A Phase III Randomized, Open-label, Multi-center, Global Study of Durvalumab Administered as Monotherapy or in Combination with Tremelimumab versus Sorafenib in First-line Treatment of Patients with Advanced Hepatocellular Carcinoma
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Study site(s) and number of subjects planned
This study will screen approximately 1600 patients, with no prior systemic therapy for advanced hepatocellular carcinoma (HCC), at XXX sites globally to randomise approximately 1200 patients.

Study design
This is a randomized, open-label, multi-center, global, Phase III study to determine the efficacy and safety of durvalumab+tremelimumab combination therapy and durvalumab monotherapy versus Sorafenib in the treatment of patients with no prior systemic therapy for unresectable or advanced HCC. The patients should not be amenable to surgical or locoregional therapy for unresectable or advanced HCC.

Patients will be randomized in a 1:1:1:1 ratio to durvalumab (1500 mg)+tremelimumab (75 mg) therapy (dose 1), durvalumab (1500 mg)+tremelimumab (225 mg) therapy (dose 2), durvalumab monotherapy, or Sorafenib in a stratified manner according to macrovascular invasion (yes vs. no), etiology (HBV vs. HCV vs. uninfected) and performance status (ECOG 0 vs. 1). Patients in all arms will continue therapy until progression.

Tumor assessments, based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), will be performed every 8 weeks (±1 week) for the first 48 weeks from the date of randomization and then every 12 weeks (±1 week) thereafter until confirmed disease progression or discontinuation, whichever is earlier. Patients, who permanently discontinue study drug for unconfirmed disease progression or for reasons other than objective disease
progression, should continue to have radiographic scans performed as per their original schedule until confirmed objective disease progression or death, whichever is earlier.

The co-primary objectives are to assess:

- Efficacy, in terms of overall survival (OS), with durvalumab + tremelimumab (dose 1) compared with Sorafenib.
- Efficacy, in terms of overall survival (OS), with durvalumab + tremelimumab (dose 2) compared with Sorafenib.
- Efficacy, in terms of OS, of durvalumab monotherapy, compared with Sorafenib.

Key secondary objectives are to assess the following:

- Efficacy, in terms of OS, of durvalumab + tremelimumab (each dose arm) compared with durvalumab monotherapy.
- Efficacy of durvalumab + tremelimumab (each dose arm) and durvalumab monotherapy, in terms of time to progression (TTP), progression free survival (PFS), overall response rate (ORR), duration of response (DoR), OS at 18 months (OS18), and OS at 24 months (OS24) when compared with Sorafenib.
- The safety and tolerability profile of durvalumab + tremelimumab (each dose arm) and durvalumab monotherapy compared with Sorafenib.
- Improvement in disease-related symptoms and Health related quality of life (HRQoL) with durvalumab + tremelimumab (each dose arm) and durvalumab monotherapy using the EORTC QLQ-30 and EORTC QLQ-HCC18 compared with Sorafenib.

A hypothesis of improved OS will be tested when approximately 462563 OS events have occurred across the durvalumab + tremelimumab combination therapy (dose 1) and sorafenib treatment arms in patients with PD-L1-low tumors (7677% maturity). All study endpoints will be analyzed at this time of the primary analysis.

**Objectives**

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

<table>
<thead>
<tr>
<th>Primary Objective:</th>
<th>Outcome Measure:</th>
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<tr>
<td>To assess the efficacy of durvalumab (1500 mg) + tremelimumab (75 mg) combination therapy compared with Sorafenib</td>
<td>OS</td>
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<td><strong>Secondary Objectives:</strong></td>
<td><strong>Outcome Measures:</strong></td>
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<tr>
<td>To assess the efficacy of durvalumab (1500 mg) +tremelimumab (225 mg) combination therapy compared with Sorafenib</td>
<td>OS</td>
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<tr>
<td>To assess the efficacy of durvalumab monotherapy compared with Sorafenib</td>
<td>OS</td>
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**Secondary Objectives:**

