Investigational Drug Substance(s)	Durvalumab (MEDI4736) and tremelimumab
ClinicalTrials.gov	NCT03638141
Study Number	ESR-17-12965
Version Number	11.0
Date	August 21, 2024

The effect of CTLA-4/PD-L1 Blockade following drug-eluting bead transarterial chemoembolization (DEB-TACE) in patients with intermediate stage of HCC using Durvalumab (MEDI4736) and Tremelimumab

IND Sponsor: Ana De Jesus-Acosta

TITLE:

The effect of CTLA-4/PD-L1 Blockade following drug-eluting bead transarterial chemoembolization (DEB-TACE) in patients with intermediate stage of HCC using Durvalumab (MEDI4736) and Tremelimumab

Johns Hopkins #: J18118, IRB00179347
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Astra Zeneca Supplied Agent: Durvalumab
Tremelimumab

IND: 140414

IND Sponsor: Ana De Jesus-Acosta, M.D.

[redacted]

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Version 7.0 / December 29, 2021
Version 8.0 / May 10, 2022
Version 9.0 / September 1, 2022
Version 10.0 / February 16, 2023
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PROTOCOL SYNOPSIS

Clinical Protocol ESR-17-12965

Study Title: The effect of CTLA-4/PD-L1 Blockade following drug-eluting bead transarterial chemoembolization (DEB-TACE) in patients with intermediate stage of HCC using Durvalumab (MEDI4736) and Tremelimumab

Protocol Number: ESR-17-12965, J18118, IRB00179347

Clinical Phase: Phase II

Study Duration: 2 years

Investigational Product(s) and Reference Therapy:

Durvalumab (MEDI4736) will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration.
Tremelimumab will be supplied as a sterile solution for IV infusion, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL (with a nominal fill of 20 mL, accounting to 400 mg/vial) of tremelimumab, in an isotonic solution at pH 5.5.

Research Hypothesis

We hypothesize that the anti-tumor effect of PD-L1/CTLA-4 blockade therapy is potentiated by the local ischemic treatment of transarterial chemo-embolization (DEB-TACE) in HCC by triggering a TH1 pro-inflammatory signal. We hypothesize that there are immediate changes in the tumor microenvironment and T cell diversity in serum after DEB-TACE. Thus, we hypothesize that the combined treatment with DEB-TACE followed by PD-L1/CTLA-4 blockade will synergistically enhance anti-tumor response in patients with HCC, and result in increased objective response rate (ORR).

Objectives:

Primary Objectives:

1. To evaluate the objective response rate (ORR) of patients with intermediate stage HCC treated with CTLA-4 (Tremelimumab) and PD-L1 (Durvalumab) with transarterial chemoembolization (DEB-TACE), according to modified response evaluation criteria in solid tumors (mRECIST).

Secondary Objectives:

1. To assess the safety of combining DEB-TACE with durvalumab and tremelimumab in patients with intermediate stage HCC

Exploratory Objectives:

1. To evaluate progression-free survival (PFS) and 6-month PFS of combining durvalumab and tremelimumab with DEB-TACE.
2. To evaluate the tumor response of non-targeted lesion evaluated by objective response (mRECIST).
3. To evaluate a 2 year overall survival (OS) of combining durvalumab and tremelimumab with DEB-TACE

4. To determine the effect of combined immune checkpoint and DEB-TACE versus DEB-TACE only on tumor microenvironment by comparing pre- and post-treatment tissue samples and peripheral blood tumor biomarkers including T cell receptor repertoire, circulating tumor cells, and circulating tumor DNA.
5. To explore potential molecular determinants of response, progression, and disease stability using next generation sequencing, other sequencing techniques, and other biomarkers.

Study Design:

This is an open-label, single institution study of combination treatment of tremelimumab and durvalumab with trans-arterial chemoembolization with drug-eluting microsphere beads (DEB-TACE) in patients with intermediate stage HCC. The purpose of this study is to determine the safety and efficacy of durvalumab and tremelimumab in this population who are receiving DEB-TACE as standard of care. Patients who have intermediate stage HCC according to Barcelona Clinic Liver Cancer (BCLC) criteria, who are eligible for locoregional treatment with DEB-TACE will be enrolled. 20 HCC patients will undergo DEB-TACE, followed by durvalumab 1500mg q4weeks and tremelimumab 300mg once within 2 weeks. Patients will continue with durvalumab q4weeks until progression of disease or the end of study or maximum 13 cycles. Patients will have radiographic surveillance every 6-8 weeks from their last DEB-TACE, and if there is residual tumor that can be targeted, patients will receive repeat DEB-TACE.

All patients will have pre- and post-TACE biopsies during the first DEB-TACE treatment and post-immunotherapy infusion biopsy.

Patients who are clinically stable at an initial confirmed progression may continue to receive study treatment, after the first overall time point assessment of PD until PD is confirmed on a follow-up scan (confirmed PD) if they do not show any significant toxicities. Patients will get a confirmatory scan, following the assessment of PD, at the next scheduled visit. Patients that continue on study after an initial PD will continue to receive durvalumab and tremelimumab at the same dose and schedule as they were treated with initially.

In addition, we will have 20 patient data for patients with HCC from our institutional database as exact matched control based on age, gender, tumor stage and Child-pugh score. We will evaluate the objective response rate (ORR) in comparison to the study group, using McNemar paired-sample test.

Number of Centers: 1

Study Population: 20

Patients with intermediate stage HCC, defined by the Barcelona Clinic Liver Cancer (BCLC) stage B with compensated cirrhosis who would be eligible for liver-directed therapy (e.g. DEB-TACE) as standard treatment.

Inclusion Criteria:

- Patients with diagnosis of HCC either by high-resolution imaging (triple-phase CT or MRI) and/or by tumor biopsy.

- Patient is not on systemic treatment for HCC. Prior local therapy with TACE is allowed if treatment was more than 1 month prior to enrollment with evidence of viable HCC or recurrence. Patients who were on tyrosine-kinase inhibitors (sorafenib, regorafenib, lenvatinib) or other systemic treatments for HCC but considered non-responders or intolerant to treatment are allowed to participate.
- Age ≥18
- ECOG performance status 0-1
- Body weight >30 kg
- HCC meeting Barcelona Clinic Liver Cancer (BCLC) stage B (intermediate stage), with measurable lesions on CT or MRI and without extrahepatic spread. Patients with BCLC stage A not considered candidates for transplant or surgery at the time of enrollment can participate if committed to remain on study for 6 months prior to consideration for alternative local therapies.
- Disease that is technically amenable to DEB-TACE. At least 1 radiographically measurable lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT or MRI.
- Patients with Child Pugh score of A or early B (score ≤8) without clinical evidence of ascites. Trace or small amounts of radiographic ascites without associated peritoneal carcinomatosis may be approved by the Protocol Chair.
- Adequate end-organ function as manifested by
  a) Absolute neutrophil count of ≥ 1000/mm3
  b) Hemoglobin ≥9.0 g/dL
  c) platelets ≥ 75,000/mm3
  d) Creatinine ≤ 2.0 mg/dL or calculated creatinine clearance > 50mL/minute
  e) AST ALT ≤ 5 x ULN (pre-treatment value)
  f) Total bilirubin: If cirrhosis present: Part of Child Pugh requirement.
     If no cirrhosis present: total bilirubin ≤ 2 mg/dL
  g) Albumin ≥ 2.5 g/dL
  h) INR ≤ 1.8
- Negative urine or serum pregnancy test or evidence of post menopausal status (female patients only, post-menopausal status defined in protocol Section 4.1)
- Patient who is willing to get tumor biopsies per the study schedule.

Exclusion Criteria:

- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
- Participation in another clinical study with an last dose of investigational product ≤ 30 days prior to start of study treatment.
- Any concurrent anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization, monoclonal antibodies) or receipt of the last dose ≤30 days prior to start of study treatment (TACE). Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
- Patients with vascular invasion or extrahepatic tumor.

- Main portal vein tumor-related thrombosis present on imaging. Non-tumor related thrombosis is allowed.
- Uncontrolled hepatic encephalopathy at the time of enrollement.
- Ascites that require ongoing paracentesis, within 4 weeks prior to the first scheduled dose, to control symptoms.
- Any contraindications for embolization, including hepatofugal blood flow or portosystemic shunt.
- Patients with detectable HBV viral load without active anti-viral treatment.
  - Patients with positive HepB surface antigen (HBsAg) and/or HepB core antibodies (anti-HBc) with detectable HBV DNA (≥10 IU/mL or above the limit of detection per local lab standard) are permitted on study if they are being treated with antiviral therapy with evidence of HBV stabilization or signs of viral response prior to enrollment. Patients who test positive for anti-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 enrollment. (see Section 7.2.1 for additional on-study testing and anti-viral requirements)
- Any prior or concurrent malignancy or myeloproliferative disorder whose natural history or treatment has the potential to interfere with safety or efficacy assessment of this study's investigational drug.
- History of leptomeningeal carcinomatosis
- History of active primary immunodeficiency.
- Active infection including tuberculosis or human immunodeficiency virus.
- Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:
  - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
  - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.
- Active or prior documented GI bleeding due to ulcer or esophageal varices bleeding within 6 months of enrollment. Note: For patients with history of esophageal variceal bleeding or assessed as high risk for esophageal variceal by the treating investigator, adequate endoscopic therapy according to institutional standards is required for assessment of esophageal varices. History of bleeding from other causes adequately treated are allowed.
- Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
  - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
  - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
  - Steroids as a premedication for hypersensitivity reactions (e.g. CT scan premedication)

- Active or prior documented autoimmune or inflammatory disease (examples end exceptions listed in Section 4.1).
- Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after last dose of durvalumab or 180 days after last dose of durvalumab + tremelimumab combination therapy
- Patients with hypothyroidism (e.g., following Hashimoto syndrome) who are not stable on hormone replacement.
- Any chronic skin condition that require systemic therapy.
- History of allogenic organ transplantation.
- History of pericarditis, cardiomyopathy or current use of defibrillator.
- Patients with celiac disease not controlled by diet alone.
- Uncontrolled intercurrent illness (see list of examples in Section 4.1)
- Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
- Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
- Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.
- Patients who have received prior anti–PD-1, anti–PD-L1 or anti–CTLA-4 including durvalumab and tremelimumab.
- Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

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

Durvalumab 1500mg Q4W plus tremelimumab 300mg once via IV infusion, starting at 2 weeks after first DEB-TACE procedure. This will be followed by durvalumab monotherapy 1500 mg via IV infusion Q4W, until progression or unacceptable toxicity (maximum 13 doses/cycles).

