Clinical Trial Protocol

An Open Label Pilot Study to Evaluate Efficacy and Safety of Durvalumab (MEDI 4736) With Hepatic Artery Infusion Chemotherapy (HAIC) in the Chinese Advanced HCC Patients With Severe Portal Vein Tumor Thrombosis (PVTT) (Vp3 or Vp4) DurHope

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Study Drug: Durvalumab, Oxaliplatin, Leucovorin, Fluorouracil

Protocol Number: ESR-20-20719

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PROTOCOL SYNOPSIS

Clinical Protocol ESR-20-20719

Study Title:

Durvalumab plus arterial FOLFOX followed by maintanance durvalumab for hepatocellular carcinoma with major portal invasion: the phase 2 DurHope study with biomolecular analyses

Protocol Number: ESR-20-20719

Clinical Phase: Phase 2

Study Duration

Patient enrollment for 15 months

Follow-up of last enrolled patients for 1 year

Investigational Product(s)

Durvalumab, Oxaliplatin, Leucovorin, Fluorouracil

Objectives

Primary Objectives:

- 1-year overall survival rate

Secondary Objective(s):

- Safety
- Objective response rate (RECIST 1.1)
- Progression-free survival (RECIST 1.1)

Exploratory Objective(s):

- PD-L1 expression
- Transcriptome analysis
- Peripheral dynamic biomarker

Study Design: Non-randomized, non-blinded, non-comparative, single-center, open-label study

Number of Patients: 30 patients

Study Population

Patients had portal vein invasion of vp3-vp4 without previous treatment for hepatocellular carcinoma

Inclusion Criteria

1. Provided written informed consent to participate in the study before the start of the study
2. Age ≥ 18 years at time of study entry
3. Diagnosis of HCC based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver (EASL)
4. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline. Tumor assessment by computed tomography (CT) scan or magnetic resonance imaging (MRI) must be performed within 30 days prior to screen
5. HCC with Vp3/4 PVTT patients who meet any of the following criteria are considered to have HCC with PVTT:
   a) Biopsy-confirmed HCC. Ultrasound-guided percutaneous tumor biopsy is performed with a gauge needle

b) HCC and PVTT confirmed by two image techniques, including contrast-enhanced ultrasound, dynamic contrast-enhanced computerized tomography and dynamic contrast-enhanced magnetic resonance imaging

6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
7. Body weight >30 kg
8. Disease not amenable to curative surgery or transplantation or patient refuses for surgery
9. No cirrhosis or cirrhotic status of Child-Pugh class A-B7
10. Adequate normal organ and marrow function as defined below:
    a) Haemoglobin ≥8.5 g/dL
    b) Absolute neutrophil count (ANC) ≥1.5 × 109 /L
    c) Platelet count ≥50 × 109/L
    d) Serum total bilirubin ≤2.0 x institutional upper limit of normal (ULN)
    e) AST (SGOT)/ALT (SGPT) ≤5 x institutional upper limit of normal
    f) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 × ULN.
    g) Serum creatinine clearance (CL) ≥ 30 mL/min or by the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance:

Males:

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

Females:

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

11. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up
12. Must have a life expectancy of at least 12 weeks
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:
    a) 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)
    b) 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)
14. Patients with HBV infection, which is 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 lab standard), must be treated with antiviral therapy, as per institutional practice, to ensure adequate viral suppression (HBV DNA ≤104 IU/mL) prior to randomization. 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 lab standard) do not require anti-viral therapy prior to randomization. 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 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
15. Patients with HCV infection must have management of this disease per local institutional practice throughout the study. HCV diagnosis is characterized by the presence of detectable

HCV ribonucleic acid (RNA) or anti-HCV antibody upon enrollment

Exclusion Criteria

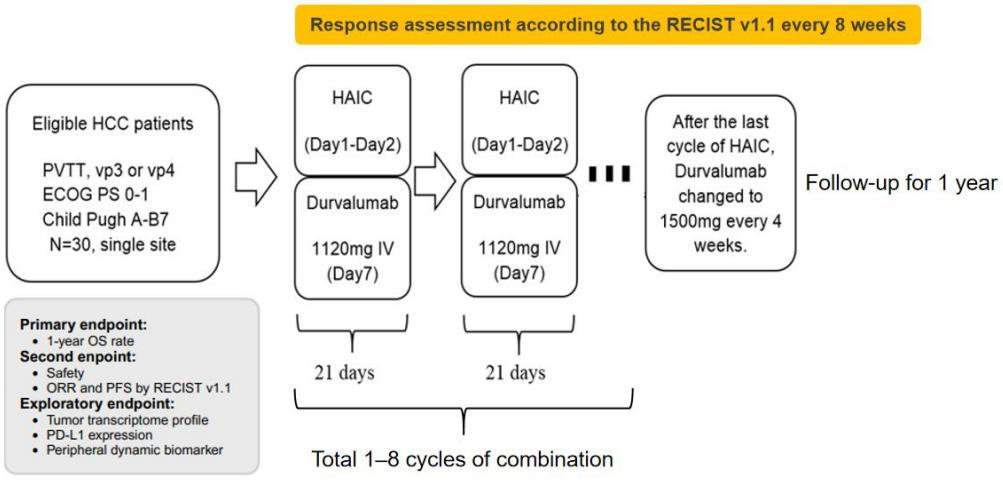
1. Evidence of hepatic decompensation including moderate ascites, gastrointestinal bleeding or hepatic encephalopathy
2. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, 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
3. Known history of human immunodeficiency virus (HIV) or organ allograft. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., 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])
4. Known or suspected allergy to the investigational agents or any agent given in association with this trial
5. Patients with clinically significant gastrointestinal bleeding within 30 days prior to study entry or evidence of bleeding diathesis
6. Known central nervous system tumors including metastatic brain disease
7. Patients who are pregnant or breastfeeding
8. History of another primary malignancy except for:
    a) 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
    b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c) Adequately treated carcinoma in situ without evidence of disease
9. Patient who had received anti PD-1, anti PD-L1 or anti CTLA-4 treatment before the first IP administration
10. Previous history of HAIC treatment
11. Previously received systemic anti-cancer therapy for HCC. Any biologic, or hormonal

therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable

12. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    a) Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    b) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    c) Steroids as premedication for hypersensitivity reactions
13. Live attenuated vaccine was inoculated 30 days before the first IP administration. (If enrolled, patients should not be inoculated live attenuated vaccine during IP treatment and within 30 days after the last IP administration)

Treatment Flow

Single-arm phase 2 trial



- HAIC (Oxaliplatin 130mg/m^2, leucovorin 200mg/m^2 and fluorouracil 400mg/m^2 via arterial bolus, then fluorouracil infusion 2400mg/m^2) every 3 weeks.
- Durvalumab 1120mg via intravenous infusion every 3 weeks
- 21 days of study treatment is regarded as 1 cycle
- Response assessment will be performed every 8 weeks with RECIST 1.1
- Patients will continue receiving Durvalumab until RECIST 1.1 defined radiological progression or intolerable AE.

Investigational Product(s), Dose and Mode of Administration:

HAIC

- Oxaliplatin 130mg/m^2, leucovorin 200mg/m^2 and fluorouracil 400mg/m^2 via arterial bolus, then fluorouracil infusion 2400mg/m^2 every 3 weeks.

Durvalumab

- 1120mg via intravenous infusion every 3 weeks.

Study Assessments and Criteria for Evaluation

Safety Assessments

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). In addition, serious adverse events, adverse events CTCAE grade ≥ 3, and will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum grade. Physical examination, vital signs, laboratory test, ECOG performance status, Child-Pugh classification compared to baseline will be summarized.

Efficacy Assessments

Response Evaluation Criteria in Solid Tumors (RECIST) Version1.1

Exploratory Analysis

Archived tumor biopsy:

- Patients' tumor biopsy will be used to test transcriptomic sequencing, the summary the result to analyzed the relationship between clinical efficacy (OS, PFS, ORR) with different gene expression and molecular pathways.
- PD-L1 testing outcome will be listed individually for each patient and summarized according to the status (Positive\Negative\Not Evaluable). Clinical efficacy (OS, PFS and ORR) will be summarized by PD-L1 expression status.

Serum and peripheral blood mononuclear cells (PBMC)

- Serum samples from patients will be evaluated by protein detection methods to detect serum biomarkers related to clinical efficacy.
- PBMC samples will be used to detect the phenotypic characteristics of peripheral immune cells to 0065plore the relationship between clinical efficacy and specific

immune cell subpopulations in peripheral blood.

Statistical Methods and Data Analysis:

Confidence intervals were estimated using the Clopper-Pearson method. Survival analyses will be performed using the Kaplan-Meier method. SPSS version 26.0 will be used for all statistical analysis.

