treatment, treatment through disease progression, and rechallenge

Any time during the treatment period, the patients who meet study discontinuation criteria (Section 3.9) and the patients with rapid tumor progression or symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible for continuing study treatment.

Crossover within the study arms will not be permitted for any of the treatment arms with the exception of rechallenge in Arm B.

7.2.1.1 Treatment through disease progression

Patients in all treatment arms may continue receiving their originally assigned treatment, at the Investigator's discretion, after the first overall time point assessment of PD by RECIST 1.1 until PD is confirmed on a follow-up scan evaluated by Confirmation of Radiological Progression criteria (Appendix B). A subsequent scan is required following the assessment of PD by RECIST 1.1, preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

Patients in all arms with confirmed PD who, in the Investigator's opinion, continue to receivebenefit from their assigned treatment and meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment (Section 7.2.1.3). However, patients who develop progression in TLs after a clear response to therapy as defined by RECIST 1.1 will not be permitted to continue therapy.

7.2.1.2 Rechallenge option for durvalumab and tremelimumab combination therapy arms

Patients in the durvalumab and tremelimumab combination arms (Arm B and Arm C), who complete their first 4 assigned dosing cycles and, in the investigator's opinion, are benefiting from study drug(s), but have evidence of PD with or without confirmation according to RECIST 1.1 during the subsequent durvalumab monotherapy dosing portion, can be rechallenged. Patients must meet eligibility criteria for rechallenge (Section 7.2.1.3), and are only eligible for rechallenge once. Rechallenge cannot begin earlier than **Cycle 6** of their assigned treatment arm.

- **Patients in Arm B** (durvalumab CCI and tremelimumab CCI arm): Patients will be rechallenged with tremelimumab CCI or tremelimumab CCI and durvalumab CCI (with prior approval from the AstraZeneca Study Physician), followed by CCI durvalumab monotherapy CCI until PD, unacceptable toxicity, or any discontinuation criterion are met.

- **Patients in Arm C** (durvalumab CCI and tremelimumab CCI arm): Patients will be rechallenged with tremelimumab CCI and durvalumab CCI followed by durvalumab monotherapy CCI until PD, unacceptable toxicity, or any discontinuation criterion are met.

Patients who meet the criteria for rechallenge for their respective treatment arm are only eligible for rechallenge once and as per their original treatment assignment.

Patients receiving rechallenge with tremelimumab CCI or tremelimumab CCI will follow the same schedule of assessments with the exception of the below assessments, which do not need to be collected a second time:

- PK

- ADA

- CCI ███████████████

- ███████████████

- Tumor biopsies

- CCI ███████████████████████████

Rechallenge is permitted only for patients randomized to the durvalumab and tremelimumab combination arms.

7.2.1.3 Criteria for treatment through progression and for rechallenge

For all patients who are treated through progression or who are rechallenged with tremelimumab in combination with durvalumab, the Investigator should ensure that the following criteria are met:

- Progression should not have occurred after confirmed response (CR or PR as defined by RECIST 1.1) in the TLs (regardless of the appearance of new lesions); ie, the response and progression events both occurred in the TLs during the same treatment period.

- No significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient.

- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in World Health Organization (WHO)/ECOG performance status to >1

- There is absence of rapid disease progression 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.

- All eligibility criteria for this study (see Sections 3.1 and 3.2), with the exception of inclusion criteria 5 and 12 and exclusion criterion 23, are met.

Patients who AstraZeneca and the Investigator determine may not continue treatment after PD will be followed up for survival. Patients 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.

7.3   Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language, as required. Durvalumab and tremelimumab will be provided with either single-panel labels or multi-language booklet labels.

Label text prepared for durvalumab will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending on the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

7.4   Storage

The Investigator, or an approved representative (eg, pharmacist), will ensure that durvalumab and tremelimumab are stored in a secured area, in refrigerated temperatures (2°C to 8°C), and in accordance with applicable regulatory requirements. Sorafenib should be stored according to the Summary of Product Characteristics ("do not store over 25°C). A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

7.5   Compliance

The administration of all study drugs should be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by reconciliation of site drug accountability logs.

7.6 Accountability

The study drugs provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Study site personnel will account for all study drugs received at the site, unused study drugs, and for appropriate destruction. Certificates of delivery, destruction, and return should be signed.

7.7 Concomitant medications and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening until 3 months after the last dose of study drug(s). Any concomitant medication(s), including herbal preparations, taken during this time will be recorded in the eCRF.

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

Restricted, prohibited, and permitted concomitant medications are described in Table 10 and Table 11 (refer also to Toxicity Management Guidelines) For patients randomized to the sorafenib CCI arm, please refer to the local prescribing information with regards to warnings, precautions, and contraindications.

Table 10   Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
For all treatment arms	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study drug(s)
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study drug(s)

Prohibited medication/class of drug:	Usage:
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study drug(s). (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding TLs, for palliative intent is acceptable [eg, by local surgery or radiotherapy].)
Live attenuated vaccines	Should not be given through 30 days after the last dose of study drug(s)
For all immunotherapy arms	
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study drug(s)-related AEs • Use in patients with contrast allergies • Use of inhaled, topical, and intranasal corticosteroids A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy-related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study

Prohibited medication/class of drug:	Usage:
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly
	Should be used with caution in the 90 days after 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.
Herbal and natural remedies, which may have immune-modulating effects	Should not be given concurrently unless agreed by AstraZeneca

AE Adverse event; CTLA-4 Cytotoxic T-lymphocyte-associated antigen-4; EGFR TKI Epidermal growth factor receptor tyrosine kinase inhibitor; mAb Monoclonal antibody; PD-1 Programmed cell death-1; PD-L1 Programmed cell death ligand 1; TL target lesion.

Table 11   Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to NTLs, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

NTL Non-target lesion.

7.7.1   Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patients' safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.7.2   Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either nonclinically or in patients. As durvalumab is a mAb and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is, therefore, not expected that durvalumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected PK drug-drug interactions. The mechanism of action of durvalumab involves binding to PD-L1; therefore, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

7.8 Post Study Access to Study Drug(s)

After the final analysis, AstraZeneca will continue to supply open-label drug to patients per their assigned study treatment until confirmed PD, unacceptable toxicity, or any of the discontinuation criteria are met (see Section 7.2).

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be prepared and signed off before enrollment of the first patient, and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data. In the event a dosing arm is discontinued from the study, it is planned that data from this arm will still be presented in the final study reporting as per the SAP. The primary objective of this study is to assess the efficacy of Arm C vs. Arm D for Overall Survival (OS, for superiority). The key secondary objectives of this study are to assess the efficacy of Arm A vs. Arm D for OS (for non-inferiority, then for superiority). Efficacy data for Arm B (which was closed for enrollment with Amendment 4) will be summarized descriptively, but will not be formally analyzed.

8.2 Sample size estimate

The study will plan to screen approximately 1650 patients in order to randomize approximately 1310 eligible patients in the global study. (This includes 1155 patients randomized to Arms A, C, D with 385 per arm; and approximately 155 patients in Arm B, randomized prior to the closure of this arm. Patients from China enrolled in the global study are included in this figure). Once global enrolment has completed, recruitment into an expansion cohort will continue in China (ie. China Tail) until a total of 180 Chinese patients have been randomized. Patients from China enrolled in the global study and the China Tail will be included in a China cohort. Details of the China cohort and analysis plan will be outlined in a China specific amendment and SAP. Patients will be randomized 1:1:1:1 to durvalumab CCI monotherapy (Arm A), durvalumab CCI plus tremelimumab CCI combination therapy (Arm B), durvalumab CCI plus tremelimumab CCI combination therapy (Arm C), or sorafenib CCI (Arm D). Following Amendment 4 Arm B will be closed for enrollment therefore new patients will be randomized in a 1:1:1 ratio into Arm A, Arm C, and Arm D.

The study is sized to characterize the OS benefit of Arm C vs. Arm D.

The sample size estimation assumes an exponentially distributed OS and a 2-month delay in separation of the OS curves for Arm C vs. Arm D, hence the use of average HR (0.70 for Arm C vs. Arm D). A non-uniform accrual (weight=2) of patients with a duration of 22 months is assumed when estimating the analysis times with a follow-up duration of 15.5 months and a total duration of 37.5 months. No adjustment has been included for dropouts.

For the efficacy comparisons, the median OS for sorafenib (Arm D) is assumed to be 11.5 months, with an 18-month OS rate of 33.8%.

Durvalumab CCI ***plus tremelimumab*** CCI ***(Arm C) versus sorafenib*** CCI ***(Arm D) - OS in FAS intent-to treat (ITT)***

The assumed OS treatment effect is an average HR of 0.70 for Arm C versus Arm D. This translates to an increase in median OS from 11.5 months to 16.5 months and in the 18-month OS rate from 33.8% to 46.8% in Arm C versus Arm D.

At the time of the second Interim Analysis (IA2), the analysis of OS will be performed when approximately 404 OS events in Arm C and Arm D combined (~52% maturity) have occurred, approximately 30 months after the first patient is randomized. This number of OS events will provide 85% power to demonstrate a statistically significant difference in OS at a 2-sided 2.22% significance level.

Final analysis of OS will be performed when approximately 515 events in Arm C and Arm D combined (~67% maturity) have occurred, approximately 37.5 months after the first patient is randomized. This number of OS events will provide 97% power to demonstrate a statistically significant difference in OS at a 2-sided 4.25% significance level. The smallest treatment difference that could be observed as statistically significant at the final analysis is an average HR of 0.84 (an increase in median OS from 11.5 months to approximately 13.7 months in Arm C versus Arm D).