Study Assessments and Criteria for Evaluation:

Safety Assessments:

To ensure that the combination is safe, the first six patients will be treated and observed for toxicity for 1 cycle before continuation with further accrual. If ≤ 1 limiting toxicity events occur in the first 6 patients, we will proceed with additional accrual to complete a total of 20 patients for the safety evaluation. If > 1 limiting toxicity events occur among the first 6 patients, then three additional patients will be enrolled (i.e. a total of 9 patients). If ≤ 2 limiting toxicity events occur in the 9 patients, we will proceed with additional accrual to complete a total of 20 patients for the safety assessment. If > 2 limiting toxicity events occur, we will pause the enrollment pending safety review.

Efficacy Assessments:

The primary endpoint is objective response using modified RECIST (mRECIST) criteria. The regimen would be considered of insufficient activity for further study if the response rate is 30%

or less, and the minimum required level of efficacy that would warrant further study with the proposed regimen is a 60% response rate.

Statistical Methods and Data Analysis:

The safety evaluation will be based on the safety population, which includes all patients who receive DEB-TACE and at least one dose of either durvalumab or tremelimumab. Frequency of toxicity and adverse events will be summarized by type and grade. Primary efficacy analysis of best overall response will be based on response-evaluable population, which includes all patients who receive DEB-TACE and both durvalumab and tremelimumab, and have baseline scan and at least one on treatment scan or die without on treatment scan. Objective response rate, defined as the percent of patients who have CR or PR per mRECIST, will be estimated along with 95% confidence interval. Kaplan-Meier curves will be used to characterize progression-free survival (PFS) and overall survival. PFS rate at 6 month will be estimated from the Kaplan-Meier curve.

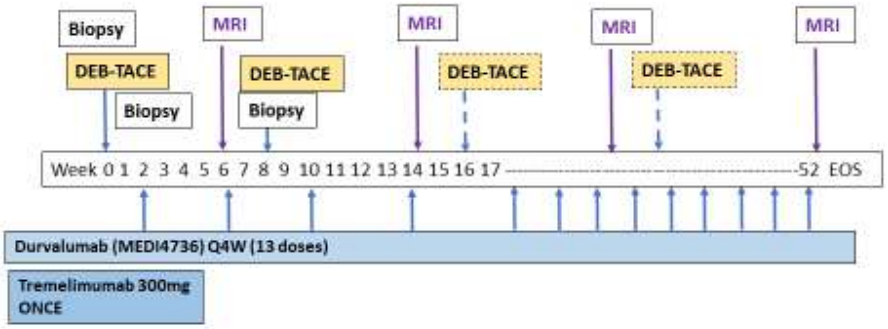
Objective response rate (ORR) from the exact matched control group (n=20) will be compared to the ORR of the study cohort using McNemar paired-sample test.

Sample Size Determination:

An optimal Simon two-stage design is planned. A total of 8 patients will be entered in the first stage. If ≤2 subjects respond, the treatment will be terminated and we will conclude the regimen is ineffective. If ≥3subjects respond, then additional 12 patients will be studied. If a total of 8 or fewer subjects respond in stage one and two combined, the regimen is considered ineffective. If a total of 9 or more respond, we conclude the regimen is promising and warrants further study. The maximum sample size will be 20 evaluable patients. To account for 10% unevaluable patients who do not receive durvalumab/tremelimumab following DEB-TACE, or do not have any on treatment scans for reasons other than death, we plan to enroll 22 patients.
This design provides 90% power to detect a 30% absolute increase in ORR, from 30% to 60%, with one-sided type I error 0.1. The chance of stopping early for lack of efficacy at the interim analysis is 0.55, if the response rate is 30%.

STUDY SCHEMA

Figure 1: Schema



20 patients with intermediate HCC (BCLC B) will receive TACE at week 0, then Immunocheckpoint blockade at week 2 (durvalumab 1500mg Q4week and tremelimumab 300mg once).
Patients with CR at week 15 will continue with repeat cycles of durvalumab.
Patients with PR or SD will receive repeat DEB-TACE (dashes) if there are targetable lesions, with ongoing durvalumab.
D: Durvalumab, T: Tremelimumab.

TABLE OF CONTENTS

PROTOCOL SYNOPSIS 3
STUDY SCHEMA 9
TABLE OF CONTENTS 10
LIST OF TABLES 13
LIST OF FIGURES 13
LIST OF APPENDICES 13
ABBREVIATIONS AND DEFINITION OF TERMS 14
1. INTRODUCTION 18
1.1 Disease background 18
1.1.1 Hepatocellular Carcinoma 18
1.1.2 Immunotherapies 18
1.1.3 Durvalumab 20
1.1.4 Tremelimumab 20
1.1.5 Durvalumab in combination with tremelimumab 20
1.2 Research hypothesis 21
1.3 Rationale for conducting this study 21
1.3.1 Hepatocellular Carcinoma (HCC) and Immune Checkpoint Inhibition 21
1.3.2 Rationale for patients with intermediate stage HCC 22
1.3.3 Justification for Viral Hepatitis and HCC 22
1.3.4 Justification for Tumor Biopsies 23
1.3.5 Durvalumab + tremelimumab combination therapy dose rationale 23
1.4 Benefit-risk and ethical assessment 26
1.4.1 Potential benefits 26
1.4.2 Overall risks 27
2. STUDY OBJECTIVE 30
2.1 Primary Objective 30
2.2 Secondary Objectives 30
2.3 Exploratory Objectives 30
3. STUDY DESIGN 31
4. PATIENT SELECTION, ENROLLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL 32
4.1 Inclusion criteria 32
4.2 Exclusion criteria 33
4.3 Withdrawal of patients from study treatment and/or study 36

4.4 Replacement of patients 37
5. INVESTIGATIONAL PRODUCT(S) 37
5.1 Durvalumab and tremelimumab 37
5.1.1 Formulation/packaging/storage 37
5.2 Dose and treatment regimens 38
5.2.1 Treatment regimens 38
5.2.2 Duration of treatment and criteria for retreatment 38
5.2.3 Study drug preparation of durvalumab and tremelimumab 39
5.2.4 Monitoring of dose administration 41
5.3 Specific procedure for DEB-TACE (Drug-eluting Bead Trans-arterial chemoembolization) 42
6. TREATMENT PLAN 42
6.1 Patient enrolment 42
6.1.1 Procedures for handling patients incorrectly enrolled 42
6.2 Dosage and administration 42
6.3 Definition of Unacceptable Toxicity 43
6.4 Dose modification and toxicity management 44
6.4.1 Durvalumab and tremelimumab 44
7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S) 46
7.1 Restrictions during the study 46
7.2 Concomitant treatment(s) 47
7.2.1 Antiviral Therapy for HBV+ Patients 48
7.2.2 Permitted concomitant medications 48
7.2.3 Excluded concomitant medications 49
8. STUDY PROCEDURES 50
8.1 Schedule of study procedures 50
8.1.1 Screening phase 50
8.1.2 Treatment phase 54
8.1.3 End of treatment 54
8.2 Description of study procedures 54
8.2.1 Medical history 54
8.2.2 Physical examination 54
8.2.3 MRI or CT 55
8.2.4 Electrocardiograms 55
8.2.5 Vital signs 55
8.2.6 Clinical laboratory tests 56
8.3 Biological sampling procedures 58
8.3.1 Biomarker sampling and evaluation methods 58
8.3.2 Tumor tissue sampling 59

8.3.3 PD-L1 Testing 59
8.3.4 Patient blood samples collected for correlative studies 60
8.3.5 Fresh tumor samples 60
8.3.6 Protocol Completion 60
8.3.7 Withdrawal of informed consent for donated biological samples 61
9. DISEASE EVALUATION AND METHODS 61
9.1 Measure of Objective Response 61
10. ASSESSMENT OF SAFETY 63
10.1 Safety parameters 63
10.1.1 Definition of adverse events 63
10.1.2 Definition of serious adverse events 64
10.1.3 Durvalumab + tremelimumab adverse events of special interest 64
10.2 Assessment of safety parameters 66
10.2.1 Assessment of severity 66
10.3 Recording of adverse events and serious adverse events 67
10.3.1 Study recording period and follow-up for adverse events and serious adverse events 68
10.3.2 Causality collection 68
10.3.3 Relationship to protocol procedures 68
10.3.4 Expectedness 69
10.3.5 Adverse events based on signs and symptoms 69
10.3.6 Adverse events based on examinations and tests 69
10.3.7 Hy's Law 69
10.3.8 Disease progression 70
10.3.9 New cancers 70
10.3.10 Deaths 70
10.3.11 Reporting of serious adverse events 70
10.3.12 Other events requiring reporting 72
11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION 74
11.1 Description of analysis sets 74
11.1.1 Safety analysis set 74
11.1.2 Efficacy analysis set 74
11.2 Methods of statistical analyses 74
11.2.1 Safety analyses 74
11.2.2 Efficacy analyses 74
11.2.3 Correlative analyses 75
11.2.4 Safety run-in 75
11.3 Determination of sample size 76
12. ETHICAL AND REGULATORY REQUIREMENTS 77
12.1 Ethical conduct of the study 77
13. STUDY MANAGEMENT 77

13.1 Monitoring of the study 77
14. DATA MANAGEMENT 77
14.1 Study governance and oversight 77
15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS 78
15.1 Identity of investigational product(s) 78
16. LIST OF REFERENCES 79