Sample Size Determination:

To determine the appropriate sample size, we used a one-stage binomial design with a one-sided alpha level of 0.05 and statistical power of 80%. Previous studies have reported a median OS of approximately 7.6 months in high-risk HCC patients treated with atezolizumab plus bevacizumab, corresponding to an estimated 1-year OS rate of 35%6,25. We hypothesized that the combination of hepatic arterial infusion chemotherapy (HAIC) and durvalumab would improve the 1-year OS rate to 60%. Assuming an anticipated dropout rate of 10%, the target sample size was set at 30 patients.

SCHEDULE OF STUDY ASSESSMENTS

Table1.Schedule of assessments for durvalumab + HAIC, treatment to progression

	Screening	HAIC + durvalumab								
Cycle[a]	**/**	**HAIC C1D1-2**	**Durva C1D3**	**HAIC C2D1-2**	**Durva C2D3**	**HAIC C3D1-2**	**Durva C3D3**	**C4-C15**	**Survival Follow up phone calls**	**For details see Section**
Day	**-30 to -1**	**0**	**Q3W ±2 days unless dosing needs to be held for toxicity reasons and; Q4W±2 days after last HAIC**						**Q12W**	
Visit window	/	/	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days	±14 days	
Informed Consent										
Informed consent: study procedures[b]	X									4.1
Study procedures										
Eligibility criteria	X	X								4.1/4.2
Physical exam (full)	X	X		X		X		X		7.1
Vital signs[c]	X	X		X		X		X		7.2
ECG[d]	X	As clinically indicated								7.3
Concomitant medications	<----------								---------->	5.3
Demography, including baseline characteristics and	X									4.1
Child-Pugh classification	X	X	X	X	X	X	X	X		7.6
Monitoring										
ECOG performance status	X	X	As clinical indicated							7.5
AE/SAEs/AESI assessment[e]	<----------								---------->	8.1
Laboratory Assessments										
Clinical chemistry[f]	X	X		X		X		X		Table 7
Hematology [f]	X	X		X		X		X		Table 6

Cycle[a]	Screening	HAIC + durvalumab							Survival Follow up phone calls	For details see Section
	/	HAIC C1D1-2	Durva C1D3	HAIC C2D1-2	Durva C2D3	HAIC C3D1-2	Durva C3D3	C4-C15		
Day	**-30 to -1**	**0**	**Q3W ±2 days unless dosing needs to be held for toxicity reasons and; Q4W±2 days after last HAIC**						**Q12W**	
TSH[g] (reflex free T3 or free T4[h])	X	X		X		X		X		Table 7
Urinalysis	X	As clinically indicated								Table 8
Pregnancy test [i]	X	X		X		X		X		8.14.1
Hepatitis B and C and HIV [j]	X	X		X		X		X		7.4
IP administration										
Durvalumab [k]	/		X		X		X	X		5.1.2
HAIC[l]	/	X	HAIC will be repeated every 3 weeks (4-8 cycles)							5.1.2
Other evaluations										
Tumor biopsy (if available)	X									6.6.2
Tumor biopsy (archival, if available, for patients who submit a newly acquired biopsy at screening for PD-L1 status)	X									6.6.2
Efficacy evaluations										
Tumor evaluation (CT or MRI) (RECIST 1.1)	X	Q6W from week6, Q2M after 6 month, Q3-6M from 1year and depends on investigator's decision(w6, w12, w18, w24,w32 , w40and w48								6.3
QoL Questionnaire	X	Q3W during HAIC+Durvalumab treatment, Q8W after last HAIC treatment								6.5

[a] HAIC + Durvalumab will be repeated every 3 weeks. Durvalumab will be given on day 3±2 days after HAIC treatment.

[b] Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 30-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to enrollment. The collection of additional biopsies upon progression is strongly encouraged. 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 30 days of enrollment.

[c] Body weight is recorded at each visit along with vital signs.

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

[e] For AEs/SAEs/AESI reported during screening, additional information such as medical history and concomitant medications may be needed.

[f] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated. If screening clinical chemistry and haematology assessments are performed within 7 days prior to Day 1 (first HAIC day), they do not need to be repeated at Day 1.

[g] If TSH is measured within 14 days prior to Day 1 (first Durvalumab infusion day), it does not need to be repeated at day 1.

[h] 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.

[i] 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 and then every 3 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion

[j] For patients with known hepatitis B, results of anti-HCV and anti-HDV antibody assays were collected only during the screening period. For patients with known hepatitis C, HCV genotype, anti-HCV antibody, HBsAg qualitative and anti-HBc determination results were collected only during the screening period.

[k] Durvalumab will be administered 3 days after the first HAIC treatment, q3w (±2 days). Results for LFTs, electrolytes and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[l] HAIC was suggested 4-8 cycles, at the doctor's decision.

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

AE Adverse event; AFP alpha-fetoprotein; C Cycle; D Day; Durva Durvalumab; ECG Electrocardiogram; HAIC Hepatic arterial chemotherapy infusio;LFT Liver function test; q3w Every3 weeks; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid- stimulating hormone.

Table2.Schedule of assessments for patients who have discontinued durvalumab treatment.

	Time Since Last Dose of durvalumab								
	Days (±3)	Months (±1week)						12months and every 6 months (±2week)	For details see Section
Evaluation	**30**	**2**	**3**	**4**	**6**	**8**	**10**		
Physical exam (full)	X								7.1
Vital signs [a]	X								7.2
Pregnancy test	X	X	X	As clinically indicated					8.14.2
AE/SAE assessment	X	X	X						8.1
Concomitant medications	X	X	X						5.3
ECOG performance status	At the time of tumor assessment, and then at the beginning of subsequent anticancer therapy.								7.5
Subsequent anticancer therapy	<----------								6.4
Survival status		X		X	X	X	X	X (every 12 weeks)	6.4
Clinical chemistry	X	X	X						Table 7
Hematology	X	X	X						Table 6
TSH [b], (reflex free T3 or free T4) [c]	X	X	X						Table 7
AFP	X	X	X						Table 7
Tumor evaluation (CT or MRI) (RECIST 1.1)	Q6W from week6, Q2M after 6 month, Q3-6M from 1year and depends on investigator's decision.								6.3

[a] Body weight is recorded at each visit along with vital signs.

[b] If TSH is measured within 14 days prior to Day 1 (first Durvalumab infusion day), it does not need to be repeated at day 1.

[c] 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.

Note: AE Adverse event; AFP alpha-fetoprotein; ECOG ; q3w Every3 weeks; q4w Every 4 weeks; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid- stimulating hormone.

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ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen-presenting cells
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CL	Clearance
C_{max}	Peak concentration
$C_{max,ss}$	Peak concentration at steady state
C_{min}	Trough concentration
$C_{min,ss}$	Trough concentration at steady state
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DC	Disease control
DCR	Disease control rate
EASL	European Association for the Study of the Liver
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAIC	Hepatic arterial chemotherapy infusion

Abbreviation or special term	Explanation
HCC	Hepatocellular carcinoma
HCl	Hydrochloride
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IgG1	Immunoglobulin G1
IgG2	Immunoglobulin G2
imAE	Immune-mediated adverse event
IRB	Institutional Review Board
IV	Intravenous(ly)
Mab	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
PVTT	Portal vein tumor thrombosis
Q3W	Every 3 weeks
Q4W	Every 4 weeks

Abbreviation or special term	Explanation
QoL	Quality of life
QTc	Time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
sPD-L1	Soluble programmed cell death ligand 1
SoA	Schedule of study assessment
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

1. INTRODUCTION

1.1 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the fourth most common cancer and the second leading cause of cancer-related death in the world (Ferlay et al 2015). In Japan, HCC is associated with chronic hepatitis caused by persistent infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) and subsequent cirrhosis of the liver. It is estimated that about 24,536cases were newly diagnosed in the Chinese Cancer Registry annual report in 2009. Advanced-stage disease is found in 25%-70% of HCC at diagnosis, with a median survival time of only 4.2-7.9 months due to limited treatment options (Llovet et al 2008). To date, sorafenib and lenvatinib is the standard of care which shown to extend overall survival for advanced hepatocellular carcinoma. However, low response rates, modest survival benefit and high-level heterogeneity of individual response, such limitations them prohibit its widespread use and more alternative therapies are highly required at present.

1.2 Hepatic arterial infusion chemotherapy (HAIC)

Hepatic arterial infusion chemotherapy (HAIC) can provide chemotherapeutic agents to liver at higher concentration with lower toxicity and has been reported favorable results in advanced HCC and liver metastases from colorectal cancer (Kemeny et al 2009). FOLFOX (infusion 5-FU,

leucovorin, and oxaliplatin) was a regimen first used in colon cancer with liver metastasis and reported to be effective both by systemic and HAIC in the clinical trials (Goere et al 2013). EACH study has provided proof to suggest that the FOLFOX regimens may become a potentially more efficacious alternative to doxorubicin with advanced HCC in HBV infected population (Qin et al 2014).