Durvalumab CCI ***monotherapy (Arm A) versus sorafenib*** CCI ***(ArmD) - OS in FAS ITT***

It is estimated that approximately 453 and 560 events can be observed at the time of the interim and final analysis respectively. The power of the NI test at margin of 1.08 is approximately 84% at final analysis.

- o The noninferiority margin of HR 1.08 is determined using 95%-95% fixed margin approach (FDA Guidance 2016; EMEA Guideline 2005) based on two phase 3 trials of sorafenib (Llovet 2008 and Cheng 2009) in first line HCC and assuming conservative 60% retention. Multiple historical trials in the same indication were also designed as NI

using including Brivanib (Johnson 2013), Sunitinib (Cheng 2013), Linifanib (Cainap 2014), and Lenvatinib (Kudo 2017).

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 12.

Table 12   **Summary of outcome variables and analysis populations**

Outcome variable	Populations
Efficacy data	
OS	FAS (ITT population)
ORR, BoR, DoR, DCR, DCR-16w, DCR-24w PFS, TTP, OS18, OS24, OS36 and PROs	FAS (ITT population) DoR will be based on the subset of patients in the full analysis set who achieved objective tumor response.
Demography	FAS set (ITT population)
PK data	PK analysis set
Immunogenicity data	
Immunogenicity data	Listings will be based on safety analysis set Summaries will be based on ADA evaluable set
Safety data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
Vital signs	Safety analysis set

AE Adverse event; BoR Best objective Response; DCR Disease control rate; DCR-16w DCR at 16 weeks; DCR-24w DCR at 24 weeks; DoR Duration of response; FAS full analysis set; ITT Intent-to-treat; ORR Objective response rate; OS Overall survival; OS18 Overall survival at 18 months;

OS24 Overall survival at 24 months; Overall survival at 36 months, PFS Progression-free survival; PK Pharmacokinetics; PRO Patient-reported outcome; TTP Time to progression.

8.3.1 Full analysis set

The FAS will include all randomized patients. The FAS will be used for all efficacy analyses (including PROs). Treatment arms will be compared on the basis of randomized study drug(s), regardless of the study drug(s) actually received. Patients who were randomized but did not subsequently go on to receive study drug(s) are included in the analysis in the treatment arm to which they were randomized.

8.3.2 Safety analysis set

The safety analysis set will consist of all patients who received at least 1 dose of study drug(s). Safety data will not be formally analyzed but summarized using the safety analysis set according to the study drug(s) received, that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the study drug(s) they actually received.

8.3.3 PK analysis set

The PK analysis set will include all patients who receive at least 1 dose of study drug(s) per the protocol for whom any postdose data are available.

8.3.4 ADA evaluable set

The ADA evaluable set will include all patients who have non-missing baseline ADA and at least 1 non-missing post-baseline ADA results. All major ADA analyses will be based on the ADA evaluable set.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

8.4.1.1 RECIST 1.1-based endpoints

Analysis of the secondary endpoints, ORR, DCR, DCR-16w, DCR-24w DoR, TTP, and PFS, will be based on the Investigator assessments using RECIST 1.1.

Blinded Independent Central Review (BICR)

A BICR of radiological scans will be performed on patients included for the first interim analysis, ie, all randomized patients who have had at least 32 weeks of follow-up at the time of the interim analysis 1 (IA1) DCO (ie. randomized ≥ 32 weeks prior to IA1 DCO).

The imaging scans will be reviewed by 2 primary radiologist reviewers using RECIST 1.1. If the overall timepoint assessments differ at any timepoint between the 2 primary reviewers, the case will be adjudicated by a third radiologist, who must choose all the overall timepoint assessments from the primary reviewer with which he agrees more. If the overall timepoint assessments are identical between the 2 primary reviewers, the timepoint responses from the reviewer who completed their assessment of baseline scans first will be used for the analyses. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE) and the relevant scan dates for each time point (ie, for visits where response or progression is or is not identified).

Further details of the BICR will be documented in the Imaging Charter.

Investigator RECIST 1.1-based assessments

All RECIST 1.1 assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to randomization. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE, unless there is evidence of progression in which case the response will be assigned as PD.

8.4.1.2   Primary endpoint, OS

OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Note: Survival calls will be made following the date of data cutoff for the analysis (these contacts should generally occur within 7 days of the data cutoff). If patients are confirmed to be alive or if the death date is post the data cutoff date, these patients will be censored at the date of data cutoff. Death dates may be found by checking publicly available death registries.

8.4.1.3 Secondary endpoints

Objective response rate

ORR (per RECIST 1.1 as assessed by the Investigator) is defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

Duration of response

DoR (per RECIST 1.1 as assessed by the Investigator) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring – date of first response +1). The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint.

DoR will not be defined for those patients who do not have documented response.

Disease control rate

DCR (per RECIST 1.1 as assessed by the Investigator) is defined as the rate of best objective response of either CR, PR, or SD according to RECIST 1.1.

DCR-16w is defined as the percentage of patients who have a best objective response of CR or PR or who have SD for at least 16 weeks (-7 days), following the start of study treatment. DCR-24w is defined as the percentage of patients who have a best objective response of CR or PR or who have SD for at least 24 weeks (-7days), following the start of treatment.

Progression-free survival

PFS (per RECIST 1.1 as assessed by the Investigator) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more consecutive missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have baseline data,

they will be censored at Day 1 unless they die within 2 visits of baseline, then they will be treated as an event with date of death as the event date.

The PFS time will always be derived based on scan/assessment dates and not visit dates.

RECIST 1.1 assessments/scans contributing toward a particular visit may be performed on different dates. The following rules will be applied:

- For Investigator assessments, the date of progression will be determined based on the earliest of the RECIST 1.1 assessment/scan dates of the component that indicates progression.

- When censoring a patient for PFS, the patient will be censored at the latest of the scan dates contributing to a particular overall visit assessment.

Time to progression

TTP (per RECIST 1.1 as assessed by the Investigator) is defined as the time from randomization until objective tumor progression; TTP does not include deaths. If patients died without progression, they will be censored at the time of death.

CCI

Proportion of patients alive at 18 months after randomization (OS18)

The OS18 will be defined as the Kaplan-Meier (KM) estimate of OS at 18 months after randomization.

Proportion of patients alive at 24 months after randomization (OS24)

The OS24 will be defined as the KM estimate of OS at 24 months after randomization.

Proportion of patients alive at 36 months after randomization (OS36)

The OS36 will be defined as the KM estimate of OS at 36 months after randomization.

8.4.2 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. "On treatment" will be defined as assessments between date of start dose and 90 days following discontinuation of study drug(s) (ie, the last dose of durvalumab, tremelimumab, or sorafenib). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

8.4.2.1 Adverse events

AEs observed up until 90 days following discontinuation of the last dose of study drug (durvalumab, tremelimumab, or sorafenib), or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study drug[s]) will be flagged in the data listings.

The safety analysis set will be used for reporting of safety data. A separate data listing of AEs occurring more than 90 days after discontinuation of study drug(s) will be produced. These events will not be included in AE summaries.

8.4.2.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the CSR. A similar review of laboratory, vital signs, and ECG data will be performed for identification of OAEs. Examples of

these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

8.4.2.3 Safety assessments

For the change from baseline summaries for vital signs and laboratory data, the baseline value will be the latest result obtained prior to the start of study drug(s).

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) using the following formula:

$QTcF=QT/RR^{(1/3)}$ where RR is in seconds

Corrected calcium product will be derived during creation of the reporting database using the following formulas:

Corrected calcium (mmol/L)=Total calcium (mmol/L)+([40–albumin (G/L)]×0.02)

The denominator used in laboratory summaries will only include evaluable patients, ie, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a predose and at least 1 postdose value recorded.

- If a CTCAE criterion does not consider changes from baseline to be evaluable, the patient need only have 1 postdose value recorded.

The denominator in vital signs data should include only those patients with recorded data.

8.4.3 Calculation or derivation of patient-reported outcome variables

All items/questionnaires will be scored according to published scoring guidelines. All PRO analyses will be based on the FAS.

8.4.3.1   EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and global health status/QoL scale. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global measure of health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global measure of health status and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded.

Definition of clinically meaningful changes - Visit Response and Best Overall Response

The global health status/QoL scale includes 2 items from the EORTC QLQ-C30: "How would you rate your overall health during the past week?" (Item 29) and "How would you rate your overall QoL during the past week?" (Item 30). Definition of clinically meaningful changes in score compared with baseline will be evaluated. A clinically meaningful change is defined as an absolute change in the score from baseline of ≥ 10 for scales from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical function (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥ 10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥ 10. At each postbaseline assessment, the change in global health status/QoL, symptoms, and functioning score from baseline will be categorized as improvement, no change, or deterioration as shown in Table 13.

Table 13   Mean change and clinically meaningful change - EORTC QLQ-C30

Score	Change from baseline	Visit response
EORTC QLQ-C30 global quality of life score	$\geq +10$ (Increase of at least 10)	Improvement
	≥ -10 (Decrease of at least 10) or "Subject too sick to complete the questionnaires (disease under investigation)"	Deterioration

Score	Change from baseline	Visit response
	Otherwise	No change
EORTC QLQ-C30 symptom scales	≥+10 (Increase of at least 10) or "Subject too sick to complete the questionnaires (disease under investigation)"	Deterioration
	≥-10 (Decrease of at least 10)	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	≥+10 (Increase of at least 10)	Improvement
	≥-10 (Decrease of at least 10) or "Subject too sick to complete the questionnaires (disease under investigation)"	Deterioration
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-C30 30-item core quality of life questionnaire.