LIST OF TABLES

Table 1. Highly effective methods of contraception (<1% failure rate) 47
Table 2. Supportive medications 48
Table 3. Prohibited concomitant medications 49
Table 4. Clinical chemistry and other miscellaneous labs 57
Table 5. Hematology 57
Table 6. Urinalysis 57
Table 7. Blood, Urine, and Tissue to be obtained from each patient 60
Table 8. List of investigational products for this study 78

LIST OF FIGURES

Figure 1. Example of TACE on tumor microenvironment 22
Figure 2. Study Schedule 51

LIST OF APPENDICES

Appendix 1 - Dosing Modification and Toxicity Management Guidelines (TMGs) 83
Appendix 2. Durvalumab dose volume calculations 108
Appendix 3. Tremelimumab dose volume calculations 109

ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AFP	Alpha-feto protein
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BCLC	Barcelona Clinic Liver Cancer
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTC	Circulating tumor cell
ctDNA	Circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4

Abbreviation or special term	Explanation
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HCC	Hepatocellular carcinoma
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product

Abbreviation or special term	Explanation
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks

Abbreviation or special term	Explanation
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
DEB-TACE	Trans-arterial chemo-embolization
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

HCC is becoming the fastest growing cancer in the world, now becoming the second most frequent cause of cancer death worldwide (Jemal et al., 2011; National Cancer Institute, 2016). There is an estimated 748,300 new liver cancer cases annually with 39,230 new cases in the US alone in 2016. The rising incidence over the past 40 years in the US currently impose a high toll in morbidity, mortality and health care costs in the US and it is expected to continue to rise with the increasing prevalence of non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease. Despite the increased awareness for screening in people at risk for HCC, only 10-30% of the patients are diagnosed in early stage where curative treatments, such as resection or liver transplantation, are offered (Kudo, Okanoue, & Japan Society of, 2007). Thus, the majority of the patients are diagnosed in intermediate to advanced stages with unresectable cancer where the prognosis remains poor with the median survival of less than a year.

The *overall aim of this study* is to investigate the use of durvalumab and tremelimumab for patients with intermediate stage hepatocellular carcinoma (HCC) who will receive liver-directed treatment with trans-arterial chemoembolization (DEB-TACE). We hypothesize that the anti-tumor effect of PD-L1/CTLA-4 blockade therapy is potentiated by the local ischemic treatment of transarterial chemo-embolization (DEB-TACE) in HCC by triggering a TH1 pro-inflammatory signal. We will test the hypothesis that combined treatment with DEB-TACE followed by PD-L1/CTLA-4 blockade will synergistically enhance anti-tumor response in patients with HCC resulting in increased objective response rate (ORR). By applying this novel concept to this particular patient cohort with intermediate stage disease burden, this study can potentially expand the current use of immunotherapy to earlier stages of HCC, with the possibility of downstaging patients to curative treatments including resection and liver transplantation.

1.1 Disease background

1.1.1 Hepatocellular Carcinoma

To date, only sorafenib, approved in 2007 and regorafenib as a 2nd line treatment in 2016 have shown marginal benefit in those with advanced cancer. Notably, patients with *intermediate stage of HCC*, who account for approximately more than 50% of all who present with HCC, are not eligible for surgery or chemotherapy as sorafenib is only FDA approved for more advanced stage of HCC (BCLC stage C). Hence, they undergo liver-directed treatments such as trans-arterial chemo-embolization (DEB-TACE) or radio-embolization, as a palliative treatment (Zeng, Lv, & Mei, 2016). While this standard of care using DEB-TACE is widely prevalent and widely used in the community, survival at 2 years remain under 50%. There is an urgent need for improved therapy options in this large group of patients.

1.1.2 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, Old, & Schreiber, 2004). PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor and to CD80 (Butte, Keir, Phamduy, Sharpe, & Freeman, 2007). PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. (Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFNγ) and can be

found on both tumor cells (TC) and tumor infiltrating IC. The binding of PD L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC, and protecting the tumor from immune elimination. PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated (Butte et al., 2007; Paterson et al., 2011).

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.

In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism (Stewart et al., 2015).

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 JR, 2014; Brahmer et al., 2012; Hirano et al., 2005; Iwai et al., 2002; Okudaira et al., 2009; Topalian et al., 2012; C. 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 N, 2015; Segal NH, 2015). In addition, high mutational burden e.g., in bladder carcinoma (Alexandrov et al., 2013) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (Fife & Bluestone, 2008). Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell

lung cancer and urothelial carcinoma. In addition, data from agents in the anti-PD-1/PD-L1class shows clinical activity in a wide range of tumor types.

1.1.3 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ; Stewart et al. 2015).

As of the DCO date (12 July 2016), a total of 2878 patients have been exposed to 1or more doses of durvalumab in ongoing open-label AstraZeneca-or MedImmune-sponsored Phase I-III monotherapy and combination therapy studies across all indications. Details on the safety profile of durvalumab monotherapy are summarized in Section 6.3. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.4 Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood (Tarhini & Kirkwood, 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date tremelimumab has been given to more than 1000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.5 Durvalumab in combination with tremelimumab

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

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab

Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue. In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date more than 800 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in Sections 1.4.2. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

1.2 Research hypothesis

A. Anti-tumor effect of PD-L1/CTLA-4 blockade therapy is potentiated by local ischemic treatment of transarterial chemo-embolization (DEB-TACE) in HCC. Combined treatment with DEB-TACE followed by PD-L1/CTLA-4 blockade will synergistically enhance anti-tumor response in patients with HCC, measured by objective response rate.
B. Locoregional treatment with DEB-TACE in HCC influences T-cell immune response in the tumor microenvironment and changes in specific immune checkpoint pathway.
    - We aim to test this hypothesis by obtaining image-guided tumor biopsy at (1) baseline, (2) after 1st DEB-TACE and (3) after combined PD-L1/CTLA-4 blockade following DEB-TACE from patients.

1.3 Rationale for conducting this study

1.3.1 Hepatocellular Carcinoma (HCC) and Immune Checkpoint Inhibition

Immune checkpoint inhibitors have brought immunotherapy into the mainstream treatment of cancer and are revolutionizing cancer therapy. Anti-PD1 (programmed cell death protein 1) immunotherapy has shown benefit in a broad range of cancer types. In several retrospective series of Asian patients, PD-L1 and HLA class I expression in HCC was shown to be prognostic for OS and relapse free survival (Gao et al., 2009; Umemoto et al., 2015). Since PD-L1expression in tumors is associated with response to anti-PD-1 therapy (Topalian et al., 2012), we and others have hypothesized that PD-L1 blockade in patients with HCC may be an effective therapy. A recent clinical study of treatment with nivolumab, a monoclonal antibody against PD-1, in patients with advanced HCC (with Child-Pugh score ≤ 7) showed 20% objective response in this advanced stage group (El-Khoueiry et al., 2017). More importantly, the therapy was well tolerated and no patients had to be withdrawn because of treatment-related adverse events.

Accumulating evidence also suggest that pre-existing antitumor immune responses and immune checkpoint molecules such as programmed death-ligand (PD-L1) are closely related to anti-PD-L1 treatment efficacy. Furthermore, eliciting tumor-specific T-cell immune responses can potentiate current checkpoint inhibitor therapy. This was suggested in mice models with liver metastasis from colorectal cancer, where combined radiofrequency ablation and anti-PD1 treatment provided longer duration of tumor regression and survival than single treatment group (Shi et al., 2016). Additionally, CTLA-4 has an inhibitory effect of T cell activation, and blockade of its target ligand (B7) shows been shown to markedly enhance T cell activation and antitumor activity in animal models. Clinically, we know that liver-directed treatments such as DEB-TACE induce inflammatory response in patients, shown with rising cytokines levels and

other inflammatory markers including neutrophils and lymphocytes obtained from peripheral blood samples (Xue et al., 2015).

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1.3.3 Justification for Viral Hepatitis and HCC

Recent study on tremelimumab and HCC has shown that their subset of the patients who had hepatitis C (HCV) actually had a reduction of HCV viral load suggesting objective enhancements

of antiviral immunity. A significant and progressive decline in serum HCV viral load was observed (median values: baseline $3.78x10^5$ copies/ml vs. day 120 $3.02x10^4$ copies/ml, $P = .02$; vs. day 210 $1.69x10^3$ copies/ml, $P = .04$) with three patients demonstrated a complete viral response for the duration of the follow- up (Sangro B, 2013). There's also evidence that CTLA-4 blockade may have antiviral effect in hepatitis B (HBV). Studies have shown cases of antibody response against hepatitis B surface antigen (X. Wang et al., 2018). We will be enrolling patients who have HCC with background etiology of viral hepatitis (HBV and HCV), as well as non-viral hepatitis. Patients with chronic active hepatitis B will with detectable viral load will be recommended to be on anti-viral treatment at the time of the study. Those with viral hepatitis will have close monitoring of their viral hepatitis status with serial blood tests.

1.3.4 Justification for Tumor Biopsies

While immunotherapy, including PD-L1 blockade, demonstrated remarkable clinical impact in a number of different solid tumors, not all tumors and patients respond to the therapy. Overexpression of PD-L1 is has been demonstrated in many types of these cancers, and it has shown that the assessment of intratumoral PD-L1 expression through immunohistochemistry could predict anti-PD1 therapy response (Brahmer et al., 2010; Topalian et al., 2012). Therefore, it is important to obtain a baseline tissue sampling of the patients in this trial to understand if specific tumoral expression of immune checkpoint pathway can be used as a selection criteria for those with treatment response. Furthermore, while we have preclinical data to suggest immune-regulatory effects of radiation or hypoxic injury, there is no published data on humans in liver cancer. It is scientifically critical to obtain more information on the tumor microenvironment from baseline stage, after embolic treatment and finally after administration of immunotherapy proposed in this study. Also, biopsies will be combined with their scheduled transarterial chemo-embolization procedure with our interventional radiologists, which also decreases the potential risk of bleeding as artery to the tumor will be embolized and allow additional clinical monitoring. If the tumor is considered technically challenging for a biopsy or if there are additional risks to the biopsy procedure, the investigators will forgo the biopsy procedure.