Many patients are diagnosed as advanced disease, and systemic therapy is recommended as the first choice in the international guidelines. In Asia, HAIC, which involves direct infusion of anticancer drugs into the hepatic artery, was developed and used for patients with advanced HCC, especially HCC with portal vein tumor thrombosis (PVTT). In the previous studies, the median overall survival (OS) and progression-free survival (PFS) were estimated to be 7-9 months and 2-6 months, respectively (Liu et al 2020).

1.3 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).

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 PD-L2 (B7-DC; CD273). The 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. 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.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti–PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical 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 antitumor immune response in cancer patients (Brahmer et al, 2012; Hirano et al, 2005; Iwai et al, 2002; 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; Rizvi et al 2015; Segal et al 2015). In addition, high mutational burden (e.g., in bladder carcinoma [Alexandrov et al, 2013]) may contribute to the responses seen with immune therapy.

1.4 Durvalumab background/non-clinical and clinical experience

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and 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 (MOA) 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 durvalumab has been given to more than 8000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 5.1. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.5 Benefit/risk and ethical assessment

1.5.1 Potential benefits

Previous studies have reported that HAIC with fluorouracil or cisplatin achieved favourable results in advanced HCC patients with PVTT, even in patients with major PVTT, which had a median OS of 5.4–9.3 months (Lin et al. 2015). HAIC with oxaliplatin and fluorouracil was recently confirmed to be effective and safe for colorectal cancer liver metastasis. At present, most of the safety and efficacy data for PVTT patients receiving HAIC with oxaliplatin and fluorouracil, which had shown that the median OS was 20.8 months and the median PFS was 9.6 months (Hu et al. 2020).

At present, most of the safety and efficacy data for HCC patients receiving durvalumab monotherapy are based on the first monotherapy study 1108 (NCT01693562) in patients with advanced solid tumors such as HCC. As of October 16, 2017, the median follow-up time of 40 patients with HCC was 16.2 months and the median OS was 13.2 months.

In this study, study drug Durvalumab and required test is covered by investigator or the patient's health insurance. Participation in this study will have additional financial or therapeutic benefits over routine care.

In conclusion, the above data suggest that HAIC plus durvalumab may bring clinical benefits to HCC patients.

1.5.2 Overall risks

In 2010, a phase I study of HAIC of oxaliplatin in advanced HCC suggested that HAIC-oxaliplatin 130 mg/m^2 every 3 weeks was well tolerated and demonstrated activity (Rathore et al.

2010). About toxicity of FOLFOX regimens, there have been studies proved that compared with intra-arterial, systemic and portal vein routes, the administration of fluorouracil via the hepatic arterial route distal to its ligation results in the highest hepatic vein drug levels with the smallest systemic/hepatic vein exposure ratio (Didolkar et al. 1989). It was identified that urinary excretion (53.8 ± 9.1%) was the predominant route of oxaliplatin elimination, and hepatic impairment had no obviously effect on the clearance of ultrafilterable platinum after oxaliplatin administration (Graham et al. 2000).

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. 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 which 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 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 hyper-thyroidism.

Risks with durvalumab include, but are not limited to, diarrhea/colitis pneumonitis/ILD, diabetes insipidus, encephalitis, immune thrombocytopenia, subcutaneous injection site reaction, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus (including diabetic ketoacidosis), hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, pemphigoid, cytokine release syndrome, uveitis, non-infective encephalitis, subcutaneous injection site reactions, immune-meditated arthritis, 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 durvalumab please always refer to the current version of the durvalumab IB.

Further information on these risks can be found in the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 15% 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 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.5 % of patients experienced an SAE that was considered to be related to durvalumab by the study 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 (See Section 8.14.7).

1.5.3 Overall benefit-risk

Although there are many treatment options for patients with advanced HCC, there are still unmet medical needs. Most patients achieved initial remission after HAIC treatment, but they were limited by the following factors, such as tumor vascularization, micrometastasis and liver function reserve after HAIC treatment. These limitations lead to residual tumor cells, some of which may not be shown by radiographs.

HAIC can directly deliver chemotherapy drugs to cancer cells through hepatic artery, which can increase the local drug concentration and enhance the killing effect of tumor cells. FOXAI study had shown that the median PFS was 6.1 months and the objective response rate (ORR) was 28.6% receiving HAIC treatment, and HCC patients have the opportunity to seek further treatment after disease progression. Chemotherapy used with HAIC, generally is oxaliplatin, can kill cancer cells by inducing ribosome biogenesis. The release of new tumor antigen can promote a permanent antitumor immune response.

PD-1 and PD-L1 pathways play an important role in HCC, suggesting that drugs that can block PD-L1 may improve clinical outcomes by reversing the immunosuppressive environment and stimulating host immune response to HCC（Gao et al 2009）. In phase I/Ib study 1108, durvalumab monotherapy showed sustained clinical efficacy and controllable safety in HCC

patients with ORR of 10.0% (95% CI: 2.8%, 23.7%), and a median OS of 13.2 months (95% CI: 6.3, 23.0 months). In another phase I study, five (26.3%) of 19 HCC patients who received Tremelimumab combined with local therapy (ablation or TACE) achieved confirmed partial response (PR) （Duffy et al 2017）.

In conclusion, the above data suggest that durvalumab treatment in combination with HAIC treatment can enhance the anti-tumor immune response, resulting in a significant and consistent clinical benefit in advanced HCC patients.

Therefore, the overall benefit-risk assessment results support the development of this study to assess the efficacy and safety of HAIC combined with durvalumab in the treatment of advanced HCC patients with PVTT.

2. OBJECTIVES

This study is a prospective, phase 2, open-label, single center study to evaluate efficacy and safety of durvalumab with hepatic artery infusion chemotherapy in the Chinese advanced HCC patients with severe portal vein tumor thrombosis.

2.1 Primary objective

The 1-year overall survival (OS) rate.

2.2 Secondary objectives

1. To assess the safety and tolerability of HAIC + durvalumab in HCC patients through collecting AE/SAE/AESI, analyzing data of physical examination, vital signs, laboratory test, ECOG performance status and Child-Pugh classification.

2. Objective Response Rate (ORR) and Progression-free Survival (PFS) (Assessed by the Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1).

2.3 Exploratory objective

To investigate the relationship between the clinical efficacy and PD-L1 expression status, gene mutations status, immune cell subpopulations in peripheral blood.

3. STUDY DESIGN

3.1 Overview of study design

3.1.1 Description of Study Design

This study is a prospective, pilot, open-label, single center study to evaluate efficacy and safety of durvalumab with hepatic artery infusion chemotherapy in the Chinese advanced HCC patients with severe portal vein tumor thrombosis. Approximately 30 patients in single site will be recruited into the study in order to power the study efficiently to measure a clinically meaningful improvement for survival. Tumor response will be assessed according to the RECIST 1.1 criteria.

The study will include subjects diagnosed with advanced stage HCC with PVTT according to the Barcelona-Clinic Liver Cancer (BCLC) and the Tumor-Node-Metastasis (TNM) staging system.

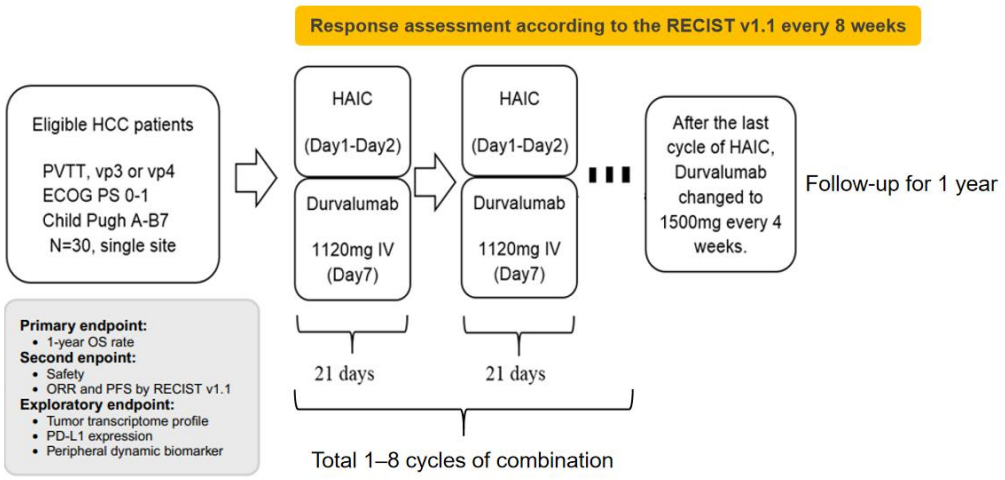
In the combined therapy phase, subjects will be given a procedure of HAIC on day 1-2. Medication was started within 2 days after catheter insertion. The therapeutic scheme was modified FOLFOX6 including oxaliplatin (130 mg/m^2 infusion for 3 hours on day 1), leucovorin (200 mg/m^2 from hour 3 to 5 on day 1) and fluorouracil (400 mg/m2 bolus, and then 2400 mg/m^2 continuous infusion 46 hours). HAIC was suggested 4-8 cycles, at the doctor's decision.