A patient's best overall response in symptoms, function, or global health status/QoL will be derived as the best response the patient achieved, based on evaluable PRO data collected during the study period. The criteria in Table 14 will be used to assign a best response in symptoms or function or global health status/QoL.

Table 14   Best response in EORTC QLQ-C30 and EORTC QLQ-HCC18 scores: FAS population

Overall score response	Criteria
Missing	Patient has no evaluable baseline or post-baseline PRO assessment
Improved	Patient meets one of the following criteria: 1. Has 2 consecutive visit responses of "improvement" at least 21 days apart 2. Has 1 visit response of "improvement" with no further assessments, and did not die within 2 PRO assessment visits

Table 14   Best response in EORTC QLQ-C30 and EORTC QLQ-HCC18 scores: FAS population

Overall score response	Criteria
No Change	Patient does not qualify for an overall score response of "improved" and meets 1 of the following criteria: 1. Has 2 consecutive visit responses of "no change" at least 21 days apart 2. Has 1 visit response of "no change" with no further assessments, and did not die within 2 PRO assessment visits
Deterioration	Patient does not qualify for an overall score response of "improved" or "no change" and meets 1 of the following criteria: 1. Has 2 consecutive visit responses of "deterioration" at least 21 days apart 2. Has 1 visit response of "deterioration" and no further assessments 3. Has 1 visit response of "improvement" or "no change" followed by death within 2 PRO assessment visits
Other	Does not qualify for one of the above (improved, no change or deterioration).

EORTC European Organisation for Research and Treatment of Cancer; FAS full analysis set; PRO patient-reported outcome; QLQ C30 30-item core quality of life questionnaire; QLQ-HCC18 18-item HCC specific quality of life questionnaire.

Time to health-related QoL or function deterioration

Time to QoL or function deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration that is confirmed at a subsequent visit (except if it was the patient's last available assessment) or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient discontinues study drug(s) or receives another anticancer therapy prior to global health status/QoL or function deterioration. Death will be included as an event only if it occurs within 2 PRO assessment visits from the last available PRO assessment.

Patients whose global health status/QoL or function (as measured by EORTC QLQ-C30) has not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the global health status/QoL or function could be evaluated. Also, if global health status/QoL or function deteriorates or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where global health status/QoL or function could be evaluated prior to the 2 missed visits.

The population for the analysis of time to global health status/QoL or function deterioration will include a subset of the FAS who have baseline scores of ≥10.

Symptom improvement rate

Responses in symptoms for each visit (improvement, deterioration, and no change based on Table 13) as well as the best overall response will be presented by treatment arm. The symptom improvement rate will be defined as the number (%) of patients with a best overall score response of "improved" in symptoms.

The denominator will consist of a subset of the FAS who have a baseline symptom score ≥10.

Global health status/QoL or function improvement rate

The global health status/QoL or function improvement rate will be defined as the number (%) of patients with best overall response of "improved" in QoL or function.

The denominator will consist of a subset of the FAS who have a baseline global health status/QoL or function score ≤90.

8.4.3.2   EORTC QLQ-HCC18

The QLQ-HCC18 is a hepatocellular cancer-specific module from the EORTC comprising 18 questions to assess HCC symptoms. The module includes 6 multi-item domain scales and 2 single-item scales. For all items and scales, high scores indicate increased symptomatology/more problems.

The scoring approach for the QLQ-HCC18 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30. Similar to the symptom scales of the EORTC QLQ-C30, higher scores represent greater symptom severity.

Definition of clinically meaningful change - visit response and best overall response

Changes in score compared with baseline will be evaluated. A clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales/items from QLQ-HCC18. For example, a clinically meaningful deterioration or worsening in pain (as assessed by QLQ-HCC18) is defined as an increase in the score from baseline of ≥10. At each postbaseline assessment, the change in symptom score from baseline will be categorized as improved, no change, or deterioration, as shown in Table 15. A patient's best overall response in symptoms will be derived as the best response the patient achieved, based on evaluable PRO data collected during the study period. The criteria in Table 14 will be used to assign a best response in symptom score.

Table 15   Mean change and clinically meaningful change - EORTC QLQ-HCC18

Score	Change from baseline	Visit response
QLQ-HCC18 symptom scales and items	≥+10 (Increase of at least 10) or "Subject too sick to complete the questionnaires (disease under investigation)"	Deterioration
	≥-10 (Decrease of at least 10)	Improved
	Otherwise	No change

EORTC European Organisation for Research and Treatment of Cancer; QLQ-HCC18 18-item HCC specific quality of life questionnaire.

Time to symptom deterioration

For each of the symptom scales/items in the QLQ-HCC18, time to symptom deterioration will be defined as the time from randomization until the date of the first clinically meaningful symptom deterioration that is confirmed at a subsequent visit (except if it was the patient's last available assessment) or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient discontinues study drug(s) or receives another anticancer therapy prior to symptom deterioration. Only deaths occurring within 2 PRO assessment visits from the last available PRO assessment will be included as events.

Patients whose symptoms (as measured by the QLQ-HCC18) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms progress or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated prior to the 2 missed visits.

The population for the analysis of time to symptom deterioration will include a subset of the FAS who have baseline scores ≤90.

8.4.3.3   CCI

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8.4.3.4 CCI

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8.4.3.5 CCI

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8.4.4 CCI

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8.4.5 Calculation or derivation of pharmacokinetic variables

8.4.5.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear, mixed-effects modelling approach. The impact of physiologically relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints will be evaluated. The results of such an analysis will be reported in a separate report. CCI

8.4.5.2   Pharmacokinetic non-compartmental analysis

The actual sampling times will be used in the PK calculations. PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. PK parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow). Samples below the lower limit of quantification will be treated as missing in the analyses.

8.4.5.3   Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab and tremelimumab. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. CCI

8.4.6   Calculation or derivation of biomarker variables

PD-L1 expression, as defined in the secondary objectives, will be assessed for evaluable patients in each cohort according to prespecified criteria that will be detailed in the SAP.

8.4.7   CCI

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8.5   Methods for statistical analyses

The formal statistical analysis of OS (primary endpoint) will be performed for the following efficacy test hypotheses (alternative hypotheses):

- H_1: Difference between durvalumab CCI plus tremelimumab CCI (Arm C) and sorafenib CCI (Arm D)

- H$_2$: Durvalumab CCI monotherapy (Arm A) not inferior to sorafenib CCI (Arm D) with noninferiority margin of 1.08

- H$_3$: Difference between durvalumab CCI monotherapy (Arm A) and sorafenib CCI (Arm D)

Efficacy data for Arm B: durvalumab CCI plus tremelimumab CCI combination therapy arm (which was closed for enrollment with Amendment 4) will be summarized descriptively, but will not be formally analyzed.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of treatment, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS (intent-to-treat [ITT] population). PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized on the safety analysis set.

Results of all statistical analysis will be presented using a 95% confidence interval (CI) and 2-sided p-value, unless otherwise stated.

Table 16 details which endpoints are to be analyzed, together with pre-planned sensitivity analyses indicating which analysis is regarded as primary for that endpoint.

Table 16   Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Overall survival	Primary analysis using a stratified log-rank test:
	Sensitivity analysis using a KM plot of time-to-censoring where the censoring indicator of the primary analysis is reversed (attrition bias)

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank test using Investigator assessments per RECIST 1.1
Time to progression	Stratified log-rank test using Investigator assessments per RECIST 1.1
Objective response rate	Logistic regression using Investigator assessments per RECIST 1.1
Duration of response	Analysis following the method described in Section 8.5.3, using Investigator assessments (RECIST 1.1)
Disease control rate	Summarized by treatment arm n (%) using Investigator assessments (RECIST 1.1)
Proportion of patients alive at 18 months	Hazard ratio using the KM estimates of OS at 18 months (following method described in Section 8.5.3)
Proportion of patients alive at 24 months	Hazard ratio using the KM estimates of OS at 24 months (following method described in Section 8.5.3)
Proportion of patients alive at 36 months	Hazard ratio using the KM estimates of OS at 36 months (following method described in Section 8.5.3)
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Time to deterioration (EORTC QLQ-C30 and EORTC QLQ-HCC18)	Stratified log-rank tests
EORTC QLQ-C30, EORTC QLQ-HCC18 and CCI ███████████	Average change from baseline using an MMRM analysis. Summary statistics including change from baseline.

EORTC   European Organisation for Research and Treatment of Cancer; CCI ████████████████████████████████████
KM Kaplan Meier; MMRM Mixed effect model repeat measurement; OS overall survival; PFS Progression free survival; QLQ-C30 30-item core quality of life questionnaire; QLQ-HCC18   18-item hepatocellular cancer health-related quality of life questionnaire.

8.5.1　　Multiple testing strategy

Two interim analyses and a final analysis are planned as described below:

IA1: The first interim analysis will be performed after approximately 100 patients per treatment arm have had the opportunity for 32 weeks of follow-up. The objective is to evaluate the efficacy of Arm A and Arm C in terms of ORR and DoR. The analysis set will include all randomized patients who have had the opportunity for at least 32 weeks of follow-up at the time of the IA1 DCO (ie, randomized ≥ 32 weeks prior to IA1 DCO). Descriptive summaries of ORR including exact 95% CIs will be presented for each treatment arm. KM plots of DoR and median DoR derived from the KM curves will also be provided. No formal comparison between arms will be performed in this interim analysis.