1.3.5 Durvalumab + tremelimumab combination therapy dose rationale

The durvalumab + tremelimumab doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

1.3.5.1 Dose rationale for combination regimen of durvalumab 1500 mg Q4W plus tremelimumab 300 mg × 1 dose

A summary of the existing PK and pharmacodynamic data has been utilized to guide the regimen selection for the combination of durvalumab 1500 mg plus single dose of tremelimumab 300 mg.

Pharmacokinetics/pharmacodynamics data

The supporting data for this regimen are based on PK and pharmacodyamic data from regimens that used tremelimumab doses of greater than 1 mg/kg from Study D4190C00006. An

approximate dose-proportional increases in PK exposure (maximum serum concentration and area under the serum drug concentration-time curve from time 0 to Day 28 post-dose) was observed with increasing doses of tremelimumab (1, 3, and 10 mg/kg). An exploratory pharmacodynamic analysis bioanalytically evaluated the effects of tremelimumab on proliferating T-cells from NSCLC patients who received tremelimumab (1, 3, or 10 mg/kg) and durvalumab (15 or 20 mg/kg) combination treatment. Monotonic increases in pharmacodynamic activity with the combination (increased activation/ proliferation markers on CD4 and CD8 T-cells in periphery) were observed with increasing doses of tremelimumab (1, 3, 10 mg/kg). The peak increase (%) from baseline of CD4+Ki67+ T-cells was observed 8 days post administration, and the peak level was significantly increased ($p \leq 0.05$) as increasing dose of tremelimumab in the range of 1 to 10 mg/kg. Study data also suggested that higher peak exposure (maximum serum concentration [Cmax]) of tremelimumab is related to a higher maximum pharmacodynamic effect in the NSCLC patient population. Overall, the PK/pharmacodynamic data suggest that tremelimumab of dose greater than 1 mg/kg with a higher peak exposure may be associated with a higher pharmacodynamic effect. Additionally, based on simulation data, the Cmax (78 μg/mL) post single dose administration of tremelimumab 4 mg/kg is approximately 4-fold higher than the predicted Cmax (19 μg/mL) post the first dose of tremelimumab 1 mg/kg, and is 3-fold higher than the predicted Cmax (25 μg/mL) post the fourth dose of tremelimumab 1 mg/kg in a Q4W×4 doses setting.

Clinical data

The safety and preliminary efficacy of combination of durvalumab 1500 mg plus single dose of tremelimumab 300 mg in unresectable HCC population will be evaluated in the ongoing Phase I/II study (Study D4190C00022). No clinical data on this regimen is available at the time of drafting of this protocol.

In summary, a single dose of tremelimumab 4 mg/kg, while maintaining a similar overall exposure, has a 3- to 4-fold higher Cmax compared to the 4 doses of tremelimumab 1 mg/kg. Therefore, this single administration of the higher dose of tremelimumab may have the potential for better anti-tumor activity while potentially avoiding any cumulative toxicity associated with repeated dosing of the 1 mg/kg tremelimumab. Therefore, the regimen of durvalumab 1500 mg plus tremelimumab 300 mg×1 dose is being evaluated in the current study.

1.3.5.2 Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up (Sangro et al., 2013; Schadendorf et al., 2015).

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

Nivolumab (anti–PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for

melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis (Gettinger et al., 2015). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis (Topalian et al., 2014) MPDL3280a (anti–PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported (Wolchok et al., 2013).

Similar long term results may be expected with use of other immune-mediated cancer therapeutics including anti–CTLA-4 antibodies such as tremelimumab, anti–PD-L1 antibodies such as durvalumab, or the combination of the two.

The durvalumab + tremelimumab combination regimen will be administered for 4 doses Q4W followed by durvalumab monotherapy Q4W until disease progression, for up to a maximum further 8 doses unless other specific discontinuation criteria are met.

1.3.5.3 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.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses=0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) (E. Wang et al., 2014). Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 kg to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal, Roskos, & Robbie, 2013; Ng, Lum, Gimenez, Kelsey, & Allison, 2006; D. D. Wang, Zhang, Zhao, Men, & Parivar, 2009; S. Zhang, Shi, Li, Parivar, & Wang, 2012). 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(D. D. 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 (S. 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 and the pharmacodynamic data as summarized above, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and a fixed dose of 300mg tremelimumab once and a fixed dose of 1500 mg Q4W durvalumab and 75 mg tremelimumab Q4W(equivalent to 1mg/kg Q4W) is included in the current study.

1.4 Benefit-risk and ethical assessment

1.4.1 Potential benefits

1.4.1.1 Durvalumab + tremelimumab

It is hypothesized that durvalumab and tremelimumab may have a synergistic anti-tumor effect above what would be anticipated from their individual anti-tumor activity. We have seen in preclinical studies which show that combination therapy (dual targeting of PD-L1 and CTLA-4) has been shown in preclinical studies with a mouse model to cause tumor regression of

[redacted]

Other combinatorial trials using nivolumab (PD1 inhibitor) plus ipilimumab (CTLA-4) for stage III or IV measurable, unresectable melanoma have recently been reported with promising results. At the maximum tolerated combination dose—1mg/kg anti-PD1 plus 3 mg/kg ipilimumab every three weeks administered concurrently, 53% of patients had an objective response, all with tumor reduction of 80% or more. Adverse effects occurred in 53% of patients and were similar in quality and intensity to those observed with ipilimumab monotherapy. Sequential administration resulted in a lower response rate and lower toxicity rate.

1.4.1.2 DEB-TACE and Immunotherapy

Accumulating evidence also suggest that eliciting tumor-specific T-cell immune responses can potentiate current checkpoint inhibitor therapy. This was suggested in mice models with liver metastasis from colorectal cancer, where combined radiofrequency ablation and anti-PD1 treatment provided longer duration of tumor regression and survival than single treatment group (Shi L et al 2016). Additionally, CTLA-4 has an inhibitory effect of T cell activation, and blockade of its target ligand (B7) shows been shown to markedly enhance T cell activation and antitumor activity in animal models. Clinically, we know that liver-directed treatments such as DEB-TACE induce inflammatory response in patients, shown with rising cytokines levels and other inflammatory markers including neutrophils and lymphocytes obtained from peripheral blood samples (Xue et al. 2015)

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1.4.2 Overall risks

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 risks can include gastrointestinal AEs such as colitis and diarrhoea, pancreatitis, pneumonitis/interstitial lung disease (ILD), renal AEs such as nephritis and increases in creatinine, hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis, endocrinopathies such as hypo- and hyper-thyroidism, hyophysitis,adrenal insufficiency, diabetes mellitus type I and diabetes insipidus, and neurotoxicities such as myasthenia gravis and Guillain-Barre syndrome.

1.4.2.1 Durvalumab

Risks with durvalumab include diarrhea, colitis, pneumonitis /ILD, encephalitis endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus (which may present as diabetic ketoacidosis), diabetes insipidus, hypophysitis and adrenal insufficiency) hepatitis/hepatotoxicity/increases in transaminases, immune thrombocytopenia, neurotoxicities, nephritis/increases in creatinine, pancreatitis, rash/pruritus/dermatitis, myocarditis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, pemphigoid, subcutaneous injection site reaction, and immune complex disease.

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 (≥10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 8% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 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 toxicity (see the Dosing Modification and Toxicity Management Guidelines in Appendix 1.

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

1.4.2.2 Tremelimumab

Risks with tremelimumab monotherapy are GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase, other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; clinical manifestations of pancreatitis; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjögren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia Further information on these risks can be found in the current version of the tremelimumab IB.

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

1.4.2.3 Durvalumab + tremelimumab

The safety of durvalumab + tremelimumab combination therapy is being evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and has so far shown a manageable safety and tolerability profile.

The potential risks with the combination of durvalumab + tremelimumab are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006 and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these potential immune-mediated toxicities.

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥10% of patients) are fatigue, diarrhoea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anaemia, constipation, cough, abdominal pain, pyrexia, back pain, hyponatremia and rash.

Approximately 13% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 13% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

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

1.4.2.4 Overall benefit-risk of DEB-TACE with Durvalumab + tremelimumab

Currently we do not have effective systemic treatment recommendation for patients with intermediate HCC, who are often outside the criteria for surgical resection but also not indicated for the FDA approved sorafenib. 2 year overall survival ranges from 30-40% at best with median survival ranging from 11-20months. This is a large subset of patients with HCC who can benefit from targeted immunotherapy while receiving locoregional treatment with DEB-TACE as standard of care. If our hypothesis proves to be true with clear benefit of combinatorial treatment, this will also increase the possibilities for patients with intermediate stage HCC to have enough tumor burden reduction to undergo curative treatments, such as resection or liver transplantation.

For this proposal, we will select those with compensated liver disease, with Child-Pugh score less than 7 (early B). The risk of side effects has been reviewed, and to prevent serious complications, we have designed this study to assess early for any adverse effects.

2. STUDY OBJECTIVE

2.1 Primary Objective

- To evaluate the objective response rate (ORR) of patients with intermediate stage HCC treated with anti-CTLA-4 (Tremelimumab) and anti-PD-L1 (Durvalumab) with transarterial chemoembolization (DEB-TACE), according to modified response evaluation criteria in solid tumors (mRECIST).

2.2 Secondary Objectives

- To assess the safety of combining DEB-TACE with durvalumab and tremelimumab in patients with intermediate stage HCC.

2.3 Exploratory Objectives

- To evaluate progression-free survival (PFS) and 6-month PFS of patients treated with the combination of durvalumab and tremelimumab with DEB-TACE.

- To evaluate the tumor response of non-targeted lesion evaluated by objective response (mRECIST).

- To evaluate a 2 year overall survival (OS) of patients treated with the combination of durvalumab and tremelimumab with DEB-TACE

- To determine the effect of combined immune checkpoint and DEB-TACE versus DEB-TACE only on tumor microenvironment by comparing pre- and post-treatment tissue samples and peripheral blood tumor biomarkers including T cell receptor repertroire and circulating tumor cells/ circulating tumor DNA.