Durvalumab 1120 mg will be administered intravenously 3±2 days after the first HAIC treatment. The combination therapy with HAIC and Durvalumab will be repeated every 3 weeks. In the durvalumab monotherapy phase, durvalumab changed to 1500mg every 4 weeks, after the last cycle of HAIC.

The primary efficacy objective for this study are one-year overall survival rate (1-year OS rate). However, subjects will receive 4-8 cycles of combined therapy (HAIC+ Durvalumab) followed by durvalumab monotherapy until RECIST 1.1 defined radiological progression, intolerable adverse events, withdraws informed consent or other termination criteria.

3.1.2 Study schema

Figure 1. ***Study Flow Chart***



ECOG：Eastern Cooperative Oncology Group；HAIC：Hepatic artery infusion chemotherapy；HCC：Hepatocellular carcinoma；IV：Intravenous injection；PS: Performance status.

3.1.3 Follow up

During the combined treatment period, subjects will have study visits on Day 1 of every cycle (every 3 weeks from start of study), At the stage of durvalumab monotherapy, subjects will have study visits on Day 1 of every cycle (repeated every 4 weeks).

CT/MRI assessment will be Q6W from week0, Q2M from 6 month, Q3-6M from 1 year and depends on investigator's decision (w0, w6,w12,w18,w24,w32,w40 and w48)

At the end of the treatment period, a safety follow-up visit will take place (90 days after stopping the last cycle of durvalumab). All potential adverse events and changes in concomitant medication will be collected. In addition, all serious adverse events should be followed to resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the subject's underlying disease.

The subject will continue taking study procedure until disease progression or intolerable AE is documented.

The end of the study for regulatory purposes will be considered the date when the last subject has completed their last end of study visit.

3.2 Rationale for this study design

3.2.1 Primary endpoint rationale

The primary endpoint of this study will be 1-year OS rate. Overall survival was selected as the primary endpoint because it is the most widely accepted direct and objective measure of clinical effectiveness.

HAIC can reduce the tumor burden of most patients, and a large proportion of them achieved complete response (Lyu et al. 2018). However, some patients treated with HAIC experienced tumor recurrence because of the limited therapeutic effect of HAIC on potential extrahepatic micro metastasis. Therefore, effective systemic therapy, such as immunosuppressive checkpoint inhibitors, is needed to prevent local and distal recurrence. Cisplatin-based HAIC has been widely employed as an alternative therapy to sorafenib for hepatocellular carcinoma patients with portal vein invasion in Japan. This procedure provides direct delivery of chemotherapeutic agents into the tumor-feeding arteries and minimizes systemic toxic effects through a first-pass effect in the liver. In advanced HCC with vp3-vp4, HAIC or HAIC plus sorafenib has shown a prolonged PFS with 4-6.4months and prolonged OS with 10.3-13.5months (He et al. 2019).

Chemotherapy used with HAIC, generally is oxaliplatin, can kill cancer cells by inducing ribosome biogenesis. The release of new tumor antigen can promote a permanent antitumor immune response. This immune response may be amplified by an immune checkpoint blockade (Bruno et al 2017). Immunotherapies (IO) that inhibit the immune checkpoint interaction between PD-1 and PD-L1 have shown substantial survival benefit in some patients with metastatic carcinomas of multiple tissue origins. Current evidence showed IO mono is not effective enough compared with current systemic therapy to prolong survival in advanced HCC. However, IO combination tyrosine kinase inhibitor (TKI) has been demonstrated to prolong survival for advanced HCC (generally for vp1-3), with up to 9.7months of PFS and up to 20.4months of OS.

HAIC focus on the local control of the tumor, in the targeted area and avoiding anticancer drug exposure in other organs. However, IO is a systemic regime to mobilize the immune system of the whole body. HAIC combined with IO may prolong the survival of advanced HCC patients with PVTT.

3.2.2 Key secondary endpoints rationale

The key secondary endpoints of this study will be PFS, ORR and safety endpoint. Tumor response will be assessed using RECIST 1.1. Assessments will be made based on changes in the diameter of surviving tumors deemed viable by a modality such as contrast CT/MRI that are observed until completion or discontinuation of the protocol treatment.

Studies have shown that the median PFS was 6.1 months and the objective response rate (ORR) was 28.6% receiving HAIC treatment, and HCC patients have the opportunity to seek further treatment after disease progression. Therefore, PFS and ORR are important secondary endpoints in this study.

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used to tabulate data for the safety population. The incidence and causality of each adverse event and serious adverse event will be tabulated by group and by CTCAE v5.0 grade. A study to evaluate the safety and efficacy of FOLFOX regimen HAIC in advanced HCC showed good safety, much better than that from systemic use of FOLFOX4. In the study, the rate of treatment-related event ≥ grade 3 severity was 7.1%, and most common AE is fatigue 63.1%, elevated aspartate aminotransferase (AST) 48.8%, weight loss 38.1%, abdominal pain 32.1% and leukopenia 28.6%. AEs with grade ≥ 3 were leukopenia 4.8%, reduced hemoglobin 1.2% and elevated AST 1.2%. In addition, a study to evaluate the safety and efficacy of durvalumab monotherapy, or combined with Tremelimumab in 2nd line advanced HCC. This study showed good safety in durvalumab monotherapy group. The rate of treatment-related event ≥ grade 3 severity was 25% (16/64). Only 1 treatment-related death (1/64). The most common AE is AST elevation 25% (16/64) and alanine aminotransferase (ALT) elevation 22% (14/64).

Biological samples will be used to explore potential biomarkers in tumor, plasma and / or serum that may affect cancer progression and / or durvalumab treatment response. Blood samples were collected to study PK and immunogenicity of durvalumab treatment.

The correlation between PD-L1 expression level and therapeutic effect was evaluated as an exploratory endpoint. PD-L1 is a target of durvalumab, and its expression is assumed to be related to clinical efficacy.

3.3 Dose rationale

3.3.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 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).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens

maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20mg/kg Q4W regimen.

3.3.2 Rationale for fixed dosing

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

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

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1120 mg Q3W durvalumab (equivalent to 15 mg/kg Q3W) during the combination therapy and 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) during monotherapy is included in the current study.

3.4 Discontinuation of Study Intervention

The patient will not receive any further study drug treatment if any of the following occurs:

1. Withdrawal of informed consent to continue the study of drug treatment. Patients can stop treatment at any time without affecting further treatment.
2. Progressive disease as defined by the RECIST criteria is confirmed by imaging and the investigator's determination that the patient no longer benefits from the study drug treatment.
3. Any AE that meets the discontinuation criteria specified in the dose adjustment and toxicity management guidelines.
4. The investigator or AstraZeneca considered that non-compliance with the study protocol required discontinuation of the study medication (e.g., refusal to comply with the planned visit).
5. Hepatic arterial infusion chemotherapy becomes technically infeasible.
6. Pregnancy or planned pregnancy.

3.5 End of study definition

The end of study is defined as the last follow up/contact of the last participant.

The investigator will withdraw all subjects from the study if the study is terminated. If AstraZeneca judge that the study patient may be at excessive risk due to a clinically significant finding, the study should be stopped.

4. PATIENT SELECTION

Patients who meet all of the following inclusion criteria and do not meet any exclusion criteria in screening tests and then observations within 30 days before enrollment will be included in the study. In this protocol, patients who do not meet the inclusion requirements are regarded as screening failure, and the enrolled patients are defined as patients who sign informed consent.

4.1 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Provided written informed consent to participate in the study before the start of the study.

2. Age ≥ 18 years at time of study entry.
3. Diagnosis of HCC based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver (EASL).
4. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline. Tumor assessment by computed tomography (CT) scan or magnetic resonance imaging (MRI) must be performed within 30 days prior to screen.
5. HCC with PVTT3-4 patients who meet any of the following criteria are considered to have HCC with PVTT:

   a) Biopsy-confirmed HCC. Ultrasound-guided percutaneous tumor biopsy is performed with a gauge needle.

   b) HCC and PVTT confirmed by two image techniques, including contrast-enhanced ultrasound, dynamic contrast-enhanced computerized tomography and dynamic contrast-enhanced magnetic resonance imaging.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Body weight >30 kg.
8. Disease not amenable to curative surgery or transplantation or patient refuse for surgery.
9. No cirrhosis or cirrhotic status of Child-Pugh class A-B7.
10. Adequate normal organ and marrow function as defined below:
    - Haemoglobin ≥8.5 g/dL
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L
    - Platelet count $\geq 50 \times 10^9$/L
    - Serum total bilirubin ≤2.0 x institutional upper limit of normal (ULN).
    - AST (SGOT)/ALT (SGPT) ≤5 x institutional upper limit of normal.
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 × ULN.
    - Serum creatinine clearance (CL) ≥ 30 mL/min or by the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance:

Males:

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

Females:

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

11. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
12. Must have a life expectancy of at least 12 weeks.
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).
14. Patients with HBV infection, which is 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 lab standard), must be treated with antiviral therapy, as per institutional practice, to ensure adequate viral suppression (HBV DNA $\leq 10^4$ IU/mL) prior to randomization. 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 lab standard) do not require anti-viral therapy prior to randomization. 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 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.