Interim Analysis 2 (IA2): The second interim analysis will be performed when approximately 404 OS events in Arm C and Arm D combined (~52% maturity), approximately 30 months after the first patient is randomized. The goal is to evaluate the efficacy of Arm C vs. Arm D (for superiority) and then Arm A vs. Arm D (for non-inferiority, then superiority) in terms of OS.

Enrollment must be completed before Interim Analysis 1 can be performed.

Final Analysis (FA): The final analysis is expected to be performed when approximately 515 OS events in Arm C and Arm D combined (~67% maturity), approximately 37.5 months after the first patient is randomized. The primary objective is to assess the efficacy of Arm C vs. Arm D in terms of OS for superiority. The key secondary objectives are to assess the efficacy of Arm A vs. Arm D in terms of OS (for non-inferiority, then superiority). Efficacy data for Arm B (which was closed for enrollment with Amendment 4) will be summarized descriptively, but will not be formally analyzed.

To strongly control the familywise error rate (FWER) at the 5% level (2-sided), an alpha level of 0.1% will be spent on the interim ORR and DoR analysis (IA1) while the remaining 4.9% alpha level will be spent on all OS analyses. The primary objective of OS will be tested (H1: Arm C vs. Arm D) with 4.9% for this comparison.

Since two analyses of OS are planned (Interim Analysis, Final Analysis), the Lan DeMets approach (Lan and DeMets 1983) that approximates the O'Brien and Fleming spending function will be used to maintain an overall 2-sided 4.9% type I error across the two planned analyses of OS (Interim and Final) for the primary comparison (H1: Arm C vs. Arm D)

If 78% of the target OS events for H1 (ie. 404/515) are available at the time of the interim analysis, the 2-sided significance levels to be applied for the interim and final OS analyses would be and 0.0222 and 0.0425, respectively. Strong control of the type 1 error will be applied testing endpoints as outlined in the MTP (Figure 5, further details in the SAP).

Figure 5   Multiple testing procedure for controlling the type 1 error
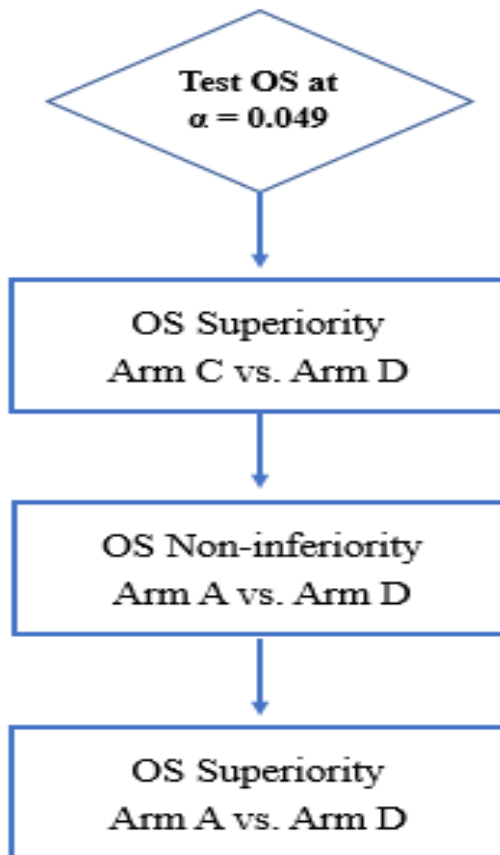
8.5.2 Analysis of the primary variable(s)

8.5.2.1 Overall survival

The primary analysis is to compare OS for Arm C vs. Arm D (for superiority) in the FAS (ITT) analysis set.

The primary OS endpoint will be analyzed using a stratified log-rank test adjusting for etiology of liver disease (Confirmed HBV versus confirmed HCV versus others), ECOG (0 versus 1), and macro-vascular invasion (yes versus no). The effect of Arm C vs. Arm D will be estimated by the HR together with its corresponding 95% CI and p-value.

The key secondary analyses are to compare OS for Arm A vs. Arm D (for non-inferiority, then superiority) in the FAS (ITT) analysis set.

The comparison of OS for Arm C vs. Arm A in the FAS (ITT) analysis set is a secondary analysis.

Secondary OS analyses will be performed using the same methodology as for the primary analysis described above.

Kaplan-Meier plots of OS will be presented by treatment arm. Summaries of the number and percentage of patients who have died, still in survival follow-up, lost to follow-up, and have withdrawn consent will be provided along with the median OS for each treatment.

The assumption of proportionality of hazard will be assessed first by examining plots of complementary log-log (event times) versus log (time) and, if these raise concerns, by fitting a time-dependent covariate to assess the extent to which this represents random variation. If a lack of proportionality of hazard is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time periods. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time unless there is extensive crossing of the survival curves. If lack of proportionality of hazard is found, this may be a result of treatment-by-covariate interactions, which will be investigated. In addition, the Kaplan-Meier curve along with landmark analyses (eg, 18- ,24-, and 36-month OS rate) will also help in understanding the treatment benefit.

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias, achieved by a Kaplan-Meier plot of time-to-censoring where the censoring indicator of OS is reversed.

The superiority boundary (ie, adjusted alpha levels) for the HR of treatment comparison at the interim and the final for the primary OS analysis will be derived based on the exact number of OS events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function (see Section 8.5.1).

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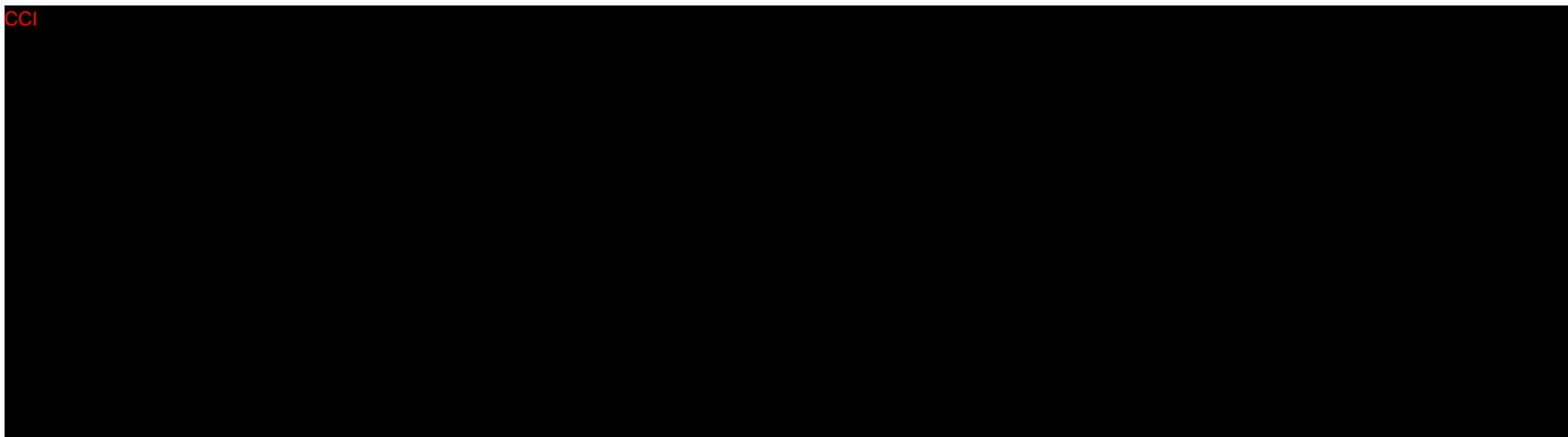
8.5.3 Analysis of the secondary variable(s)

8.5.3.1 Progression-free survival

Analysis of PFS (per RECIST 1.1 using Investigator assessments) will be performed to compare Arm A vs. Arm D and Arm C vs. Arm D as well as to compare Arm C vs. Arm A using the same methodology as for OS.

8.5.3.2 Time to progression

Analysis of TTP will be performed to compare Arm A vs. Arm D and Arm C vs. Arm D as well as to compare Arm C vs. Arm A using a stratified log-rank test as described for OS.

8.5.3.3 Objective response rate

At IA1, only descriptive summaries of ORR including exact 95% CIs will be presented for each treatment arm (Arm A and Arm C). The analysis set will include all randomized patients who have had the opportunity for at least 32 weeks of follow-up at the time of

the IA1 data cutoff (ie, randomized ≥32 weeks prior to IA1 DCO). ORR results will be presented by Investigator assessment (using RECIST1.1) and BICR (using RECIST1.1 and mRECIST).

At the final analysis, the ORR (per RECIST 1.1 using Investigator assessments) will be compared between Arm A vs. Arm D and Arm C vs. Arm D as well as to compare Arm C vs. Arm A. Logistic regression models adjusting for the same factors as the primary endpoint (etiology of liver disease, ECOG, and macro-vascular invasion) will be fitted. The results of the analysis will be presented in terms of an odds ratio together with its associated 95% CI and p-value. This analysis will be performed in the FAS (ITT) analysis set.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). Overall visit response data will be listed for all patients (ie, the FAS). For each treatment arm, best objective response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

8.5.3.4   Disease control rate

The DCR, DCR-16w and DCR-24w based on Investigator assessments per RECIST 1.1 will be summarized (ie, number of patients [%]) per treatment arm.

8.5.3.5   Duration of response

Descriptive data will be provided for the DoR based on Investigator assessments per RECIST 1.1 in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached). This analysis will be performed in the FAS (ITT) analysis set.

8.5.3.6   OS18,OS24 and OS36

OS18, OS24 and OS36, along with their 95% CI, will be summarized (using the Kaplan-Meier curve) and presented by treatment arm. The HR and CI will be presented using the method described by Klein et al (Klein et al 2007).

This analysis will be performed in the FAS (ITT) analysis set.