- To explore potential molecular determinants of response, progression, and disease stability using next generation sequencing, other sequencing techniques, and other biomarkers.

3. STUDY DESIGN

This is an open-label, single institution, single arm study of combination treatment of durvalumab and tremelimumab in patients with intermediate stage HCC (BCLC B) undergoing trans-arterial chemoembolization.

Patients will be recruited from the Johns Hopkins Multidisciplinary Liver Cancer Clinic, general liver clinic, inpatient admissions with newly diagnosed HCC, and direct referrals to Interventional Radiology for DEB-TACE treatment. Once their diagnosis and staging is confirmed in Liver radiology tumor board as intermediate stage, patients will be screened for enrollment.

Enrolled patients will proceed with DEB-TACE procedure along with pre-treatment biopsy of tumor and surrounding non-tumor tissue. Following their DEB-TACE procedure, patients will be followed in 7-10 days in hepatology clinic with labs for any new decompensating signs or symptoms. If the patient does not have any ongoing new decompensation, they will proceed with a 2nd biopsy, followed by 1st infusion of durvalumab 1500mg and tremelimumab 300mg 2 weeks after DEB-TACE. This will be followed by durvalumab 1500mg q4weeks until progression of disease, the end of study, or maximum 13 cycles.

All patients will receive repeat DEB-TACE every 8 weeks if there is residual tumor that can be targeted. A third biopsy will be done after 2 doses of durvalumab infusion during their second DEB-TACE procedure at week 8, unless the patient has CR.

Patients will have an MRI (or CT if contraindicated) at Week 6 and Week 14, then every 3 months unless additional DEB-TACE is needed. Patients who are clinically stable at initial disease progression may continue to receive study treatment until PD is confirmed on a follow-up scan (confirmed PD) if they do not show any significant toxicities. Patients will get a confirmatory scan, following the assessment of PD, at the next scheduled visit. Patients will continue to receive durvalumab and tremelimumab with the same dose and schedule as they were treated with initially.

Additionally, 20 patients from the institutional database will be selected as exact matched control based on age, gender, tumor stage and Child-Pugh score. We will evaluate the objective response rate (ORR) in comparison to the study group, using McNamer paired-sample test.

Considering approximately 3-5 new patients with HCC seen through our tumor board and multidisciplinary liver cancer clinic per week, with an average of 300-400 DEB-TACE cases per year, we expect to finish the enrolment in 12 months of time.

4. PATIENT SELECTION, ENROLLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all of the inclusion criteria (**Section 4.1**) and none of the exclusion criteria (**Section 4.2**) for this study. Under no circumstances will there be exceptions to this rule.

4.1 Inclusion criteria

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

1. Written informed consent and any locally-required authorization (e.g., HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the patient prior to performing any protocol-related procedures, including screening evaluations.

2. Age ≥18 years at time of study entry

3. Patients with diagnosis of HCC either by high-resolution imaging (triple-phase CT or MRI) and/or by tumor biopsy.

4. Patient is not on systemic treatment for diagnosis of HCC. Prior local therapy (eg.TACE, radioembolization, radiation) is allowed if treatment was more than 1 month prior to enrollment with evidence of viable HCC or recurrence. Patients who were on tyrosine-kinase inhibitors (sorafenib, regorafenib, lenvatinib) or other systemic treatments for HCC but considered non-responders or intolerant to treatment are allowed to participate.

5. HCC meeting Barcelona Clinic Liver Cancer (BCLC) stage B (intermediate stage), with measurable lesions on CT or MRI and without extrahepatic spread. Patients with BCLC stage A not considered candidates for transplant or surgery at the time of enrollment can participate if committed to remain on study for 6 months prior to consideration for alternative local therapies.

6. Disease that is technically amenable to DEB-TACE. Cases will be discussed with interventional radiology. At least 1 measurable lesion, that can be measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT or MRI.

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

8. Body weight >30kg

9. Child-Pugh Score of A or early B (score ≤8) without clinically significant ascites. Trace or small amounts of radiographic ascites without prior concern for malignant ascites or not associated with peritoneal carcinomatosis may be approved by the Protocol Chair.

10. Liver associated lab values:
    - AST ALT ≤ 5x ULN (pre-treatment)
    - Total bilirubin: If cirrhosis present: Part of Child Pugh requirement.

If no cirrhosis present: total bilirubin ≤ 2 mg/dL

11. Lab parameters to ensure adequate organ function (other than liver):
    - Absolute neutrophil count of ≥ 1,000/mm3
    - Hemoglobin ≥ 9.0g/dL
    - Platelets ≥ 75,000/mm3
    - Albumin ≥ 2.5 g/dL
    - INR ≤1.8 mg/dL
    - Creatinine ≤ 2.0 mg/dL or calculated creatinine clearance > 50mL/minute or Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

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

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

12. 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).

13. 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.

14. Patient who is willing to get tumor biopsies per the study schedule.

4.2 Exclusion criteria

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

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

2. Participation in another clinical study with last dose of an investigational product ≤ 30 days prior to start of study treatment.

3. Any concurrent anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumour embolization, monoclonal antibodies) or receipt of the last dose ≤30 days prior to start of study treatment (TACE). Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

4. Patients with vascular invasion or extrahepatic tumor.

5. Main portal vein tumor-related thrombosis present on imaging. Non-tumor related thrombosis is allowed.

6. Uncontrolled hepatic encephalopathy at time of enrollement.

7. Ascites that require ongoing paracentesis, within 4 weeks prior to the first scheduled dose, to control symptoms.

8. Any contraindications for embolization, including hepatofugal blood flow or portosystemic shunt.

9. Patients with detectable HBV viral load without active anti-viral treatment.
    - Patients with positive HepB surface antigen (HBsAg) and/or HepB core antibodies (anti-HBc) with detectable HBV DNA (≥10 IU/mL or above the limit of detection per local lab standard) are permitted on study if they are being treated with antiviral therapy with evidence of HBV stabilization or signs of viral response prior to enrollment. Patients who test positive for anti-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 enrollment. (See Section 7.2.1 for additional on-study testing and anti-viral requirements)

10. Any prior or concurrent malignancy or myeloproliferative disorder whose natural history or treatment has the potential to interfere with safety or efficacy assessment of this study's investigational drug
11. History of leptomeningeal carcinomatosis.

12. History of active primary immunodeficiency.

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

14. Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria:
    - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

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

15. Active or prior documented GI bleeding due to ulcer or esophageal varices bleeding within 6 months Note: For patients with history of esophageal variceal bleeding or assessed as high risk for esophageal variceal by the treating investigator, adequate endoscopic therapy according to institutional standards is required for assessment of esophageal varices. History of bleeding from other causes adequately treated are allowed.

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

17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

18. 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]).

19. Patients with hypothyroidism (e.g., following Hashimoto syndrome) who are not stable on hormone replacement.

20. Any chronic skin condition that require systemic therapy.

21. History of allogenic organ transplantation.

22. History of pericarditis, cardiomyopathy or current use of defibrillator.

23. Patients with celiac disease not controlled by diet alone.

24. 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.

25. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

26. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or180 days after the last dose of durvalumab + tremelimumab combination therapy.

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

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

29. Patients who have received prior anti–PD-1, anti–PD-L1 or anti–CTLA-4 including durvalumab and tremelimumab.

30. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

31. Procedures for withdrawal of incorrectly enrolled patients are presented in **Section 4.3.**

4.3 Withdrawal of patients from study treatment and/or study

Permanent discontinuation of Durvalumab and Tremelimumab

An individual patient will not receive any further investigational product if any of the following occur in the patient in question:

- An individual patient will not receive any further durvalumab + tremelimumab combination therapy or if their weight falls to 30kg or less
- An individual patient will not receive any further tremelimumab monotherapy if their weight falls to 35kg or less
- Withdrawal of consent
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
- Pregnancy or intent to become pregnant
- Any AE that meets criteria for discontinuation as defined in **Appendix 1**.
- Unacceptable toxicity (See **Section 6.5** for definition)
- Grade ≥3 infusion reaction
- Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmation of PD and investigator determination that the patient is no longer benefiting from treatment with durvalumab + tremelimumab. Patients who are permanently

discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment

- Patients who are permanently discontinued from receiving investigational product will be followed for safety per Section 10 and Study Schedule in Section 8, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the patient is lost to follow-up or enrolled in another clinical study. All patients will be followed for survival and information about subsequent cancer therapies. Patients who discontinue treatment without confirmed disease progression will continue to receive standard of care scans. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

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 (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

4.4 Replacement of patients

If a patient is lost to follow up after the first DEB-TACE or deemed not appropriate for further treatment with durvalumab or tremelimumab due to medical complications, patients will be replaced. If patients do not have treatment scans for reasons other than death, patients will be replaced.

5. INVESTIGATIONAL PRODUCT(S)

[redacted]

[redacted]

Tremelimumab

[redacted]

5.2 Dose and treatment regimens

5.2.1 Treatment regimens

All patients in this study will receive durvalumab and tremelimumab 2 weeks after initial DEB-TACE treatment. Patients will subsequently continue with their combination immunotherapy, while receiving DEB-TACE Q8W. Patients will only receive repeat DEB-TACE if there is residual tumor that can be targeted.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.2.3 Study drug preparation of durvalumab and tremelimumab

[redacted]

[redacted]

[redacted]

[redacted]

5.2.4 Monitoring of dose administration

[redacted]

[redacted]

5.3 Specific procedure for DEB-TACE (Drug-eluting Bead Trans-arterial chemoembolization)

For this study, patients will continue to receive DEB-TACE as standard of care. Patients undergoing trans-arterial chemoembolization are pre-medicated with analgesics, antibiotics and anti-emetics per clinical standards.