15. Patients with HCV infection must have management of this disease per local institutional practice throughout the study. HCV diagnosis is characterized by the presence of detectable HCV ribonucleic acid (RNA) or anti-HCV antibody upon enrollment.

4.2 Exclusion criteria

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

1. Evidence of hepatic decompensation including moderate ascites, gastrointestinal bleeding or hepatic encephalopathy.
2. 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.
3. Known history of human immunodeficiency virus (HIV) or organ allograft. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., 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]).
4. Known or suspected allergy to the investigational agents or any agent given in association with this trial.
5. Patients with clinically significant gastrointestinal bleeding within 30 days prior to study entry or evidence of bleeding diathesis.

6. Known central nervous system tumors including metastatic brain disease.
7. Patients who are pregnant or breastfeeding.
8. History of another primary malignancy except for
    a) 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
    b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c) Adequately treated carcinoma in situ without evidence of disease.
9. Patient who had received anti PD-1, anti PD-L1 or anti CTLA-4 treatment before the first IP administration.
10. Previous history of HAIC treatment.
11. Previously received systemic anti-cancer therapy for HCC. Any biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
12. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
    a) Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    b) Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    c) Steroids as premedication for hypersensitivity reactions.
13. Live attenuated vaccine was inoculated 30 days before the first IP administration. (If enrolled, patients should not be inoculated live attenuated vaccine during IP treatment and within 30 days after the last IP administration.)

4.3 Withdrawal of patients from study treatment and/or study

Permanent discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone

contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter survival follow-up (see the SoAs).

Patients who permanently discontinue drug for reasons other than objective RECIST disease progression should continue to have RECIST scans performed Q6W from week0, Q2M from 6 month, Q3-6M from 1 year and depends on investigator's decision.

If a patient is discontinued for RECIST 1.1-defined progression, then the patient should have 1 additional follow-up scan performed 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.

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 the SoAs as an alternative.

Lost to follow-up

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

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

•Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

•In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

Withdrawal of consent

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

Patients who withdraw consent for further participation in the study will not receive any further IP 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 always 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)

•Withdrawal to the use of any samples

4.4 Premature Termination of Study/Closure of Center

The investigator has the right to close the study, at any time, although this should occur only after consultation between involved parties.

If there is a reasonable reason and has been fully informed before the expected suspension, the investigator can start the closure procedure of the study/center at any time.

The reasons for the closure of the study/center by the investigator/sponsor may include but are not limited to:

- Lack of patients recruited by investigator.
- The investigator failed to comply with protocol, ethics committee/institutional review board or local health department requirements, sponsor procedures or the criterions for the quality control of clinical trial of drugs.
- Suspension of further research intervention.

5. TREATMENT PLAN

5.1 Treatments to be Administered

5.1.1 Investigational Product(s)

Durvalumab

Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca as a 500 mg vial or 120 mg vial concentrate for solution for infusion. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine- hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The label-claim volume is 10 mL. Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Any excursions outside to the intended storage conditions is to be reported. Investigational product must be kept in original packaging until use to prevent prolonged 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 must not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours. A dose of 1120 mg will be administered during HAIC + durvalumab treatment using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 22.4 mL (i.e. 1120 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

After the last cycle of HAIC, a durvalumab dose of 1500 mg (for participants >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30 mL (i.e. 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤30 kg during whilst receiving 1500 mg dose, weight-based dosing at 20 mg/kg will be administered using an IV bag size selected such that the final concentration is within 1 to 15 mg/mL.

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

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

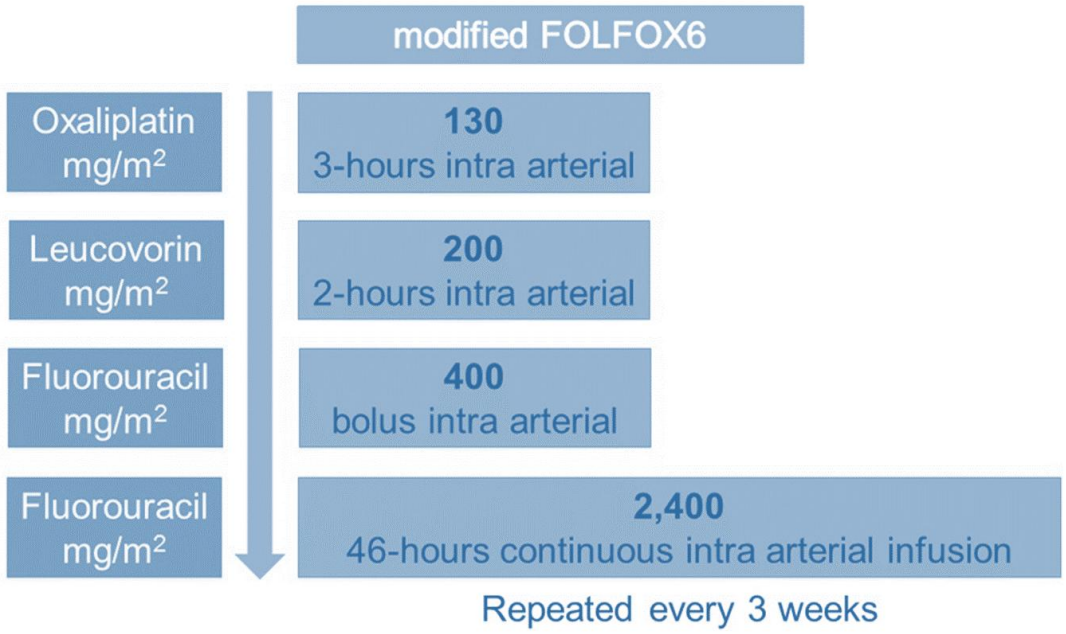
The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time.

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

Procedure of HAIC

For HAIC, a micro-catheter was inserted and located in common hepatic artery or proper branch (feeding artery). An arterial catheter was inserted using an image-guided procedure through the femoral artery. Firstly, the femoral artery was percutaneously punctured using the Seldinger technique. Then, the catheter was inserted to the celiac trunk or superior mesenteric artery for arteriography. When more than one feeding artery of HCC was detected, the smaller arteries were embolized with gelatin sponge particles. A micro-catheter was inserted through the arterial catheter and located at the common hepatic artery or proper hepatic arterial branch (feeding artery). When blood flow into the gastroduodenal artery was confirmed by micro-catheter angiography, the route was embolized with a coil or micro-coil to prevent reflux of chemotherapeutic drugs to the stomach and duodenum. The peripheral end of the micro-catheter was locked with a heparin lock (10 ml, 10,000 units, 1: 1,000 dilution) to prevent clotting of the catheter. The peripheral part of catheter that exposing to outside of body was covered with medical sterile gauze and fastened on the skin of thigh using medical rubberized fabric and bandage. Medication was started within 2 days after catheter insertion. After treatment, catheters were removed from patient's body. Catheter insertion was repeatedly performed before every cycle of treatment. Medication was started within 2 days after catheter insertion. The therapeutic scheme (*See Figure 2*) was modified FOLFOX6 including oxaliplatin (130 mg/m2 infusion for 3 hours on day 1), leucovorin (200 mg/m2 from hour 3 to 5 on day 1) and Fluorouracil (400 mg/m2 bolus, and then 2400 mg/m2 continuous infusion 46 hours). All drugs were given by hepatic arterial infusion.

Figure 2. Treatment schedule of HAIC.