8.5.4   Patient-reported outcomes

The main PRO measures identified in the secondary objectives are global health status/QoL, physical function and fatigue scales along with single items appetite loss and nausea of the EORTC QLQ-C30; shoulder pain, abdominal pain, and abdominal

distension symptom scales of the EORTC QLQ-HCC18. Statistical analyses comparing treatment arms will include: visit specific and overall (across all visits) adjusted mean change from baseline scores (using mixed-effect model for repeated measurement [MMRM], time to deterioration, visit response (improvement, no change, and deterioration) as well as best overall response.

Absolute and change from baseline scores for each visit will be presented as descriptive analysis. Appropriate plots and graphs will be presented. Compliance rates summarizing questionnaire completion at each visit will be tabulated.

8.5.4.1   EORTC QLQ-C30

The primary assessment of HRQoL or symptom will focus on comparing mean change from baseline in the global health status/QoL, functions (physical, role, cognitive, social and emotional) and fatigue scores along with single-item symptoms appetite loss and nausea (from the EORTC QLQ-C30 questionnaire) between all immunotherapy arms and the sorafenib arms. The analysis population for mean change in HRQoL or symptoms data will be the FAS (ITT) set and will include all randomised patients with an evaluable baseline assessment and at least one evaluable post baseline assessment. Change from baseline will be derived using a MMRM analysis of all the post-baseline scores for each visit. The model will include treatment, visit, and treatment by visit interaction as explanatory variables and the baseline score as a covariate. Adjusted mean change from baseline estimates per treatment group and corresponding 95% CIs will be presented along with an overall estimate of the treatment difference, 95% CI and p-value.

Time to deterioration will be analyzed using a stratified log-rank test as described for the primary OS endpoint. Separate analysis will be conducted for global health status/QoL, functions (physical, role, cognitive, social and emotional respectively) and fatigue. The effect of all immunotherapy arms versus sorafenib CCI will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

Summary tables of visit responses for each EORTC QLQ-C30 scale/item score (global health status/QoL, 5 functions and all symptoms) and for each visit (improvement, deterioration and no change) will be presented by treatment arm. In addition, summary tables of the best overall response will be provided for the following domains by treatment arm: global health status/QoL, functions (physical, role, cognitive, social, and emotional) and fatigue along with single-item symptoms appetite loss and nausea. Occurrence of symptom and QoL/function improvement based on best overall response will be compared between Arm A vs. Arm D and Arm C vs. Arm D a logistic regression model as described for ORR. The odds ratio , p-value, and 95% CI will be presented graphically on a forest plot.

Finally, summaries of absolute and unadjusted change from baseline values of each EORTC QLQ-C30 scale/item will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate.

8.5.4.2   EORTC QLQ-HCC18

The primary assessment of symptoms comparing mean change from baseline using the MMRM as described for the EORTC QLQ-C30 will be repeated for shoulder pain, abdominal pain, and abdominal distention symptoms of the EORTC QLQ-HCC18. All assumptions and outputs as described for the EORTC QLQ-C30 are applicable.

Similarly, the time to deterioration as described for the EORTC QLQ-C30 will be evaluated for shoulder pain, abdominal pain, and abdominal distention symptoms of the EORTC QLQ-HCC18.

For shoulder pain, abdominal pain, and abdominal distention symptom scales of the EORTC QLQ-HCC18, time to deterioration will be presented using a Kaplan-Meier plot as well as the HR together with the corresponding 95% CI and p-values. Summaries of the number and percentage of patients experiencing a clinically meaningful deterioration or death, and the median time to deterioration, will also be provided for each treatment arm.

Summary tables of visit responses for each EORTC QLQ-HCC18 scale/item score and for each visit (improvement, deterioration and no change) will be presented by treatment arm. In addition, summary tables of best overall response will be provided for the following symptom scales by treatment arm: shoulder pain, abdominal pain, and abdominal distention. Occurrence of improvement based on best overall response will be compared between Arm A vs. Arm D and Arm C vs. Arm D using a logistic regression model as described for ORR. The odds ratio , p-value and 95% CI will be presented graphically on a forest plot.

As described for the EORTC QLQ-C30, summaries of absolute and unadjusted change from baseline values of each EORTC QLQ-HCC18 scale/item will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate.

8.5.4.3   CCI

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8.5.4.4 CCI

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8.5.4.5 CCI

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8.5.5 CCI

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8.5.6 Subgroup analyses

8.5.6.1 Subgroup analyses for OS

Subgroup analyses will be conducted comparing OS between Arm C vs. Arm D in the following subgroups of the FAS (but not limited to):

- Sex (male versus female)

- Age at randomization (<65 versus ≥65 years of age)

- PD-L1 expression (high versus low)

- Etiology of liver disease (Confirmed HBV versus confirmed HCV versus others)

- ECOG performance status (0 versus 1)

184 (251)

- Macro-vascular invasion (yes versus no)

- Extrahepatic spread (yes versus no)

- Region (Asia excluding Japan versus Japan versus rest of the world)

- AFP <400ng/ml versus ≥400ng/ml)

- BCLC stage (B versus C)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors. Forest plots will be performed.

No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of OS.

Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate (Cox 1972). A model will be constructed containing treatment and the stratification factors to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test.

Interactions between treatment and stratification factors will also be tested to rule out any qualitative interaction using the approach of Gail and Simon (Gail and Simon 1985).

Additionally, for each subgroup, the HR for Arm C vs. Arm D and 95% CI will be calculated from a Cox proportional hazards model with treatment as the only covariate. These will be presented on a forest plot including the HR and 95% CI.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and OS will not be formally analyzed. In this case, only descriptive summaries will be provided.

8.5.6.2 Subgroup analyses for secondary endpoints

Analyses described in Section 8.5.3 will be performed comparing PFS, ORR, TTP, DoR, DCR, DCR-16w and DCR-24w, between Arm C vs. Arm D in the following subgroups:

- PD-L1 expression (high versus low)

- Etiology of liver disease (confirmed HBV versus confirmed HCV versus others)

8.5.7 Safety data

Safety and tolerability data will be presented by treatment arm using the safety population.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient. The number and percentage of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced. Any safety summaries examining rechallenge with tremelimumab may be produced separately as described in the SAP.

Other safety data will be assessed in terms of serum chemistry, hematology, vital signs, and ECGs. Exposure to study drug(s), time on study, dose delays (all arms), and dose reductions (sorafenib CCI arm) will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

8.5.8 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day, and a summary will be provided for all evaluable patients.

8.5.9 Immunogenicity data

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable anti-durvalumab and anti-tremelimumab antibodies. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab and anti-tremelimumab antibodies.

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8.5.10 CCI

CCI

8.5.11 Biomarker data

The relationship of PD-L1 expression and, if applicable, of CCI to clinical outcomes (including but not restricted to) of PFS, ORR, and OS will be assessed.

PD-L1 expression determined by IHC will be reported in the CSR. CCI

8.5.12 CCI

CCI

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca 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 IWRS, WBDC, and any ePRO 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).

9.2   Monitoring of the study

During the study, an AstraZeneca 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, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study drug(s) accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the patient

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

9.2.1   Source data

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

Source data are any data generated as a result of the patient's inclusion in the study (including run-in and/or follow-up related to the study) and include all related medical examinations and other records.

9.2.2   Study agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the CSA, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of the Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients, and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place or before patients are enrolled.

9.2.3   Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3   Study timetable and end of study

The study will remain open until the last patients' treatment discontinuation.

The study is expected to start in Q4 2017 and to end by Q4 2021 (final primary analysis). Long-term follow-up data may be collected in eCRFs post final primary analysis for approximately 3 years, as outlined in Table 22.

Long-term follow-up: Subjects continuing treatment should be followed for below assessments Q4W (+/-1 week). Subjects who have discontinued from treatment should be followed for below assessments Q8W (+/-1 week). All SAEs and reports of pregnancy experienced by patients whilst receiving treatment or within 90 days of treatment discontinuing must continue to be reported to the Sponsor within the usual timelines (ie, immediately, or no later than 24 hours of when the site become aware of the SAE) directly in the EDC. If long-term follow-up is collected post final primary analysis, then the end of study is defined as the last visit of the last patient in the study.

Table 22. Schedule of study assessment and relevant eCRF pages to be completed during long-term follow-up

Assessment	Relevant eCRF page
Informed Consent	CONSENT
Survival assessent	SURVIVE
Durvalumab, tremelimumab, Sorafenib exposure (applicable only for patients continuing treatment post final analysis)	EX, EX1, EX2, EX3, EX4
Discontinuation (only for patients continuing treatment post final analysis)	DOSDISC
Statement of death	DEATH
Termination	DS
Subsequent anti-cancer therapy	CAPRX1, CAPRXR2
Pregnancy	PREG
All SAEs experienced by patients whilst receiving treatment or within 90 days of treatment discontinuing. If SAE is reported then all data relevant to the SAE (e.g. concomitant medications, laboratory data, dosing data, new medical or surgical history) should be submitted as part of the SAE report.	SAE

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with durvalumab plus tremelimumab combination therapy.

9.4   Data management by AstraZeneca

Data management will be performed by a chosen vendor according to the Data Management Plan.

The data collected through designated third party sources will be obtained and reconciled against study data.

AEs and medical/surgical history will be classified according to the terminology of the latest version of the MedDRA. Medications will be classified according to the WHO Drug Dictionary. All coding will be performed by the chosen vendor.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed, and locked, clean file will be declared. Any treatment revealing data may thereafter be added, and the final database will be locked.