6. TREATMENT PLAN

6.1 Patient enrolment

6.1.1 Procedures for handling patients incorrectly enrolled

Patients who are incorrectly enrolled and do not meet the eligibility criteria, but are not yet initiated on treatment should be withdrawn from the study. The treating physician will determine subsequent treatment plans**.**

6.2 Dosage and administration

[redacted]

[redacted]

[redacted]

6.3 Definition of Unacceptable Toxicity

The combination of tremelimumab and durvalumab has been previously tested in a dose-escalation study performed by AstraZeneca employing dose ranges of 1-10mg/kg q4weeks (tremelimumab) and10-20mg/kg q2-4weeks (durvalumab). Patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical activity. This cohort had a lower number of treatment-related Grade ≥3 AEs or treatment related SAEs. No dose-limiting toxicities were reported. This is the dose level we will be administering for this study. Also, PK analysis indicated only minor impact of body weight (WT) on PK of both agents so to minimize errors and for ease of use the company have moved to a fixed-dose schedule of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1mg/kg Q4W).

Unacceptable toxicities will be evaluated from the time of first administration of durvalumab or tremelimumab until the Week 6 evaluation (prior to the second dose of durvalumab). Patients who do not remain on the study through the completion of this safety run-in period for reasons other than DLT will be replaced with another patient (see **Section 11.2.4** for details of safety run-in). Grading of unacceptable toxicities will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

An unacceptable toxicity will be defined as any toxicity occuring during the study that meets the criteria below. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be unacceptable toxicities:

- Any Grade 4 irAE
- Any ⩾Grade 3 colitis
- Any Grade 3 or 4 non-infectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ⩽Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ⩽Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN (other than the 1st week following DEB-TACE)
- Any Grade ≥ 3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.

- Any grade ≥ 2 myocarditis
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 dermatologic AEs that are considered mild in severity but only considered grade 3 because of >30% body surface involvement
- Diarrhea, nausea, or vomiting that resolves to < grade 3 within 24 hours of intervention
- Grade 3-4 hyperglycemia
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be an unacceptable toxicitiy regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days. Isolated Grade 3 amylase or lipase abnormalities that are not associated with clinical signs/symptoms or findings on imaging consistent with pancreatitis

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as an unacceptable toxicity.

6.4 Dose modification and toxicity management

6.4.1 Durvalumab and tremelimumab

[redacted]

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 1) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

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

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

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

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Table 1. Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

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

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

Blood donation

Patients should not donate blood while participating in this study.

7.2 Concomitant treatment(s)

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

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to **Section 6.4** for guidance on management of IP-related toxicities.

7.2.1 Antiviral Therapy for HBV+ Patients

Patients with HBV infection, characterized by positive hepB surface antigen (HBsAg) and/or HepB core antibodies (anti-HBc) 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 ≤2000 IU/mL) prior to enrollment. Patients must remain on antiviral therapy for the study duration and for 6 months after the last dose of study medication. These subjects will be tested at every cycle to monitor HBV DNA levels

Patients who test positive for anti-hepatitis B core (anti-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 enrollment. These subjects willbe 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.

7.2.2 Permitted concomitant medications

Table 2. 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 below	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
Inactivated viruses, such as those in the influenza vaccine	Permitted

7.2.3 Excluded concomitant medications

Table 3. Prohibited concomitant medications

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).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)

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

8. STUDY PROCEDURES

8.1 Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis

For all patients

- Tumor efficacy (modified RECIST) assessment dates are affected by dose delays as subsequent treatment with DEB-TACE will be delayed with the same interval change.
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc. required for dosing should be performed within 3 days prior to dosing.
- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible

8.1.1 Screening phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All patients must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, patients will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window. See **Figure 2** for all screening procedures.

Figure 2 : Study Schedule

Week	Pre-study (Day -28 to Day 0)	0	1	2 +/- 7d	6 +/- 7d	8 +/- 7d	9[a]	10 +/- 7d	14 +/- 7d	16 +/- 7d	17[a]	Weeks 18, 22, 26, 30, 34, 38, 42, 46, 50 +/- 7d	17-52	Time since last dose of Durvalumab				Q6 months +/- 2 wks
														EOT[o] 30 days +/- 7d	2 months +/- 7d	3 months +/- 7d	6, 9, 12 months +/- 2 wks	
TACE[a]		X				X[a]				X[a]			Q3months Hepatology visit starting **week 17**[e] Q3months MRI starting **week 14**					
Durvalumab				X	X			X	X			X						
Tremelimumab				X														
Informed Consent	X																	
Demographics	X																	
Medical history	X																	
Physical exam[b] and Vital signs[c]	X		X	X	X		X	X	X		X	X		X				
Concomitant Meds	X		X	X	X	X	X	X	X	X	X	X		X	X	X		
Adverse Event Evaluation[d]	X		X	X	X	X	X	X	X	X	X	X		X	X	X		
ECOG Performance Status	X		X	X	X		X	X	X		X	X		X	X	X		
Hepatology Visits			X				X			X	X							
Oncology Visits	X			X	X			X	X			X		X				
MRI / CT[e]	X				X				X			X[e]		X[e]				
ECG[f]	X			X														
Urinalysis[g]	X																	
CMP[h]	X			X	X	X		X	X	X		X		X	X	X		
CBC with differentials[h]	X			X	X	X		X	X	X		X		X	X	X		
PT, INR, PTT [h, i]	X			X	X	X		X	X	X		X		X				
Thyroid Panel [h, j]	X			X	X	X		X	X			X		X				
Creatinine clearance [h]	X																	
Magnesium[h]	X																	
Gamma-glutamyl transferase (GGT)[h]	X																	
Alpha-fetoprotein (AFP)[h]	X			X	X			X	X			X		X				
Amylase/Lipase[h]	X																	
LDH[h]	X																	
HBV, HCV, HIV[h, k]	X			X[k]	X[k]			X[k]	X[k]			X[k]		X				
HLA-A,B,C phenotyping	X																	

Urine hCG or serum βhCG [l]	X																	
Research Blood [m, p]		X		X		X								X				
Research urine [m, p]		X		X		X								X				
Liver Biopsies [p]		X		X		X												
Archival Tissue [q]	X																	
Subsequent anticancer therapy[n]														X	X	X	X	X
Survival Status[n]															X	X	X	X

In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

a. DEB-TACE will be repeated every 8 weeks as long as there is residual tumor that can be targeted after the first dose (we expect most patients will receive at least 2 doses, and more than 3 doses of DEB-TACE are possible). Patients with a complete response by mRECIST will stop DEB-TACE and continue the rest of the study regimen. When DEB-TACE will no longer be given, the entire DEB-TACE visit and evaluations (e.g. Week 16) and follow-up visit 1 week after the skipped DEB-TACE (e.g. Week 17) may be dropped.
b. Full physical examination at baseline; targeted physical examination at other time points
c. Patients will have their blood pressure and pulse measured before, during, and after the infusion at the following times (based on a 60-minute infusion):
   - At the beginning of the infusion (at 0 minutes)
   - At 30 minutes during the infusion (±5 minutes)
   - At the end of the infusion (at 60 minutes ±5 minutes)
d. for AEs/SAEs reported during prescreening additional information such as medical history and concomitant medications may be needed.
e. **Timing of MRI/CTscans:** Scans at baseline and Week 6 (+/- 7 days), then every 8 weeks (+/- 7 days) for the first 15 weeks, then every 3 months (-3/+1 weeks) unless repeat TACE is done. Scans may be done earlier if clinically indicated and subsequent scans should reset to every 3 months from this new scan date when possible. EOT tumor assessments do not need to be repeated if performed within 28 days of EOT visit. **For patients who have completed study treatment and achieved disease control**: tumor assessments should be performed every 8-12 weeks until confirmed PD by mRECIST by investigational site. **For patients who discontinue study treatment due to PD**: tumor assessments should be performed according to local clinical practive and may be submitted to investigational site for review (these are optional).
f. ECG during screening and at the Week 2 visit within 1hr prior to the start of the first study treatment. Thereafter as clinically indicated. Baseline and abnormal ECG at any time in triplicate, others single.
g. Urinalysis performed at Screening and as clinically indicated
h. Labs and research bloods may be done within 3 days of scheduled visits. Results for safety bloods must be available and reviewed before commencing an infusion.
i. Coagulation tests: prothrombin time done at each indicated visit., aPTT and INR only performed at Screening and as clinically indicated.
j. TSH only. Free T3 and free T4 will be measured if TSH is abnormal or if there is clinical suspicion of an adverse event related to the endocrine system.
k. Screening: HBV surface antigen (HBsAg), anti-HBV core antibody (anti-HBc), anti-HCV antibody, and HIV-1/2 Ab. HBV viral load if HBsAg and/or anti-HBc positive. Hepatitis serologies do not need to be repeated if done within 3m prior to enrollment. On Study Labs: HBV antigen and/or antibody positive patients allowed to participate per eligibility criteria will have HBV viral load monitored prior to each subsequent durvalumab treatment visit.
l. Pre-menopausal female patients of childbearing potential only
m. Approximately 40 ml of blood and 100 ml urine will be collected at 4 time points (Week 0, Week 2, Week 8, and at end of study. Blood and urine should be collected before any treatment.
n. Patients will be contacted for survival status and information about subsequent anticanter therapies (by phone, email, or visit) monthly for the first 3 months after last dose of study treatment, then every 3 months until 1 year, then every 6 months thereafter until study closes or patient withdraws from follow-up.
o. All required EOT procedures may be completed within ±7 days of the end of treatment visit (EOT). Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.
p. Research samples will be collected at the discretion of the PI based on availability of supplies and safety of patient and staff. If patient not deemed candidate for TACE on week 8, we will still collect biopsy, research blood/urine samples. These blood/urine samples can be obtained any time prior to or including at the next in person treatment visit. Biopsy should be obtained through IR at week 8 (+/-14 days).

q. Archival tissue samples may be collected if patient had a standard of care biopsy of tumor or non-tumor liver or other HCC metastatic sites (see section 8.3.2)

8.1.2 Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments.