Durvalumab doses

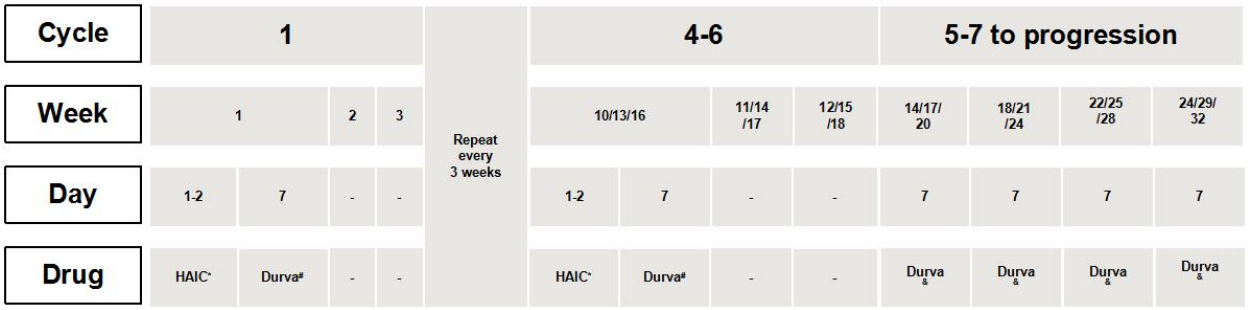
In this study, patients will receive intravenous infusion of 1120 mg durvalumab q3w, starting treatment no earlier than 3±2 days after the first HAIC treatment and continued until the last HAIC cycle:

1. The initial dose of durvalumab will be given at least 3±2 days after the first HAIC treatment.

2. Durvalumab monotherapy will begin at least 14 days after the completion of the last cycle HAIC until progressive disease, intolerable toxicity, withdrawal of informed consent, or compliance with other discontinuation criteria. When switching from 1120 mg q3w to 1500 mg durvalumab q4w, at least 14 days interval will be allowed between two doses of durvalumab. *See Figure 3.*The 14 days interval provides investigator with flexibility to switch to monotherapy as soon as possible after the last HAIC cycle. If durvalumab monotherapy is not initiated within the last 7 weeks of HAIC treatment, the AstraZeneca research team or research physician should be contacted and delayed clinical reasons should be provided.

3. Patients whose weight falls to 30 kg or below (≤30 kg) whilst receiving 1500 mg durvalumab, should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg.

Figure 3. HAIC + Durvalumab Combined Therapy Dosing Schedule



Note:

HAIC*: Oxaliplatin 130 mg/m^2 for 3 hours on day 1; leucovorin 200 mg/m^2 from hour 3 to 5 on day 1; fluorouracil 400 mg/m^2 in bolus, and then 2400 mg/m^2 continuous infusion over 46 hours.

Durva#: Patients will receive 1120 mg durvalumab via intravenously infusion q3w during HAIC treatment.

Durva&: Patients will receive durvalumab monotherapy (1500 mg durvalumab q4w) after the completion of the last cycle HAIC until progressive disease, intolerable toxicity, withdrawal of informed consent, or compliance with other discontinuation criteria.

5.1.2 Duration of treatment and criteria for treatment through progression

All treatment will be administered beginning on Day 1 until clinical progression or RECIST 1.1-defined radiological progression (refer to Appendix 14.2) unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (Section 4.3).

During the treatment period, patients who are clinically stable at an initial RECIST 1.1-defined PD may continue to receive study treatment at the discretion of the Investigator and patient as long as they are deemed to be receiving clinical benefit. A follow-up scan is to be collected after the initial RECIST 1.1 defined PD, 4-8 weeks after the prior assessment of PD, and this follow-up scan is evaluated using the post-progression evaluation criteria outlined. Patients with PD who continue to receive IP at the discretion of the Investigator and patient can receive treatment until they are no longer deemed to be receiving clinical benefit, and image acquisitions and tumor assessments should continue on their regular imaging schedule for the duration of treatment.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible for continuing durvalumab.

Crossover within the study will not be permitted.

Patients who meet RECIST 1.1-defined PD may undergo retreatment as described below:

- Patients who complete the 4-8 dosing cycles of the combination of HAIC and durvalumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of RECIST 1.1 defined PD, during the durvalumab monotherapy portion of the combination regimen may restart treatment with the combination.
- Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart their assigned treatment (HAIC + durvalumab combination therapy) with the combination upon evidence of RECIST 1.1 defined PD that occurs during the 12 months follow-up period.

For all patients who are treated through progression and for patients who are restarting HAIC + durvalumab combination therapy, the Investigator should ensure that:

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient. The patient may not have experienced a toxicity that required permanent discontinuation of study treatment.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in 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
- The patient still fulfills the eligibility criteria for this study (see Section 4.1 and 4.2) with the exception of inclusion criteria and exclusion criteria (eg, 10 and 11 *teams*)

Patients who AstraZeneca and the Investigator determine may not continue treatment after RECIST 1.1-defined 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 with tumor assessments until RECIST 1.1-defined PD plus an additional follow- up scan or until death (whichever comes first) and followed for survival.

5.2 Dose modification

5.2.1 FOLFOX regimen

If a subject experience several toxicities and there are conflicting recommendations, the recommended dose adjustment that reduces the dose to the lowest level will be used. Dose reduction of FOLFOX regimens (to 80% of dose) was allowed in cases of intolerable (grade 3 or 4) drug related toxicities including neutropenia or thrombocytopenia, diarrhoea despite the use of antidiarrheics, fever, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and creatinine elevation that did not recover to normal level within one treatment cycle, and peripheral sensory neuropathy. Dose delays were only allowed within 1 week after the date of a regularly scheduled treatment. If further dose reduction is required, the subject should be discontinued from the study. Disease assessment and imaging scan were undertaken according to the original study protocol, regardless of dose delays.

5.2.2 Durvalumab of dose administration

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

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion- related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion- related reaction is Grade 3 or higher in severity, study drug will be discontinued. The

standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature (otherwise requires new infusion preparation). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines (See Section 8.14.7).

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

For dosing modification and toxicity management guidelines for immune-mediated, infusion-related, and non-immune-mediated reactions of Durvalumab therapy, see detail in toxicity and management guidelines for durvalumab.

5.3 Concomitant treatment(s)

Patient should inform the investigator as soon as possible of all drugs taken from the study screening period to clinical treatment, including the 90 days follow-up period after the last IP administration.

Any drugs (including over-the-counter, prescription or herbal health products) received by the patient during the registration period or during the study period, as well as the reason for use, the date of administration (including the start and end dates), and the administration information (including dose, unit and frequency) must be recorded.

Patients should not take any drugs, including over-the-counter drugs, without consulting the investigator.

5.3.1 Drug interactions

To date, there is no data on drug-drug interactions in durvalumab preclinical or clinical studies. Due to the fact that durvalumab is mAb, i.e. protein drugs, it can be degraded into small molecular peptides and amino acids, which are excreted through the clearance of kidney and reticuloendothelial system. Therefore, durvalumab is not expected to induce or inhibit the cytochrome P450 pathway, a major drug metabolizing enzyme. Therefore, no pharmacokinetic

drug interactions are expected. Durvalumab MoA includes binding to PD-L1 and therefore no significant pharmacodynamic drug interactions are expected with common combinations. In addition, appropriate clinical monitoring will be conducted in all planned clinical studies to assess any potential drug interactions.

5.3.2 Permitted concomitant medications

Table 4. Supportive Medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., 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 non-target lesions, etc.])	Should be used, when necessary, for all patients
Additional HAIC treatment according to the specific conditions of the disease.	Permission after consulting the investigator and sponsor.
Inactivated viruses, such as those in the influenza vaccine	Permitted

5.3.3 Excluded concomitant medications

Table 5. Prohibited Concomitant Medications

Prohibited medication/class of drug:	Usage:

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
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 whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
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 the I-O infusions. The following are allowed exceptions:* • *Use of immunosuppressive medications for the management of IP-related AEs,* • *Use in patients with contrast allergies.* • *In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.* *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 (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).*

Prohibited medication/class of drug:	Usage:
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

6. ASSESSMENT OF EFFICACY

6.1 Imaging examination schedule

Within 30 days before enrollment, radiologic examination, which includes chest / abdomen / pelvic dynamic contrast-enhanced CT / MRI, is needed to evaluate the baseline tumor size and improve tumor staging. A bone scan should also be obtained if bone metastases are suspected per standard of care procedures and investigators' discretion.

During the combined treatment period, subjects will have study visits on Day 1 of every cycle (every 3 weeks from start of study), At the stage of durvalumab monotherapy, subjects will have study visits on Day 1 of every cycle (repeated every 4 weeks). Tumor assessment by CT/MRI will be performed by Q6W from week0, Q2M from 6 month, Q3-6M from 1year and depends on investigator's decision.

6.2 Image acquisition and evaluation

All Images (including other hospital scans) will be continuously collected and stored.

6.3 Tumor assessment

The primary efficacy endpoint was one-year overall survival rate in the full-analysis-set (FAS) population. Progression free survival (PFS) is one of the secondary efficacy endpoints, which is defined as from time of treatment until disease progression or death according to RECIST 1.1 criteria (refer to Appendix 14.2). Objective response rate (ORR) evaluations will be based on made by CT/MRI imaging, Q6W from week0, Q2M from 6 month, Q3-6M from 1year and depends on investigator's decision.