Limited data collection may continue after the final primary analysis database lock per section 9.3.

Serious adverse event reconciliation

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 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 International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Subject data protection

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

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, or general physician, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also, Regulatory Authorities may require access to the relevant files, although the patient's medical information and the genetic files would remain physically separate.

10.3 Ethics and regulatory review

An EC/IRB 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 patients. The Investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC/IRB should approve all advertising used to recruit patients for the study.

AstraZeneca 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 EC annually.

Before enrollment of any patient 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.

AstraZeneca will handle the distribution of any of these documents to the national Regulatory Authorities.

AstraZeneca will provide Regulatory Authorities, EC/IRBs, and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator, if applicable as per local requirements, is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the Principal Investigator so that he or she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study

- Ensure each patient is notified that they are free to discontinue from the study at any time

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient 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 patient

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

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 (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant IRB/EC and, if applicable, also the national Regulatory Authority, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to the IRB/EC, see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's IRB/EC 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/EC.

10.6 Audits and inspections

Authorized representatives of AstraZeneca, a Regulatory Authority, or an EC 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 to check if 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 AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

11. LIST OF REFERENCES

Aaronson et al 1993
Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

Abou-Alfa et al 2006
Abou-Alfa GK, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, et al. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. J Clin Oncol 2006;24(26):4293-300.

Adnane et al 2006
Adnane L, Trail PA, Taylor I, Wilhelm SM. Sorafenib (BAY 43-9006, Nexavar), a dual-action inhibitor that targets RAF/MEK/ERK pathway in tumor cells and tyrosine kinases VEGFR/PDGFR in tumor vasculature. Methods Enzymol 2006;407:597-612.

Alexandrov et al 2013
Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Blankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.

Altekruse et al 2009
Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009 20;27(9):1485-91.

Antonio et al 2016
Antonio S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol 2016;17(3):299-308.

Basch et al 2009
Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationship with clinical outcomes. J Natl Cancer Inst 2009;101:1624-32.

Benson et al 2018

Benson AB, D'Angelica MI, Abbott DE, Abrams TA, Alberts SR, et al. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers. National Comprehensive Cancer Network 2018; version 2, pages 40-44. Available from: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf (account registration needed).

Blazeby et al 2004

Blazeby JM, Currie E, Zee BC, Chie WC, Poon RT, Garden OJ. Development of a questionnaire module to supplement the EORTC QLQ-C30 to assess quality of life in patients with hepatocellular carcinoma, the EORTC QLQ-HCC18. Eur J Cancer 2004;40(16):243-444.

Bosetti et al 2008

Bosetti C, Levi F, Boffetta P, Lucchini F, Negri E, La Vecchia C. Trends in mortality from hepatocellular carcinoma in Europe, 1980-2004. Hepatology 2008;48(1):137-45.

Brahmer et al 2012

Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-65.

Brose et al 2014

Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, et al. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet 2014;384(9940):319-28.

Bruix et al 2012

Bruix J, Raoul LJ, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma. J Hepatol 2012;57(4):821-9.

Butte et al 2007

Butte MJ, Keir ME, Phamduy TB, Freeman GJ, Sharpe AH. PD-L1 interacts specifically with B7-1 to inhibit T cell proliferation. Immunity 2007;27:111-22.

Cainap et al 2014

Cainap C, Qin S, Huang W, Chung Ik, Pan H, Cheng Y, et al. Linifanib versus sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. J Clin Oncol 2014; 33:172-179.

Chang et al 2007
Chang YS, Adnane J, Trail PA, Levy J, Henderson A, Xue D, et al. Sorafenib (BAY 43-9006) inhibits tumor growth and vascularization and induces tumor apoptosis and hypoxia in RCC xenograft models. Cancer Chemother Pharmacol 2007;59(5):561-74.

Cheng et al 2009
Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10(1):25-34.

Cheng et al 2012
Cheng AL, Guan Z, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma according to baseline status: subset analyses of the phase II sorafenib Asia-Pacific trial. Eur J Cancer 2012;48(10):1452-65.

Cheng et al 2013
Cheng AL, Kang YK, Lin DY, Park JW, Kudo M, Qin S, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013; 31:4067-4075.

Chie et al 2012
Chie WC, Blazeby JM, Hsiao CF, Chiu HC, Poon RT, Mikoshiba N, et al. International cross-cultural field validation of an European Organization for Research and Treatment of Cancer questionnaire module for patients with primary liver cancer, the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire HCC18. Hepatology 2012;55(4):1122-9.

Cox 1972
Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972;34(2):187-220.

Davila et al 2004
Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Hepatitis C infection and the increasing incidence of hepatocellular carcinoma: a population-based study. Gastroenterology 2004;127(5):1372-80.

Devlin et al 2016

Devlin H, Shah K, Feng Y, Mulhern B, Van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Office of Health Economics 2016.

Drake et al 2013

Drake CG, McDermott DF, Sznol M, Choueiri TK, Kluger HM, Powderly JD, et al. Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): long-term patient follow-up [abstract 4514]. J Clin Oncol 2013;31(Suppl).

Duffy et al 2017

Duffy AG, Ulahannan SV, Makorova-Rusher O, Rahmer O, Wedemeyer H, Pratt D, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol 2017;66(3):545-51.

Dunn et al 2004

Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

Dunnett and Tamhane 1992

Dunnett CW, Tamhane AC. A step-up multiple test procedure. J Amer Statist Assoc 1992;87(417):162-70.

Ellis et al 2008

Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials. Contemp Clin Trials 2008;29(4):456-65.

El-Serag et al 2003

El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139(10):817-23.

EMEA Guideline (issued July 2005). Guideline on the choice of the non-inferiority margin. Doc. Ref. EMEA/CPMP/EWP/2158/99.

Escudier et al 2009

Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Staehler M, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27(20):3312-8.

EuroQol Group 1990

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16(3):199-208.

EuroQol Group 2015

EuroQol Group. EQ-5D-5L user guide: basic information on how to use the EQ-5D-5L instrument [cited 05 January 2016]. Available from: URL: https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf.

Fairman et al 2014

Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, et al. Pharmacokinetics of durvalumab, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumours. Journal of Clinical Oncology, 2014 ASCO Annual Meeting Abstracts;32(5s):(suppl; abstr 2602).

Fayers et al 2001

Fayers P, Aaronson NK, Bjordal K, Curran D, Groenvold M on behalf of the EORTC Quality of Life Study Group. EORTC QLQ-C30 Scoring Manual: 3rd Edition 2001. Available on request.

FDA Guidance for Industry (issued November 2016). Non-Inferiority Clinical Trials to Establish Effectiveness. Available from: URL: https://www.fda.gov/media/78504/download.

Fife and Bluestone 2008

Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev. 2008;224:166-82.

Gail and Simon 1985

Gail M, Simon R. Testing for qualitative interactions between treatment effects and patient subsets. Biometrics 1985;41(2):361-72.

Gandhi et al 2014

Gandhi S, Sapna Khubchandani S, Iyer R. Quality of life and hepatocellular carcinoma. J Gastrointest Oncol 2014;5(4):296-317.

Gao et al 2009

Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009;15(3):971-9.

Golden-Mason et al 2007

Golden-Mason L, Palmer B, Klarquist J, Mengshol JA, Castelblanco N, Rosen HR. Upregulation of PD-1 expression on circulating and intrahepatic hepatitis C virus-specific CD8+ T cells associated with reversible immune dysfunction. J Virol 2007;81(17):9249-58.

Hashim et al 2016

Hashim D, Boffetta P, La Vecchia C, Rota M, Bertuccio P, Malvezzi M, et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol 2016;27(5):926-33.

Hato et al 2014

Hato T, Goyal L, Greten TF, Duda DG, Zhu AX. Immune checkpoint blockade in hepatocellular carcinoma: current progress and future directions. Hepatology 2014;60(5):1776-82.

Herdman et al 2011

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20(10):1727-36.

Hirano et al 2005

Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089-96.

Hodi et al 2014

Hodi FS, Sznol M, Kluger HM, McDermott DF, Carvajal RD, Lawrence DP, et al. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a Phase I trial [ASCO abstract 9002]. J Clin Oncol 2014;32(Suppl).

Huz et al 2012

Huz JI1, Melis M, Sarpel U. Spontaneous regression of hepatocellular carcinoma is most often associated with tumour hypoxia or a systemic inflammatory response. HPB (Oxford) 2012;14(8):500-5.

Iwai et al 2002

Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293-7.

Johnson et al 2013

Johnson PJ, Qin S, Park JW, Poon R, Raoul JL, Philip PA, et al. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. J Clin Oncol 2013; 31:3517-3524.

Kato et al 2001

Kato A, Miyazaki M, Ambiru S, Yoshitomi H, Ito H, Nakagawa K, et al. Multidrug resistance gene (MDR-1) expression as a useful prognostic factor in patients with human hepatocellular carcinoma after surgical resection. J Surg Oncol 2001;78(2):110-5.

Keating and Santoro 2009

Keating GM, Santoro A. Sorafenib: a review of its use in advanced hepatocellular carcinoma. Drugs 2009;69(2):223-40.

Keir et al 2008

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.

Klein et al 2007

Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med 2007;26(24):4505-19.

Kudo et al 2018

Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unrectable hepatocellular carcinoma: a randomized phase 3 non-inferiority trial. Lancet 2018; 391:1163-72.

Lan and DeMets 1983

Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.

Lencioni et al 2014

Lencioni R, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, et al. GIDEON (Global Investigation of therapeutic Decisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. Int J Clin Pract 2014;68(5):609-17.