Patients will be treated with DEB-TACE. Transarterial chemoembolization is percutaneous procedure performed under conscious sedation. (See **Section 5.3** for details). Following DEB-TACE, patients will have surveillance imaging at 7 weeks, and if there are viable tumor lesions that can be targeted by DEB-TACE (either SD or PR), patients will be scheduled for another procedure. We estimate that patients may receive upto 4 DEB-TACE treatments in 1 year time of the study.

From the time of first DEB-TACE, patients will receive their first combined immune checkpoint inhibition in 2 weeks, and continue with q4week cycle schedule as described in detail in **Section 3.1**.

8.1.3 End of treatment

End of treatment (EOT) visit is defined as approximately 30 days after the last dose of study treatment. All required procedures may be completed within ±7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for patients who have completed durvalumab and tremelimumab treatment are provided in the Study Schedule above.

All patients will be followed for survival and subsequent anti-cancer therapies until the end of the study regardless of further treatments.

8.2 Description of study procedures

8.2.1 Medical history

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

Physical examinations will be performed on study days noted in the Schedule of Assessments.

8.2.2 Physical examination

Physical examinations will be performed according to the assessment schedule. 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 10**.

8.2.3 MRI or CT

Patients will be recommended to have an MRI at week 6 following their first DEB-TACE date. If MRI is contraindicated for any medical reasons (e.g. history of metals in the body, severe claustrophobia), patients may have a CT scan (liver-dedicated CT). Tumor response will be assessed according to the modified RECIST criteria (mRECIST). mRECIST takes into account reduction in viable tumor using contrast-enhanced radiologic imaging rather than strict tumor size. Details of response measurement are under Section 9. If there is complete response at the 1st surveillance imaging, patients will continue with their monthly infusion with durvalumab and tremelimumab for total of 4 cycles, with repeat MRI as scheduled at week 14. If there's ongoing CR, they will have MRI monitoring every 3 months. For all other response after the 1st MRI, patients will get repeat DEB-TACE, along with scheduled immunotherapy treatment and scans per the study schedule.

8.2.4 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening, baseline 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. ECG during screening and at the Week 2 visit within 1 hr prior to the start of the first study treatment. Thereafter as clinically indicated. Baseline and abnormal ECG at any time in triplicate, others single..

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 10.3.1.

8.2.5 Vital signs

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

First infusion

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 in the I-O arms 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 and tremelimumab.

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. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

8.2.6 Clinical 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 **Table 2** through **Table 5**).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). 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 4** (clinical chemistry), **Table 5** (hematology), and

Table 6 (urinalysis).

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

The following laboratory variables will be measured:

Table 4. Clinical chemistry and other miscellaneous labs

Albumin Alkaline phosphatase[a] ALT[a] Amylase[b] AST[a] Bicarbonate[c] Bilirubin, total[a] Calcium Chloride[c] Creatinine Creatinine clearance[c] Gamma glutamyltransferase[c] Glucose Lactate dehydrogenase Lipase[b] Magnesium[c] TSH T3, free[d] T4, free[d]	[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin. [b] It is preferable that both amylase and lipase parameters are assessed. 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 screening, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated. [d] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system Abbreviations: ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid Stimulating Hormone

Table 5. Hematology

Absolute neutrophil count Hemoglobin Absolute lymphocyte count Platelet count	Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated

Table 6. Urinalysis

Urinalysis should be done at baseline (screening) and then as clinically indicated

Bilirubin Blood Color and appearance Glucose Ketones pH Protein Specific gravity	Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to **Appendix 1** for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of IP (see Study Schedule in Section 8).

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 10.3.6.

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.

8.3 Biological sampling procedures

8.3.1 Biomarker sampling and evaluation methods

Peripheral blood samples will be collected as per the study schedule. Samples will be processed for CTCs, and plasma for ctDNA analysis. All the samples will be stored in the Translational Research Enhancement Core of the Hopkins Conte GI Center.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.3.6 Protocol Completion

Following completion of this study, samples will remain in storage as described above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material. The PI will report destroyed samples to the IRB if samples become

unsalvageable because of environmental factors or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher.

8.3.7 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented.

All biological samples from that patient stored in our Core Center will be immediately identified, disposed of /destroyed, and the action documented. Furthermore, clinical or research data collected from the patient will also be destroyed from the database. We will notify both the patient and AstraZeneca.

9. DISEASE EVALUATION AND METHODS

9.1 Measure of Objective Response

Tumor response to treatment will be assessed by modified response evaluation criteria in solid tumors (mRECIST) which takes into account reduction in viable tumor using contrast-enhanced radiologic imaging rather than strict tumor size (Lencioni R, 2011). Conventional RECIST criteria can be misleading when applied to locoregional therapies in HCC and mRECIST adapted the concept of viable tumor-tumoral tissue showing uptake in arterial phase of contrast-enhanced radiologic imaging techniques. mRECIST has been adapted by the AASLD-JNCI (Journal of the National Cancer Institute) guidelines. The measurement of the longest diameter of the viable tumor may be challenging in lesions showing partial internal necrosis. Therefore, the measurement of the viable tumor should be performed on CT or MRI obtained in the arterial phase, when the contrast between viable vascularized tumor tissue and non-enhancing necrotic tissue is the highest. The longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured. The measurement of the viable tumor diameter should not include any major intervening areas of necrosis.

Assessment of Target Lesion Response: mRECIST Assessment for HCC Following the AASLD-JNCI Guideline
CR = Disappearance of any intratumoral arterial enhancement in all target lesions
PR = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD = Any cases that do not qualify for either partial response or progressive disease
PD = 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 treatment started

AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

As response to immunotherapy may be delayed compared to conventional chemotherapy, patients with PD will have confirmatory assessment after 4 weeks from the initial assessment of PD in the absence of clinically significant deterioration. Treatment with durvalumab + tremelimumab would continue between the initial assessment of progression and confirmation for progression. In addition, patients may continue to receive durvalumab + tremelimumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment until the next surveillance imaging.

Patients who have disease control following completion of 12 months of treatment or patients who are withdrawn from durvalumab + tremelimumab treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Study Schedule in Section 8Error! Reference source not found.).

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic mRECIST assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as mRECIST modified for confirmation of progression
- When scans are evaluated by Investigator and by BICR, to reduce informative censoring by Investigator assessments (Investigator assesses PD at a time-point earlier than does BICR).

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

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

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,
- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),
- And/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive PD's, the first PD by mRECIST and the second PD using the confirmation of progression criteria

(above). If the first PD by mRECIST is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

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

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

Following confirmed progression, patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the follow-up schedules of assessments.

Patients in the durvalumab + tremelimumab combination arm who complete 4 doses/dosing cycles (with clinical benefit per Investigator judgment) and subsequently have PD during treatment with durvalumab alone may restart combination treatment if they meet eligibility criteria for retreatment (see **Section 5.2.2**). Patients who restart treatment after PD must have a baseline tumor assessment within 28 days of restarting treatment with durvalumab + tremelimumab combination therapy; all further scans should occur every 8 weeks (±7 days) relative to the date of previous scheduled study scan until confirmed disease progression

10. ASSESSMENT OF SAFETY

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

10.1 Safety parameters

10.1.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

Laboratory abnormalities: Laboratory abnormalities present at the screening visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, all grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as AEs. A grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator (i.e. it induces clinical signs or symptoms or requires therapy).

10.1.2 Definition of 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 >24 hours
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the patient
- Is a pregnancy or pregnancy outcome of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, or stillbirth.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above:

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

Events **not** considered to be SAEs are hospitalizations for:

- Admissions as per protocol for a planned medical/surgical procedure or to facilitate a procedure.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy) .
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).
- Admissions for monitoring of treatment-related infusion reactions that do not otherwise meet the criteria for a SAE.

10.1.3 Durvalumab + tremelimumab adverse events of special interest

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

AESIs for durvalumab ±tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

AESIs observed with durvalumab ±tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminast increasses
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- 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
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see **Appendix 1**). These guidelines have been prepared by 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.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see **Appendix 1**) 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.

Saturation of peripheral oxygen (SpO2)

- Other items

When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:

- ILD Markers (KL-6, SP-D) and β-D-glucan
- Tumour markers: Particular tumour markers which are related to disease progression.
- Additional Clinical chemistry: CRP, LDH

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0.

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 10.1.2. 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.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded in RedCap database using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE (and SAE 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
- Description of the SAE

The grading scales found in the revised 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).

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.3.1 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab + tremelimumab).

During the course of the study all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

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.

10.3.2 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.”

A guide to the interpretation of the causality question is found in Appendix 1.

10.3.3 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.

10.3.4 Expectedness

Unexpected AE: An AE, which varies in nature, intensity or frequency from information on the investigational drug/agent provided in the product IB, package insert or safety reports. Any AE that is not included in the IB, package insert, safety reports or informed consent is considered "unexpected".

Expected (known) AE: An AE, which has been reported in the IB, package insert or safety reports. An AE is considered "expected", only if it is included in the IB document as a risk.

10.3.5 Adverse events based on signs and symptoms

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

10.3.6 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.

10.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. This precludes the week following DEB-TACE. Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.3.8 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.

10.3.9 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.

10.3.10 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 an SAE

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 eCRF. 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.

AstraZeneca/MedImmune retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

10.3.11 Reporting of serious adverse events

All SAEs (including deaths) occurring from time of signature of informed consent through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy will be collected and reported.

SAEs will be reported promptly to the IND Sponsor and AstraZeneca within 24 hours of initial notification of the SAE. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

SAE reports and any other relevant safety information are to be sent to:

[redacted]

A **cover page** should accompany the **SAE** form when submitting to AstraZeneca indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-17-12965)

- Sponsor must also indicate, either in the SAE report or the cover page, the **causality** of events **in relation to all study medications** and if the SAE is **related to disease progression**, as determined by the principal investigator.

10.3.11.1 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regard to the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up
- Death

As soon as relevant information is available, a follow-up SAE report will be submitted to the IND Sponsor and AstraZeneca.

10.3.11.2 Institutional Review Board (IRB)

All serious adverse events will be reported to the IRB per institutional standards. Upon receipt, follow-up information will be given to the IRB (as soon as relevant information is available) per institutional standards.