6.4 Survival tracking

After study drug treatment ends, subjects will be contacted every 2 months to determine survival status if this was not reached at the time of the primary end point analysis. If the subject has received any subsequent anti-cancer therapy following end of treatment, details should be collected. Post study follow up will end at last overall survival (OS) analysis.

If a subject discontinues due to an adverse event or clinical laboratory abnormality, the subject should be followed-up until the event resolves, the subject stabilized, or 30 days, whichever is shorter. If a subject die within 30 days of the last dose of study treatment, the SAE complementary form should be completed in the usual.

6.5 Clinical efficacy evaluation

Quality of Life(QOL) Questionnaire will designed by Investigator, which will be collected and assessed in this study. During HAIC+Durvalumab treatment, will assessed Q4W, during durvalumab monotherapy, will be collected every 8 weeks(two treatment cycle).

6.6 Biological sample analysis

6.6.1 Blood sample

Blood samples will not be collected and analysed by any testing institution but only tested in the study site.

6.6.2 Tissue sample

Tissue Samples at Screening. If available, archival tissue samples will be obtained at baseline for exploratory research on PD-L1 expression level. A representative FFPE tumor specimen in a paraffin block is preferred, or approximately 3 slides containing unstained, freshly cut, serial

sections along with an associated pathology report. Samples collected via resection is preferred. Core-needle biopsy is acceptable. If no available archival tissue sample at baseline, an optional screening biopsy may be performed. The Informed Consent Form will contain a separate section that addresses this optional screening biopsy. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies.

7. ASSESSMENT OF SAFETY

7.1 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). 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 8.8.

7.2 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the SoAs. Body weight is also recorded at each visit along with vital signs.

First infusion of durvalumab

On the first infusion day, patients will be monitored and vital signs collected/recorded in eCRF prior to, during and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from patients before, during, and after each infusion 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 [i.e., the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

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.

Subsequent infusions

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated.

Vital sign results should be reported as AEs are described in Section 8.8. For all infusion related AEs, vital signs should be recorded in eCRF.

7.3 Electrocardiogram

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. 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.

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 the finding.

Situations in which ECG results should be reported as AEs are described in Section 8.8.

At Screening, a single ECG will be obtained on which QTcF must be <470 ms.

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 (e.g., 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 8.8.

7.4 Laboratory tests

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs).

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. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). If possible, all pregnancy outcomes (spontaneous abortion, selective termination of pregnancy, ectopic pregnancy, normal delivery or congenital malformations) occurring between the first administration date and 90 days after the last IP administration should be followed up and recorded. 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 6 (hematology), Table 7 (clinical chemistry), and Table 8 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

Note: HBV positive patients must continue to receive antiviral treatment during the period of study and within 6 months after the last administration.

The following laboratory variables will be measured:

Table 6. Hematology Laboratory Tests

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

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 counts 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. Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin [a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase [b]	Thyroid-stimulating hormone [e]

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. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 0 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 0), and if clinically indicated.

[d] Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 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

Table 8. Urinalysis Tests[f]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[f] Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

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 IP

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 8.8. Elevated transaminase is usually observed after HAIC treatment. Therefore, investigator should take it into account when determining the causal relationship.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP 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.

7.5 ECOG performance status

ECOG performance status will be assessed at the times specified in the assessment schedules (see the SoAs) based on the following criteria (refer to Appendix 14.3).

7.6 Child-Pugh classification

The severity of liver cirrhosis is determined by Child-Pugh score, and the results are recorded in eCRF according to the requirements of SoA. For specific Child-Pugh classification methods, please refer to Appendix 14.4.

7.7 Gastroscopy

Gastroscopy should be assessed during the whole study, to determine whether patients have gastrointestinal erosion, ulcers, bleeding, also to evaluate the risk of adverse events like gastrointestinal bleeding. Gastroscopy should be performed before first HAIC or no later than 2 weeks after first HAIC, and before 5th HAIC or no later than 2 weeks after. During durvalumab monotherapy, should be performed every 3-6 months.

7.8 Other safety assessments

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (See Section 8.14.7) 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.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan

(ii) Tumor markers: Particular tumor markers which are related to disease progression.

Additional Clinical chemistry: CRP, LDH

Safety parameters

8. ADVERSE EVENTS

8.1 Adverse Event Definitions

8.1.1 Adverse events

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

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

An AE includes but is not limited to any clinically significant worsening of a patient's pre- existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

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

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

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

8.1.2 Adverse drug reaction

An Adverse Drug Reaction (ADR) is an Adverse Event suspected to be causally related to the medicinal product.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure.

8.1.3 Serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the patient
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.
- Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **Non-Serious** AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and

should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

- The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is *not* the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

8.1.4 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious.

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

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. 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 (e.g. Guillain-Barré, and myasthenia gravis)

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (See Section 8.14.7).These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

8.2 Adverse Event Collections

8.2.1 Collection mode

AE and/or SAE will be reported by the patient (or caregiver, agent/legally authorized representative as appropriate). When collecting AE and/or SAE, open and non-guided oral questioning should be preferred to avoid bias.

8.2.2 Collection schedule

AEs and SAEs will be actively collected from the time of the patient signing the informed consent form until the safety follow-up period is completed (90 days after the last dose of durvalumab). In the survival follow-up period, AEs related to AZ products will be reported spontaneously by investigators to AZ. If an event that starts post the defined safety follow up

period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

After the patient has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study patients. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor.

8.2.3 Follow up and collection

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 are followed up by the Investigator for as long as medically indicated, but without further recording in specify where this information will be recorded e.g. eCRF.

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

8.3 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The grading scales found in the National Cancer Institute CTCAE 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 CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).
The determination of severity for all other events not listed in the CTCAE should be made by

the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

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

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

8.4 Recording of adverse events and serious adverse events

The following variables will be collected for each AE:

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

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- 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 fulfilled
- 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 (See Section 8.5)
- Description of the SAE

The grading scales found in the NCI CTCAE version 5.0 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 CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.5 Causality collection

The Investigator will assess causal relationship between the IPs 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.”

8.6 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 (i.e., SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., 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.

8.7 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 specify where this information will be recorded e.g. 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.

8.8 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the CSR. Deterioration 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 IPs.

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 (e.g., 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.

8.9 Hy's Law

Not applicable for this study.

8.10 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP 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.

8.11 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 the administration of the IP and have been identified after the patient's inclusion in this study.

8.12 Deaths

All deaths that occur during the study 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 specify where this information will be recorded e.g. 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 specify where this information will be recorded e.g. eCRF.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in specify where this information will be recorded e.g. eCRF.
- A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety.

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

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

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (See Section 8.14.7). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

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

8.14 Safety reporting and medical management

8.14.1 Reporting of Adverse Events

The investigators are responsible for informing the EC and the Regulatory Authority of the adverse events as per China regulations.

The investigators are also responsible for reporting all SAEs within 24 hours after awareness to AZ Data Entry site and reporting non-serious ADRs related to Durvalumab to AZ Data Entry Site within 5 calendar days after awareness. Investigators should report AESIs which is also a SAE within 24 hours and within 5 calendar days for AESIs of non-serious ADRs (AESIs of Durvalumab).

For all SAEs and non-serious ADRs (related to Durvalumab)where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca of any follow-up information on a previously reported SAE/ non-serious ADR (related to Durvalumab) within the same timeframe as initial reports of when he or she becomes aware of it.

Contact information of AZ Data Entry Site:

E-mail: AEMailboxClinicalTrialTCS@astrazeneca.com

Fax: +1 302 886 4114

8.14.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received durvalumab.

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca’s designated fax line: +1 302 886 4114 or email: AEMailboxClinicalTrialTCS@astrazeneca.com if a secure line is set up.

8.14.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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.

8.14.3 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 HAIC + durvalumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

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 HAIC + durvalumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period should, if possible, be followed up and documented.

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca's designated fax line: +1 302 886 4114 or email: AEMailboxClinicalTrialTCS@astrazeneca.com if a secure line is set up.

8.14.4 Toxicity management guidelines

Following general guidelines for toxicity management:

1. Use maximum supportive treatment to deal with each toxicity, if applicable, suspend IP causing toxicity. If symptoms are relieved, consider continuing to administer IP and continuing supportive treatment. Dosage adjustment is allowed if medically applicable.

2. All dose adjustments should clearly document the reasons and methods.

All toxicities will be graded according to NCI CTCAE, Version5.0.

Durvalumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the Toxicity Management Guidelines (see section 14.5).

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 should be permanently discontinued (see section 4.4.)

Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy by the reporting investigator.

FOLFOX regimen

If a subject experience several toxicities and there are conflicting recommendations, the recommended dose adjustment that reduces the dose to the lowest level will be used. Dose reduction of FOLFOX regimens (to 80% of dose) was allowed in cases of intolerable (grade 3 or 4) drug related toxicities (see section 5.2.1).