Litwin et al 1998

Litwin MS, Lubeck DP, Henning JM, Carroll PR. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: results of the CaPSURE database. J Urol 1998;159(6):1988-92.

Liu et al 2006
Liu L, Cao Y, Chen C, Zhang X, McNabola A, Wilkie D. Sorafenib blocks the RAF/MEK/ERK pathway, inhibits tumor angiogenesis, and induces tumor cell apoptosis in hepatocellular carcinoma model PLC/PRF/5. Cancer Res 2006;66(24):11851-8.

Llovet 2005
Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroentrol 2005;40(3):225-35.

Llovet et al 2008a
Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Xhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008;100(10):698-711.

Llovet et al 2008b
Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359(4):378-90.

Llovet et al 1999
Llovet JM1, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329-38.Melero et al 2017
Melero I, Sangro B, Cheung Yae T, Hsu C, Kudo M, Crocenzi TS, et al. Nivolumab dose escalation and expansion in patients with advanced hepatocellular carcinoma (HCC): The CheckMate 040 study. J Clin Oncol 2017;35 (suppl 4S:abstract 226).

Miroux et al 2010
Miroux C, Vausselin T, Delhem N. Regulatory T cells in HBV and HCV liver diseases: implication of regulatory T lymphocytes in the control of immune response. Expert Opin Biol Ther 2010;10(11):1563-72.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferonalpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet 2013;52:1017-27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275-84.

Okazaki and Honjo 2007

Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19(7):813-824.

Okudaira et al 2009

Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

Osoba et al 1998

Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16(1):139-44.

Pardee and Butterfield 2012

Pardee AD, Butterfield LH. Immunotherapy of hepatocellular carcinoma: Unique challenges and clinical opportunities. Oncoimmunology 2012;1(1):48-55.

Pardoll 2012

Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

Parkin et al 2005

Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55(2):74-108.

Paterson et al 2011

Paterson AM, Brown KE, Keir ME, Vanguri VK, Riella LV, Chandraker A, et al. The PD-L1:B7-1 pathway restrains diabetogenic effector T cells in vivo. J Immunol 2011;187:1097-105.

Peng et al 2008

Peng G, Li S, Wu W, Tan X, Chen Y, Chen Z. PD-1 upregulation is associated with HBV-specific T cell dysfunction in chronic hepatitis B patients. Mol Immunol 2008;45(4):963-70.

Powles et al 2014

Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515(7528):558-62.

Pugh et al 1973

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophagus varices. Br J Surg 1973;60(8):646-9.

Qin et al 2016

Qin A, Coffey DG, Warren EH, Ramnath N. Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. Cancer Med 2016;9:2567–2578.

Rizvi et al 2015

Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with nonsmall cell lung cancer (NSCLC). J Clin Oncol 2015;33:Abstract 8032.

Robins 1993

Robins JM. Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers. Proceedings of the Biopharmaceutical Section, American Statistical Association 1993;24-33.

Robins and Tsiatis 1991

Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Communications in statistics 1991;20(8):2609-31.

Ryerson et al 2016

Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer 2016;122(9):1312-37.

Sangro et al 2013

Sangro B, Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol 2013;59(1):81-8.

Segal et al 2015

Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015;33:Abstract 3011.

Sprangers and Aaronson 1992

Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. J Clin Epidemiol 1992;45(7):743-60.

Stewart et al 2015

Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015;3(9):1052-62.

Tarhini and Kirkwood 2008

Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. Expert Opin Biol Ther 2008;8:1583-93.

Topalian et al 2012

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.

Torre et al 2015

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65(2):87-108.

Wang et al 2009

Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Wang et al 2014

Wang E, Kang D, Bae KS, Marshall MA, Pavlov D, Parivar K. Population pharmacokinetic and pharmacodynamics analysis of tremelimumab in patients with metastatic melanoma. J Clin Pharmacol 2014;54(10):1108-16.

Wilhelm et al 2006

Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov 2006;5(10):835-44.

Wolchok et al 2013

Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122-33.

Zhang et al 2008

Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Anti-tumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. Cytotherapy 2008;10(7):711-9.

Zhu 2006

Zhu AX. Systemic therapy of advanced hepatocellular carcinoma: how hopeful should we be? Oncologist 2006;11(7):790-800.

Zou and Chen 2008

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008;8(6):467-77.

Appendix A   Additional Safety Information: Further guidance on the definition of a serious adverse event (SAE)

Life threatening

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

Hospitalization

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

Important medical event or medical intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

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

- Angioedema not severe enough to require intubation but requiring intravenous (IV) hydrocortisone treatment

- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine

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

- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization

- Development of drug dependency or drug abuse

A guide to interpreting the causality question

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

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

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

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

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

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

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

Introduction

This Appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for this study with regard to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for determination of confirmation of radiological progression.

Definitions of measurable, non-measurable, target and non-target lesions

Measurable:

A lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis[1] diameter of ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[2]).

- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination (manual palpation) that is not measurable by CT or MRI.

- Previously irradiated lesions[3]

- Brain metastasis

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[1] The short axis is defined as the longest axis perpendicular to long axis
[2] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).
[3] Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as Target Lesions (TLs).

Target Lesions

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline. Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

Tumor lesions selected for fresh screening biopsy should not be selected as Target Lesions, unless imaging occurred at least ~2 weeks after biopsy, allowing time for healing.

Non-Target Lesions (NTLs):

Additional measurable lesions not recorded as TLs and non-measurable lesions (or sites of disease) should be identified as NTLs at baseline.

Imaging Modalities

A summary of the methods of assessment (imaging modalities) to be used for RECIST 1.1 assessment of Target Lesions, Non-Target Lesions, and New Lesions is provided in Table 17.

Table 17   **Summary of methods of assessment**

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan
		FDG-PET/CT

CT computed tomography; FDG-PET/CT ^{18}F-fluoro-deoxyglucose positron emission tomography/CT; MRI magnetic resonance imaging.

CT and MRI

CT and MRI, each preferably with IV contrast, are generally considered to generate the best currently available and reproducible anatomical images for measurement of TL, assessment of non-target lesion (NTL), and identification of any New Lesions.

It is recommended that CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumour burden at baseline and follow-up visits. Any other areas of disease involvement (eg, pelvis, brain) should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to intravenous CT contrast, a non-contrast CT examination of the chest and an MRI with intravenous MRI contrast of the abdomen is appropriate. In patients with severely compromised renal function a non-contrast CT examination of the chest and abdomen is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over IV contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility and scanner across all imaging time points per patient.

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Chest X-ray

Chest X-ray assessment will not be used for assessment of TL. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

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

Ultrasound

Ultrasound examination will not be used for RECIST assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Endoscopy and laparoscopy

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

Tumor markers

Tumor markers on cytological or histological (biopsy) samples will not be used for tumor response assessments as per RECIST 1.1.

Histology and Cytology

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

Results of cytological examination for the neoplastic origin of any effusion (e.g. ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to New Lesions or progression of NTLs, respectively.

Isotopic bone scan

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

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan which cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a PD assessment at that timepoint.

FDG-PET/CT

[18]F-Fluoro-deoxyglucose positron emission tomography/computed tomography/CT (FDG-PET/CT) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[4] not present on baseline or prior 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 or prior FDG-PET scan available, and no evidence of new lesions on CT/MRI scans then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to verify new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically-based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumour measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with intravenous contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that 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.

Tumor response evaluation

Schedule of evaluation

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including the entire liver and both adrenal glands) must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient, eg, new lesions at follow-up.

Baseline assessments should be performed no more than 28 days before the date of randomization, and ideally should be performed as close as possible to the date of randomization. Efficacy by RECIST 1.1 for all patients will be assessed according to the

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[4] A positive FDG-PET scan lesion should be reported only when an uptake (e.g. SUV) greater than twice that of the surrounding tissue or liver is observed.

schedules of assessment. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled imaging visits.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

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

Special cases:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.

- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.

- If a TL splits into two or more parts, then record the sum of the diameters of those parts.

- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.

- When a TL has had any intervention eg, definitive radiotherapy, embolization, surgery, etc. during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST case report form.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL.

Table 18 Evaluation of target lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters
Stable disease (SD)	Neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) – 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 from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or NE (eg missing anatomy) or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides NE as a TL response

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (Table 19).

Table 19 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/non PD	Persistence of one or more NTL.

Table 19   **Evaluation of non-target lesions**

Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

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

New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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

Symptomatic deterioration

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

Patients with 'symptomatic deterioration' requiring discontinuation of treatment without objective radiological evidence of disease progression at that time should continue to undergo tumor assessments where clinically feasible.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table 20.

Table 20   Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/non-PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no target and/or non-target lesions at baseline).

Confirmation of Radiological Progression

Patients who are clinically stable at an initial RECIST 1.1-defined progression (PD) can continue to receive study treatment at the discretion of the Investigator and patient. A follow-up scan is collected after the initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD, and the Confirmation of Radiological Progression criteria described below are applied for tumor assessments of this follow-up scan. Patients with confirmed radiological PD who continue to receive study treatment at the discretion of the Investigator and patient (following consultation with AstraZeneca) can receive treatment until no longer having clinical benefit.

Confirmation of radiological progression guidelines are set for the following reasons:

- For patient management and treatment decisions

- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiological RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiological progression CCI

- When scans are evaluated by Investigator and by BICR, additional scans can reduce informative censoring by Investigator assessments (if the Investigator assesses PD but collects no follow-up scans, and the BICR reviewer does not identify RECIST PD among the available scans, then this patient would be censored for PFS by BICR).