<table>
<thead>
<tr>
<th>To further assess the efficacy of durvalumab+tremelimumab (each dose arm) and durvalumab monotherapy compared with Sorafenib</th>
<th><strong>Outcome Measures:</strong></th>
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<tr>
<td>TTP, PFS, ORR, DoR, OS18, and OS24 using Investigator assessments according to RECIST 1.1</td>
<td>• TTP, PFS, ORR, DoR, OS18, and OS24 using Investigator assessments according to RECIST 1.1</td>
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<tr>
<td>PFS2 using local standard clinical practice</td>
<td>• PFS2 using local standard clinical practice</td>
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<thead>
<tr>
<th>To assess the efficacy of durvalumab+tremelimumab combination therapy (each dose arm) compared with durvalumab monotherapy</th>
<th><strong>Outcome Measures:</strong></th>
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<tr>
<td>OS</td>
<td>• OS</td>
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<tr>
<td>TTP, PFS, DoR and ORR using Investigator assessments according to RECIST 1.1</td>
<td>• TTP, PFS, DoR and ORR using Investigator assessments according to RECIST 1.1</td>
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<tr>
<th>To assess disease-related symptoms and HRQoL in patients treated with durvalumab+tremelimumab (each dose arm) and durvalumab monotherapy compared to Sorafenib</th>
<th><strong>Outcome Measures:</strong></th>
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<tr>
<td>EORTC QLQ-C30: Global health status, physical function, fatigue</td>
<td>• EORTC QLQ-C30: Global health status, physical function, fatigue</td>
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<tr>
<td>EORTC QLQ-HCC18: Shoulder pain, abdominal pain, abdominal swelling</td>
<td>• EORTC QLQ-HCC18: Shoulder pain, abdominal pain, abdominal swelling</td>
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<td>EQ-5D-5L</td>
<td>• EQ-5D-5L</td>
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<tr>
<th>To assess patient-reported treatment tolerability directly using specific PRO-CTCAE symptoms</th>
<th><strong>Outcome Measures:</strong></th>
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<tbody>
<tr>
<td>Collection of approximately 20 patient-reported outcomes version of CTCAE (PRO-CTCAE) symptoms via an electronic device solution</td>
<td><strong>Outcome Measures:</strong></td>
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<tr>
<th>To investigate the immunogenicity of durvalumab monotherapy and durvalumab + tremelimumab (each dose arm) combination therapy</th>
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<td>Presence of ADAs for durvalumab and tremelimumab (confirmatory results: positive or negative)</td>
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<td><strong>Safety Objective:</strong></td>
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<tr>
<td>To assess the safety and tolerability profile of durvalumab+tremelimumab (each dose arm) and durvalumab monotherapy compared with Sorafenib</td>
<td>AEs, physical examinations, laboratory findings, and vital signs</td>
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<th><strong>Exploratory Objective:</strong></th>
<th><strong>Outcome Measure:</strong></th>
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| To assess the efficacy of durvalumab+tremelimumab combination therapy (each dose arm) compared to durvalumab monotherapy by PD-L1 status | • OS  
  • TTP, PFS, DoR and ORR using Investigator assessments according to RECIST 1.1 |
| To investigate the relationship between the progressive changes in AFP level and efficacy parameters | Association of AFP expression level with OS, TTP, PFS, ORR, DoR and DCR |
| To investigate the efficacy of durvalumab and tremelimumab combination (each dose arm), durvalumab monotherapy, and sorafenib by baseline gene expression | Association of IFNγ and immune related genes as measured by mRNA expression from baseline tumor biopsies and blood with OS, TTP, PFS, ORR, DoR and DCR |
| To investigate the efficacy of durvalumab and tremelimumab combination (each dose arm), durvalumab and tremelimumab monotherapy, and sorafenib by intratumoral immune cell presence | Association of immune cell numbers, specifically CD8+ T cells, in baseline tumor samples with OS, TTP, PFS, ORR, DoR and DCR |
**Figure 1: Study Design**

**Target subject population**

The study population includes patients aged 18 years or older with a diagnosis of unresectable, advanced HCC and Barcelona Clinic Liver Cancer stage B (that is not amenable to transarterial chemoembolization) or stage C and has Child-Pugh A liver disease. Patients must not have received any systemic therapy for advanced 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.

**Subject selection**
Each subject 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.

**Inclusion criteria**

For inclusion in the study subjects should fulfil the following criteria:

1. Age ≥18 years at the time of screening.

2. 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.

3. Patients with unresectable or advanced HCC that has been either:
   - Confirmed on histopathological findings from tumor tissue
   - In the absence of histological confirmation, patients should have clinical findings consistent with a diagnosis of liver cirrhosis and a liver mass measuring at least 2 cm with characteristic vascularization (intense inhomogeneous enhancement seen in the hepatic arterial-dominant phase and contrast washout in the late portal venous phase) seen on either triphasic CT scan or MRI with gadolinium.

4. Barcelona Clinic Liver Cancer stage B (that is not amenable to transarterial chemoembolization) or stage C.

5. Patients must not have received any systemic therapy for advanced 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.