9. DATA COLLECTION AND MANAGEMENT

9.1 Data Collection

For studies using Electronic Data Capture, the designated investigator staff will enter the data required by the protocol into the eCRF. Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. This includes clinical data from safety assessments.

9.2 Data Management

For studies using eCRFs, the research group will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the Electronic Data Capture system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities terminology.

10. STATISTICAL METHODS AND DATA ANALYSIS

10.1 Statistical and Analytical Plans

10.1.1Analysis Populations

Efficacy and safety analysis will be performed in a full-analysis-set (FAS) population, which includes all subjects receiving at least one dose of study treatment.

10.1.2 Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized by descriptive statistics.

10.1.3 Primary Efficacy analysis

The OS12 will be defined as the Kaplan-Meier estimate of OS at 12 months. OS12 will be summarized using the Kaplan-Meier method.

10.1.4 Interim analysis

An interim analysis is planned for the evaluation of safety and efficacy:

The objective of IA is to explore the signal of safety and efficacy. The planned data cut off (DCO) for IA will occur when at least 50% patients enrolled and follow up for 3m. ORR and safety will be summarized. If results are unfavorable, the trial may be stopped for futility.

10.1.5 Other Efficacy analysis

Objective Response Rate is defined as the number (%) of patients with measurable disease with at least 1 visit response of CR or PR. Data obtained up until progression or last evaluable assessment in the absence of progression will be included in the assessment of ORR. However, any CR or PR which occurred after a further anti-cancer therapy was received will not be included in the numerator for the ORR calculation (where the FAS will be the denominator).

Progression-free survival is defined as the time from first dose of treatment until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from study therapy or receives another anti-cancer 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 assessment.

However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within 2 visits of baseline.

Overall survival is defined as the time from the date of first dose of treatment in this study until death due to any cause. Any subject not known to have died at the time of analysis will be censored based on the last recorded date on which the subject was known to be alive.

Time-to-event data (PFS, OS) will be summarized using Kaplan-Meier estimates of the median event time and quartiles together with their 95% Cis, given the maturity of 60%.The Kaplan-Meier curves will be provided.

10.1.6 Safety analysis

Descriptive summary tables will be presented on all safety parameters. Subjects will be monitored for adverse events using the NCI-CTCAE version 5.0. Treatment-emergent adverse events drug-related adverse events, procedure-related, SAE, AESI and safety laboratory parameters will be summarized CTC grade.

10.1.7 Biomarker analysis

1) Archived tumor biopsy:

- patients' tumor biopsy will be used to test transcriptomic sequencing, the summary the result to analyzed the relationship between clinical efficacy(OS, PFS, ORR) with different gene expression and molecular pathways.

- PD-L1 testing outcome will be listed individually for each patient and summarized according to the status (Positive\Negative\Not Evaluable). Clinical efficacy (OS, PFS and ORR) will be summarized by PD-L1 expression status.

2) Archived/fresh Serum and peripheral blood mononuclear cells(PBMC)

- Serum samples from patients will be evaluated by protein detection methods to detect serum biomarkers related to clinical efficacy.

- PBMC samples will be used to detect the phenotypic characteristics of peripheral immune cells to 0065plore the relationship between clinical efficacy and specific immune cell subpopulations in peripheral blood.

10.2 Determination of sample size

To determine the appropriate sample size, we used a one-stage binomial design with a one-sided alpha level of 0.05 and statistical power of 80%. Previous studies have reported a median OS of approximately 7.6 months in high-risk HCC patients treated with atezolizumab plus bevacizumab, corresponding to an estimated 1-year OS rate of 35%6,25. We hypothesized that the combination of hepatic arterial infusion chemotherapy (HAIC) and durvalumab would improve the 1-year OS rate to 60%. Assuming an anticipated dropout rate of 10%, the target sample size was set at 30 patients.

11. USE OF DATA AND PUBLICATION

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, whilst free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

12. ETHICAL CONSIDERATIONS

12.1 Ethics Committee (EC) or Institutional Review Board (IRB)Ethics and regulatory review

Documented approval from appropriate independent Ethics Committee(s)/IRBs will be obtained for all participating centers/countries prior to study start, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the Ethics Committee approval must be obtained and also forwarded to the sponsor. The Ethics

Committees must supply to the sponsor, upon request, a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics Committee is organized and operates according to GCP and applicable laws and regulations.

12.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation form, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior EC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the EC/IRB/sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

12.3 REGULATORY AUTHORITY APPROVALS/AUTHORIZATIONS

Regulatory Authority approvals/authorizations/ notifications, where required, must be in place and fully documented prior to study start.

12.4 INFORMED CONSENT

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the ECs/IRB written approval/favorable opinion of the written Informed Consent Form and any other written information to be provided to subjects. The

written approval of the EC/IRB together with the approved subject information/Informed Consent Forms must be filed in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

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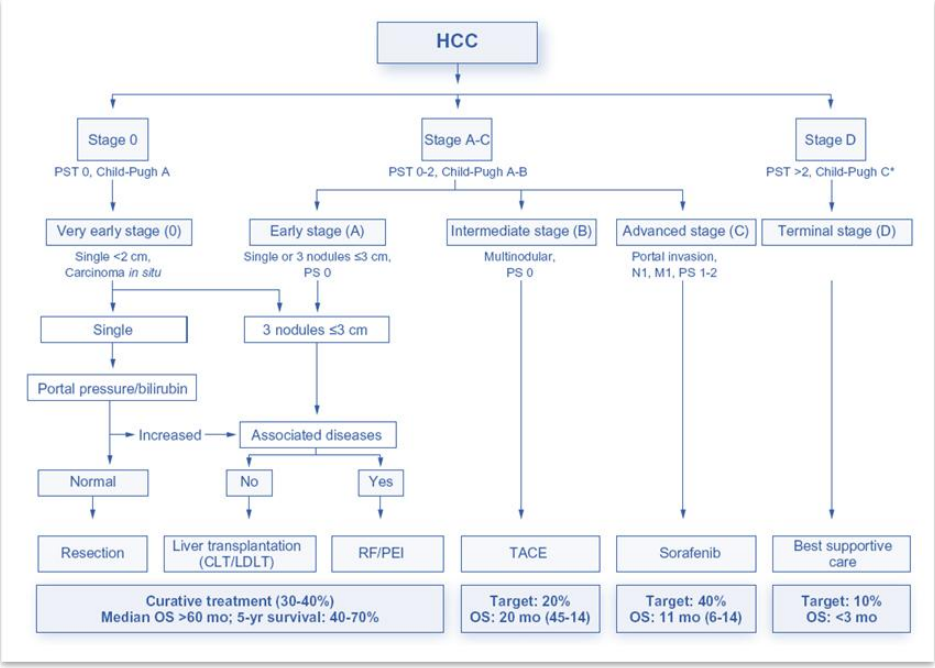
14. APPENDICES

14.1 The Barcelona Clinic Liver Cancer (BCLC) staging system

Clinical staging is crucial for risk stratification during cancer management. The BCLC system are most widely studied and will be assessed at screening for all patients participating in this study. It includes variables related to tumor stage, liver functional status, physical status and cancer related symptoms. Only BCLC Stage C HCC patients are eligible for participating in this study, provided that the patients meet all other eligibility criteria.



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14.2 RECIST 1.1 criteria

Complete response is the disappearance of any intratumoral arterial enhancement in all target lesions; Partial response is at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions; Progressive disease is an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the

diameters of viable (enhancing) target lesions recorded since the treatment started; Stable disease is any cases that do not qualify for either partial response or progressive disease.

According to these amendments, progressive disease will also be declared on the appearance of one or more new lesions, as per RECIST.

- A newly detected hepatic nodule will be classified as HCC — and therefore will be declared as evidence of progression —when its longest diameter is at least 10 mm and the nodule shows the typical vascular pattern of HCC on dynamic imaging, that is, hypervascularization in the arterial phase with washout in the portal venous or late venous phase.
- Lesions larger than 10 mm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm interval growth in subsequent scans.
- An individual radiological event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiological testing.
- Finally, for non-enhancing atypical lesions, the conventional RECIST criteria will be applied.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	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 = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026.

14.3 ECOG Performance Status Classification

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

Reference: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Onco. 1982; 5:649-655.

14.4 Child–Pugh Classification

	Score*		
Measure	**1 point**	**2 points**	**3 points**
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time, sec (seconds prolonged)	<4	4–6	>6
Encephalopathy grade	None	1–2	3–4

* Child-Pugh A: 5 or 6 points; Child-Pugh B: 7-9 points; Child-Pugh C: >9 points

Reference: Child CG, Turcotte JG (1964). Surgery and portal hypertension. In: The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders:50-64.