Confirmation of Radiological Progression Criteria:

An immediate prior RECIST 1.1-defined radiological PD would be considered confirmed if any of the following criteria are met in the subsequent follow-up scan (acquired preferably at the next regularly scheduled imaging visit but no sooner than 4 weeks after the RECIST 1.1-defined PD scan):

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits, each with an absolute increase of at least 5 mm in sum of diameters compared to nadir (as per RECIST 1.1 definition)

- *and/or* significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint (as per RECIST 1.1 definition)

- *and/or* significant progression (worsening) of pre-existing new lesions at the follow-up scan timepoint compared with the immediate prior timepoint (unique definition)

and/or additional (brand) new unequivocal lesions at the follow-up scan timepoint (as per RECIST 1.1 definition)

NOTE: In order to have confirmed radiological progression, there should be two consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the confirmation of radiological progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, in the absence of significant clinical deterioration, then the patient may continue with assessments until the next PD by RECIST 1.1, which will also require a follow-up scan

evaluated using the Confirmation of Radiological Progression criteria. **If the first PD (by RECIST 1.1) is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

Central Review

All images will be collected, quality checked, and stored centrally by an Imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. The management of patients will be based solely upon the results of the RECIST 1.1 and confirmation of radiological progression assessments conducted by the Investigator.

Further details of the BICR will be documented in the Independent Review Charter, (also referred to as 'Imaging Charter').

Specifications for radiological imaging

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

If specified, all images will be collected, quality checked and stored centrally by the imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the investigative site as source data and transfer to the imaging CRO will be provided in a separate document. The management of patients will be based solely upon the local assessments conducted by the Investigator.

Also if specified, further details of the Blinded Independent Central Review (BICR) will be documented in the Independent Review Charter (also referred to as the 'Imaging Charter').

CT Scan

CT scans of the chest and abdomen (and pelvis when indicated) should be contiguous throughout all the anatomic region of interest.

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

a. **Anatomic coverage:** Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas

that may be involved based on signs and symptoms of individual patients. 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 tumour measurements but also identification of new disease.

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

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvis) MRI with contrast. If MRI cannot be performed then CT without i.v. contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

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

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

MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis (and other anatomies e.g. neck) 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 optimised for the specific body part being imaged as well as the scanner utilised. CT of the chest is typically recommended over MRI due to significant motion artifacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

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

References

Eisenhauer et al 2009

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix C   International Airline Transportation Association 6.2 Guidance Document

Labelling and shipment of biohazard samples

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

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

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

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Examples of Category B pathogens include hepatitis A, B, C, D, and E viruses as well as human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

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

Exempt includes all other materials with minimal risk of containing pathogens.

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

and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D CCI

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Appendix E   Actions Required in Cases of Increases in Liver Biochemistry and Evaluation 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) $\geq 3 \times$ upper limit of normal (ULN) together with total bilirubin (TBL) $\geq 2 \times$ 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 $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ 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 $\geq 3 \times$ ULN

- AST $\geq 3 \times$ ULN

- TBL $\geq 2 \times$ 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)

- 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.

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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

If no, follow the process described in Potential Hy's Law criteria metsection 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 Potential Hy's Law criteria met section 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.

Appendix F   Durvalumab Weight-based Dose Calculation

For patients weighing ≤30 kg, durvalumab dosing is dependent on patient weight.

1.   Cohort dose: X mg/kg

2.   Patient weight: Y kg

3.   Dose for patient: XY mg = X (mg/kg) × Y (kg)

4.   Dose to be added into infusion bag:

    –   Dose (mL) = XY mg / CCI where CCI is durvalumab nominal concentration.

5.   The corresponding volume of durvalumab should be rounded to the nearest tenth milliliter (0.1 mL). Dose adjustments for each cycle are only needed for >10% change in weight.

6.   The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

    –   Number of vials = Dose (mL) / CCI

Example:

1.   Cohort dose: CCI

2.   Patient weight: 30 kg

3.   Dose for patient: CCI

4.   Dose to be added into infusion bag:

5.   Dose (mL) = CCI

6.   The number of vials required for dose preparation:

Number of vials = CCI = 2 vials

Appendix G   Tremelimumab Weight-based Dose Calculation

For patients weighing ≤30 kg, tremelimumab dosing is dependent on patient weight.

1.   Cohort dose: X mg/kg

2.   Patient weight: Y kg

3.   Dose for patient: XY mg = X (mg/kg) × Y (kg)

4.   Dose to be added into infusion bag:

    −   Dose (mL) = XY mg / CCI   where CCI is tremelimumab nominal concentration.

The corresponding volume of tremelimumab should be rounded to the nearest tenth milliliter (0.1 mL). Dose adjustments for each cycle are only needed for >10% change in weight.

5.   The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / CCI

OR

Number of vials = Dose (mL) / CCI

Example:

1.   Cohort dose: CCI

2.   Patient weight: 30 kg

3.   Dose for patient: CCI

4.   Dose to be added into infusion bag:

5.   Dose (mL) = CCI

6.   The number of vials required for dose preparation:

Number of vials = CCI = 1 vial

OR

Number of vials = CCI = 2 vials

Appendix H   Patient-reported outcomes

EORTC QLQ-C30

Study Number: D419CC00002		Site Number:
Subject Number: E_ _ _ _ _ _ _	Visit Number:	Assessment Date:

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):   31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3.	Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

QLQ-C30_v3.0_1995_Orig_WS_Paper_English-US_17Jul2017_D419CC00002

Study Number: D419CC00002		Site Number:
Subject Number: E_ _ _ _ _ _ _	Visit Number:	Assessment Date:

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

   1   2   3   4   5   6   7

Very poor   Excellent

30. How would you rate your overall quality of life during the past week?

   1   2   3   4   5   6   7

Very poor   Excellent

QLQ-C30_v3.0_1995_Orig_WS_Paper_English-US_17Jul2017_D419CC00002

CCI

CCI

EORTC QLQ-HCC18

Study Number: D419CC00002		Site Number:
Subject Number: E_ _ _ _ _ _	Visit Number:	Assessment Date:

ENGLISH

EORTC QLQ – HCC18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Did you feel thirsty?	1	2	3	4
32. Have you had problems with your sense of taste?	1	2	3	4
33. Have you lost muscle from your arms or legs?	1	2	3	4
34. Have you had abdominal swelling?	1	2	3	4
35. Have you been concerned by the appearance of your abdomen?	1	2	3	4
36. Have you been concerned by your skin or eyes being yellow (jaundiced)?	1	2	3	4
37. Have you had itching?	1	2	3	4
38. Have you had pain in your shoulder?	1	2	3	4
39. Have you had abdominal pain?	1	2	3	4
40. Have you had fevers?	1	2	3	4
41. Have you had chills?	1	2	3	4
42. Have you worried about getting enough nourishment?	1	2	3	4
43. Have you felt full up too quickly after beginning to eat?	1	2	3	4
44. Have you worried about your weight being too low?	1	2	3	4
45. Have you been less active than you would like to be?	1	2	3	4
46. Have you found it difficult to finish things?	1	2	3	4
47. Have you needed to sleep during the day?	1	2	3	4

During the past four weeks:

	Not at all	A little	Quite a bit	Very much
48. Has the disease or treatment had any effect on your sex life?	1	2	3	4

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Appendix I   Hepatitis stratification

Patients will be stratified to the HBV positive cohort if they test positive for HBsAg or have occult HBV infection (postivie anti-HBc with detectable HBV DNA) (Table 21).

Patients Subjects will be stratified to the HCV positive cohort if they test positive for HCV or have a history of HCV infection

Table 21 **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, 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 HBV DNA load ≥10 IU/ml: Yes HBV DNA load <10 IU/ml: 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 10IU/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: Yes If HBV DNA load <10 IU/ml: No

Note: If the limit of detection in local and central lab is higher than 10 IU/ml, sites should follow the local lab standard.

DNA deoxyribonucleic acid; IgM Immunoglobulin M; HBc Hepatitis B core; HBs Hepatitis B surface; HBsAg Hepatitis B surface antigen; HBV Hepatitis B virus.

Appendix J   T, N, M, Fibrosis scoring, & BCLC

Table 1. Definition for T,N,M according to AJCC TNM staging for HCC (8th ed.)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 2. AJCC Prognostic Groups

Stage	T	N	M
IA	T1a	N0	M0
IB	T1b	N0	M0

II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Fibrosis Score

The fibrosis score as defined by Ishak is recommended by NCCN guideline because of its prognostic value in overall survival. This scoring system uses a 0-6 scale.

F0: Fibrosis score 0-4 (none to moderate fibrosis)

F1: Fibrosis score 5-6 (severe fibrosis or cirrhosis)

BCLC

TABLE 4.   The BCLC Staging Classification

Stage	PST	Tumor Status		Liver Functional Status
		Tumor Stage	Okuda Stage	
Stage A: early HCC				
A1	0	Single	I	No portal hypertension and normal bilirubin
A2	0	Single	I	Portal hypertension and normal bilirubin
A3	0	Single	I	Portal hypertension and abnormal bilirubin
A4	0	3 tumors <3 cm	I–II	Child-Pugh A–B
Stage B: intermediate HCC	0	Large multinodular	I–II	Child-Pugh A–B
Stage C: advanced HCC	1–2*	Vascular invasion or extrahepatic spread*	I–II	Child-Pugh A–B
Stage D: end-stage HCC	3–4[†]	Any	III[†]	Child-Pugh C[†]

Stage A and B: All criteria should be fulfilled.
Stage C: At least one criteria *: PST 1–2 or vascular invasion/extrahepatic spread.
Stage D: At least one criteria [†]: PST 3–4 or Okuda stage III/Child-Pugh C.

(Llovett et all 1999.)