6. Patients with concomitant HBV or HCV infection should meet the following criteria:
   - Patients with concomitant HBV infection must have a confirmed diagnosis of HBV characterized by the presence of anti-HBc, and be sufficiently suppressed with active antiviral treatment (per local institutional practice) prior to enrollment to ensure adequate viral suppression (HBV DNA < 2000 IU/mL).
   - Patients with concomitant HCV infection must have confirmed diagnosis of HCV characterized by the presence of detectable HCV RNA or anti-HCV antibody upon enrollment.

7. Child-Pugh Score class A.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrollment


10. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines

11. No prior exposure to immune-mediated therapy including, but not limited to, anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-programmed cell death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.

12. Adequate organ and marrow function as defined below:
   - Hemoglobin ≥9.0 g/dL
   - Absolute neutrophil count ≥1.0×10⁹/L
   - Platelet count ≥75×10⁹/L
   - Serum bilirubin ≤2.0× the upper limit of normal (ULN).
   - ALT and AST ≤5× ULN
   - Calculated creatinine clearance (CL) >40 mL/min as determined by Cockcroft-Gault (using actual body weight)

   Males
   Creatinine CL=\frac{\text{Weight (kg)} \times (140-\text{Age})}{72 \times \text{serum creatinine (mg/dL)}} (mL/min)

   Females:
   Creatinine CL=\frac{\text{Weight (kg)} \times (140-\text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 (mL/min)

13. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. 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 or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

– 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, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

**Exclusion criteria**

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

1. Patients with known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC.

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

3. Previous investigational product assignment in the present study.

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

5. Participation in another clinical study with an investigational product during the last 28 days prior to the first dose of study treatment.

6. Any unresolved toxicity NCI 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.

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

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


11. 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]). 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 without active disease in the last 5 years may be included but only after consultation with the study physician
   - Patients with celiac disease controlled by diet alone

12. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

13. 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 IP and of low potential risk for recurrence
   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   - Adequately treated carcinoma in situ without evidence of disease

15. 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.

16. History of active primary immunodeficiency

17. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), or human immunodeficiency virus (positive HIV 1/2 antibodies).

18. Current or prior use of immunosuppressive medication within 14 days before the first dose of study treatment. 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)

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

20. 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+tremelimumab combination therapy

21. Known allergy or hypersensitivity to study drugs or their excipients.

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

**Duration of treatment**

Unless specific treatment discontinuation criteria are met, for patients in all arms, the treatment will continue until disease progression.

**Progression during treatment**

Patients in the immunotherapy arms (durvalumab with or without tremelimumab arms) may continue receiving therapy in the setting of unconfirmed progressive disease (PD), at the Investigator’s discretion, until PD is confirmed. According to Response Evaluation Criteria in
Solid Tumors version 1.1 (RECIST 1.1) modified for confirmation of progression, a confirmatory scan is required following an overall time point assessment of progression (PD), preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD. Patients in immunotherapy arms with PD by RECIST 1.1(unconfirmed and confirmed) who, in the Investigator’s opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment for as long as they are gaining clinical benefit. However, patients in the immunotherapy arm(s) will not be permitted to continue immunotherapy if progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) to immunotherapy treatment in the target lesions (regardless of the appearance of new lesions) ie, the response and progression events both occurred in the target lesions while receiving immunotherapy during the same treatment period.

Patients in the durvalumab+tremelimumab arms who have completed the 4 dosing cycles with durvalumab+tremelimumab (with clinical benefit per Investigator judgement) but subsequently have PD during treatment with durvalumab alone may restart treatment with durvalumab+tremelimumab provided they meet eligibility criteria for re-treatment.

**Follow up of patients post discontinuation of study drug**

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

**Survival**

All patients randomised in the study should be followed up for survival.

**Investigational product, dosage and mode of administration**

**Durvalumab + tremelimumab combination therapy (dose 1)**

- Durvalumab 1500 mg plus tremelimumab 75 mg via IV infusion Q4W, starting on Week 0, for up to a maximum of 4 months (4 doses/cycles) with the last administration on Week 12, followed by durvalumab monotherapy 1500 mg via IV infusion Q4W, starting on Week 16, until confirmed PD or discontinuation.
  
  (Note: Whenever a subject’s weight falls to 30 kg or below, the patient will receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W and 1 mg/kg tremelimumab Q4W until the weight improves to >30 kg, at which point the patient will start receiving the fixed dosing of durvalumab 1500 mg plus tremelimumab 75 mg Q4W).