10.3.11.3 Food and Drug Administration (FDA)

All reporting to the FDA will be completed by the IND Sponsor.

Expedited IND Safety Reports

7 Calendar-Day Telephone or Fax Report:
The IND Sponsor is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the investigational agent. Such reports are to be telephoned or faxed (301-827-9796) to the FDA within 7 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

15 Calendar-Day Written Report:
The IND Sponsor is required to notify the FDA of any SAE that is unexpected and related to the investigational agent in a written IND Safety Report.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning

similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. Follow-up information will be submitted to the FDA as soon as relevant information is available.

IND Annual Reports

In accordance with the regulation 21 CFR § 312.33, the IND Sponsor shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the adverse events and progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.33 for a list of the elements required for the annual report. All IND annual reports will be submitted to the FDA by the IND Sponsor.

10.3.12 Other events requiring reporting

10.3.12.1 Overdose

Use of durvalumab or tremelimumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab or tremelimumab, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

10.3.12.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the IND Sponsor and AstraZeneca.

Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately, and the pregnancy should be reported to the IND Sponsor and AstraZeneca.

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.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab 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 durvalumab + tremelimumab 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.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

10.3.12.3 Medication Error

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

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

Medication error includes situations where an error:

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

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

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

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

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error

- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, the IND Sponsor and AstraZeneca should be notified within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 Safety analysis set

Safety analysis set includes all patients who receive any study treatment including DEB-TACE or at least one dose of either durvalumab or tremelimumab.

11.1.2 Efficacy analysis set

Evaluable population for objective response includes all patients who receive DEB-TACE and both of durvalumab/tremelimumab, and have baseline scan with measurable disease, and either have at least one on treatment scan or die without any on treatment scans.

11.2 Methods of statistical analyses

11.2.1 Safety analyses

Safety will be summarized by the percentage of patients with AEs, by type and grade according to NCI CTCAE version 5.0 and attribution. The analysis will be based on safety analysis set.

11.2.2 Efficacy analyses

The primary endpoint is objective response. Objective response rate, defined as the percent of patients with at least one visit response of CR or PR via mRECIST and will be based on the Evaluable Population.

As a secondary endpoint, the response of non-target lesions will be described. Other secondary efficacy endpoints include duration of response, 6-month progression-free survival , and overall survival (OS). Duration of response is defined as date of having CR or PR to the date of progression per mRECIST among the patients who have CR or PR. Progression free survival will be defined as the time from the date of start of the treatment until the documentation of disease progression according to mRECIST or death due to any cause, whichever occurs first. Patients who have not progressed or died at the time of the analysis will be censored at the time of the latest date of assessment from their last evaluable mRECIST assessment. Kaplan-Meier

curves will be used to characterize PFS and OS, and 6-month PFS will be estimated from Kaplan-Meier.

11.2.3 Correlative analyses

[redacted]

Genomic sequencing library construction, whole genome/exome sequencing, whole transcriptome sequencing, microbial sequencing, neoepitope prediction, mutation burden, and bioinformatic analysis may be performed either at an on-campus laboratory or at an off-campus sequencing service. All the samples will be de-identified before sending to any laboratory for sequencing. The FASTQ files, BAM files and VCF files will be generated and analyzed. Other sequencing assays may be performed on a subset of samples according to specific requirements of collaboration projects. Genomic sequencing data will be stored and computations conducted using a JH IT managed subscription of Azure.

11.2.4 Safety run-in

To ensure that the combination is safe, the first six patients will be treated and observed for toxicity for 1 cycle before continuation with further accrual. If ≤ 1 limiting toxicity events occur in the first 6 patients, we will proceed with additional accrual to complete a total of 20 patients for the safety evaluation. If >1 limiting toxicity events occur among the first 6 patients, then three additional patients will be enrolled (i.e. a total of 9 patients). If ≤ 2 limiting toxicity events occur in the 9 patients, we will proceed with additional accrual to complete a total of 20 patients for the safety evaluation. If > 2 limiting toxicity events occur, we will pause the enrollment pending safety review.

11.3 Determination of sample size

The standard of care treatment with DEB-TACE results in a objective response rate (ORR) of 30%. The regimen would be considered of insufficient activity for further study if the ORR is 30% or less, and the minimum required level of efficacy that would warrant further study with the proposed regimen is a 60% response rate. An optimal Simon two-stage design is planned. A total of 8 patients will be entered in the first stage. If ≤2 subjects respond, the treatment will be terminated and we will conclude the regimen is ineffective. If ≥3subjects respond, then additional 12 patients will be studied. If a total of 8 or fewer subjects respond in stage one and two combined, the regimen is considered ineffective. If a total of 9 or more respond, we conclude the regimen is promising and warrants further study. The maximum sample size will be 20 evaluable patients. To account for 10% unevaluable patients who do not receive durvalumab/tremelimumab following DEB-TACE, or do not have any on treatment scans for reasons other than death, we plan to enroll 22 patients.

This design provides 90% power to detect a 30% absolute increase in ORR, from 30% to 60%, with one-sided type I error 0.1. The chance of stopping early for lack of efficacy at the interim analysis is 0.55, if the response rate is 30%.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

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

13. STUDY MANAGEMENT

13.1 Monitoring of the study

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. All data will be collected in a timely manner and reviewed by the principal investigator or a co-principal investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB, and the Sponsor. The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator and co-PI will personally conduct and supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

14. DATA MANAGEMENT

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (RedCap) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with Johns Hopkins security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant. At the end of the study, data will be stored according to JHH and FDA Schedule regulations as applicable.

Loss or destruction of data: If there is a major breech in the protection of subject confidentiality and trial data, the IRB will be notified.

DATA SHARING PLANS De-identified human data generated in this research for future research in a NIH-funded or approved public repository at the time of publication or shortly thereafter.

14.1 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be

addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

15.1 Identity of investigational product(s)

Table 8. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	*50 mg/mL solution for infusion after dilution*	MedImmune
Tremelimumab	*20 mg/mL solution for infusion after dilution*	MedImmune

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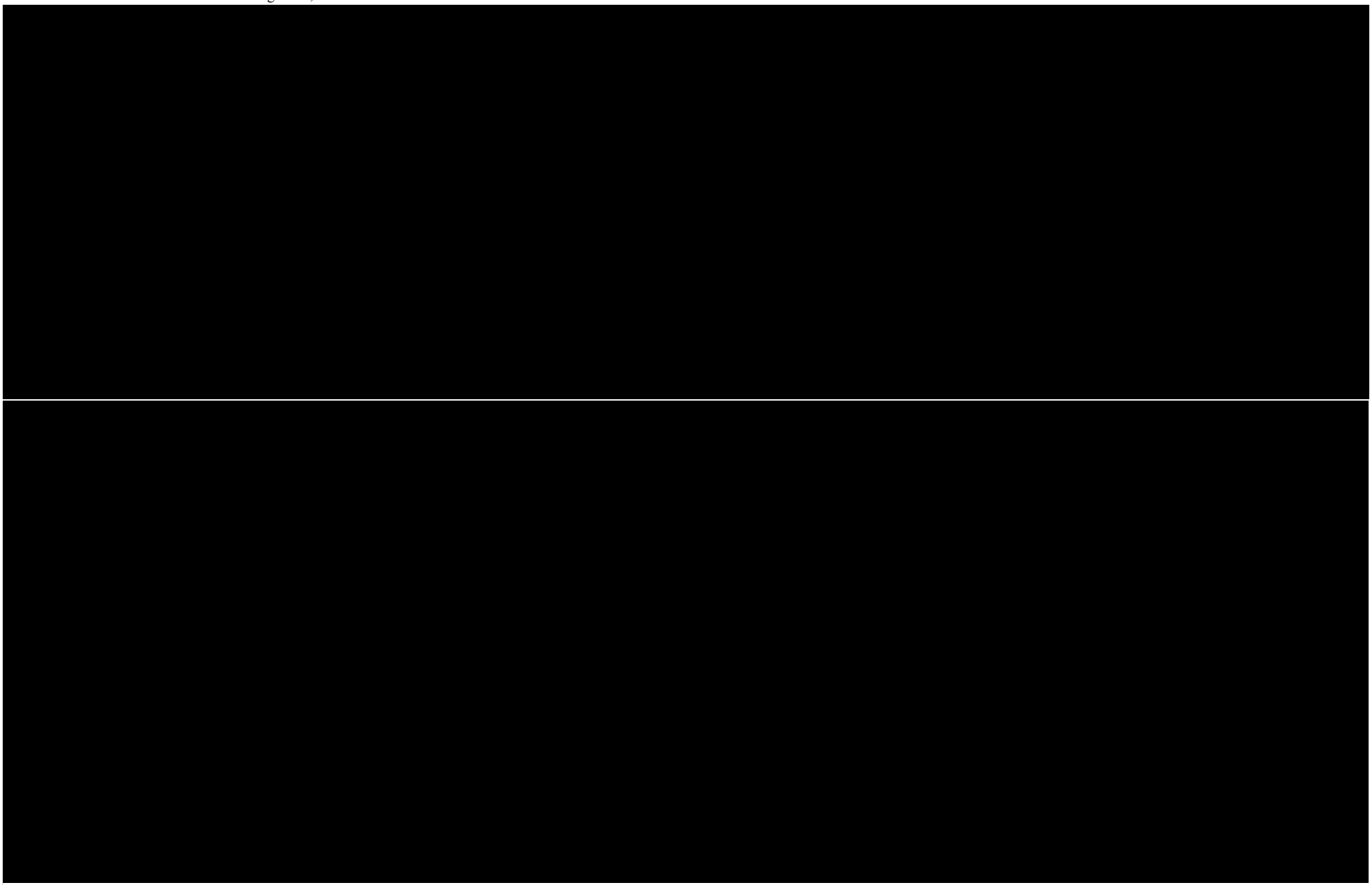

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Appendix 2. Durvalumab dose volume calculations

Example:

Appendix 3. Tremelimumab dose volume calculations

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Example:

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