**Durvalumab + tremelimumab combination therapy (dose 2)**

- Durvalumab 1500 mg plus tremelimumab 225 mg via IV infusion Q4W, starting on Week 0, for up to a maximum of 4 months (4 doses/cycles) with the last administration on Week 12, followed by durvalumab monotherapy 1500 mg via IV infusion Q4W, starting on Week 16, until confirmed PD or discontinuation.
(Note: Whenever a subject’s weight falls to 30 kg or below, the patient will receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W and 3 mg/kg tremelimumab Q4W until the weight improves to >30 kg, at which point the patient will start receiving the fixed dosing of durvalumab 1500 mg plus tremelimumab 225 mg Q4W).

**Durvalumab monotherapy**

- Durvalumab 1500 mg via IV infusion Q4W, starting on Week 0, until confirmed PD or discontinuation. (Note: Whenever a subject’s weight falls to 30 kg or below, the patient will receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient will start receiving the fixed dosing of durvalumab 1500 mg Q4W).

**Sorafenib therapy**

- Sorafenib 400 mg (two 200-mg tablets) orally twice daily, until confirmed PD or discontinuation. (Note: Suspected sorefenib related toxicities should be managed based on the approved product label for each country.)

**Statistical methods**

To control for type I error, an alpha of 0.05 will be used for OS. The study will be considered positive (a success) if the OS analysis results are statistically significant. All tumor-assessment-related endpoints are assessed by site Investigator.

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 investigational product are included in the ITT population.

Approximately 1200 patients will be randomized in a 1:1:1:1 ratio to durvalumab (1500 mg) + tremelimumab (75 mg) combination therapy (dose 1), durvalumab (1500 mg) + tremelimumab (225 mg) combination therapy (dose 2), durvalumab monotherapy, or sorafenib. The randomization will be stratified based on macrovascular invasion (yes vs no), etiology (HBV vs HCV vs uninfected), and performance status (ECOG 0 vs 1).

A hypothesis of improved OS will be tested when approximately 462 OS events have occurred across the durvalumab + tremelimumab combination therapy (dose 1) and sorafenib treatment arms in patients with PD-L1-low tumors (77% maturity).

**Durvalumab + tremelimumab (dose 1) versus sorafenib (OS in ITT)**
If OS at 18 months were 42.3% with durvalumab + tremelimumab combination therapy (dose 1) and 28.7% with sorafenib (with 10.0-month median OS) in the ITT population and assuming the true average OS hazard ratio (HR) is 0.70, 462 OS events will provide at least 95% power to demonstrate statistical significance at a 2-sided 2.32% alpha level (overall 2.5%), allowing for 1 superiority interim analysis and 1 futility interim analysis, both conducted at approximately 70% of target events. The smallest treatment difference that could be statistically significant at the final analysis is an average HR of 0.81. With a 20-month recruitment period and a minimum follow up period of 20 months assumed, it is anticipated that the final analysis will be performed 40 months after the first patient has been recruited.

**Durvalumab + tremelimumab (dose 2) versus sorafenib (OS in ITT)**

If OS at 18 months were 46.2% with durvalumab + tremelimumab combination therapy (dose 2) and 28.7% with sorafenib (with 10.0-month median OS) in the ITT population and assuming the true average OS HR is 0.63, 450 OS events will provide at least 99% power to demonstrate statistical significance at a 2-sided 2.32% alpha level (overall 2.5%), allowing for 1 superiority interim analysis and 1 futility interim analysis, both conducted at approximately 70% of target events. The smallest treatment difference that could be statistically significant at the final analysis is an average HR of 0.81. With a 20-month recruitment period and a minimum follow up period of 20 months assumed, it is anticipated that the final analysis will be performed 40 months after the first patient has been recruited.

**Durvalumab monotherapy versus sorafenib (OS in ITT)**

If OS at 18 months were 40.4% with durvalumab monotherapy and 28.7% with sorafenib (with 10.0-month median OS) in the ITT population and assuming the true average OS HR is 0.74, 468 OS events will provide at least 85% power to demonstrate statistical significance at a 2-sided 2.32% alpha level (overall 2.5%), allowing for 1 superiority interim analysis and 1 futility interim analysis, both conducted at approximately 70% of target events. The smallest treatment difference that could be statistically significant at the final analysis is an average HR of 0.81. With a 20-month recruitment period and a minimum follow up period of 20 months assumed, it is anticipated that the final analysis will be performed 40 months after the first patient has been recruited.

OS, PFS and TTP, based on the programmatically derived RECIST 1.1 from investigator assessments, will be analyzed using a stratified log-rank test (stratified for etiology [HBV vs HCV vs uninfected], ECOG [ 0 vs 1], and macro-vascular invasion [yes vs no]). The effect of treatment will be estimated by the HR together with corresponding ([1-adjusted alpha] × 100%) confidence interval and p-values.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm.

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