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Investigational Drug Substance	Durvalumab (MEDI4736) and Yttrium-90 Microspheres
Protocol Number	ESR-18-13764 / D419DC00024
Version Number	2.0
Date	06 April 2021

A Single-arm, Open-label Pilot Study Evaluating Safety and Efficacy of Radioembolization with Yttrium-90 Microspheres in Combination with Durvalumab (MEDI4736) in Locally Advanced and Unresectable Hepatocellular Carcinoma (HCC) (SOLID)

Sponsor: Yoon Jun Kim

Investigational Product: Durvalumab (MEDI4736) and Yttrium-90 Microsphere (TheraSphere®)

Development Phase: Phase I/IIa

Version/Date: 2.0/06 April 2021

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I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki and local regulations (as applicable).

Principal Investigator

Prof. Yoon Jun Kim	Signature	Date

PROTOCOL SYNOPSIS

Clinical Protocol: ESR-18-13764 / D419DC00024

Study Title: A Single-arm, Open-label Pilot Study Evaluating Safety and Efficacy of Radioembolization with Yttrium-90 Microspheres in Combination with Durvalumab (MEDI4736) in Locally Advanced and Unresectable Hepatocellular Carcinoma (HCC) (SOLID)
Protocol Number: ESR-18-13764 / D419DC00024
Clinical Phase: Investigator-Initiated Study
Study Duration: 1) Patient recruitment period: approximately 12 months 2) Treatment and follow-up period: treatment i.e. transarterial radioembolization (TARE) up to 3 times + durvalumab until progressive disease (PD), and thereafter, follow-up for safety 30 days after radioembolization with yttrium-90 microspheres or the last dose of durvalumab
Investigational Product and Concomitant 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. TARE with yttrium-90 microspheres will be supplied per standard regimen.
Research Hypothesis The aim of this Phase 1/2a pilot study is to assess the safety and to analyze the tumor response of patients with locally advanced and unresectable HCC receiving combination treatment with durvalumab plus radioembolization with yttrium-90 microspheres.
Objectives: **Primary Objective:** The primary objective of this study is to evaluate time to progression (TTP) from enrolment using Modified Response Evaluation Criteria in Solid Tumors (mRECIST). **Secondary Objective(s)**: The secondary objectives of the study include evaluation of: - Overall Survival (OS) from first dose of study drug until the time of data cut-off, as determined by the Investigator. - The objective response rate (ORR) of the target lesion(s) and non-target lesion(s) at Week 8 and thereafter, every 8 weeks following radioembolization as evaluated by mRECIST - The safety of durvalumab until 30 days after radioembolization with yttrium-90 microspheres or the last dose of durvalumab, regardless of causality.

Exploratory Objectives: Biomarker Exploration

- Tumor tissues: To evaluate expression levels of PD-L1 and genomic analysis (tumor mutational burden) prior to treatment
- Plasma sample collection for future genomic analysis: Prior to the start of treatment, at Week 8 and at the time of PD

Study Design:

This is a single-arm, open-label study to analyze the tumor response of patients with locally advanced and unresectable HCC receiving combination treatment of durvalumab plus radioembolization with yttrium-90 microspheres.

Number of Centers: 1

Number of Patients: 24 planned

Study Population:

Patients with locally advanced and unresectable HCC.

Inclusion Criteria:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.
2. Male or female, aged ≥19 years at time of study entry.
3. Diagnosed with unequivocal HCC confirmed histologically or diagnosed radiologically according to American Association for the Study of Liver Diseases practice guideline.
4. Locally advanced HCC, defined as Barcelona clinic liver cancer (BCLC) staging intermediate (B) stage or BCLC advanced stage (C) without extrahepatic metastasis.
5. Must have at least 1 untreated measurable disease (untreated target lesion i.e. a viable lesion that has never been treated with locoregional treatment [transarterial chemoembolization {TACE}, TARE, percutaneous ethanol injection therapy, or radiofrequency ablation]).
6. Child-Pugh score ≤7 points.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Life expectancy of ≥12 weeks.
9. Body weight >30 kg.
10. Adequate normal organ and marrow function as defined below:
    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count (ANC) ≥1500 per mm^3
    - Platelet count ≥75,000 per mm^3
    - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). (This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with the Investigator).
    - Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT])/ alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) ≤5 x institutional ULN

- Measured creatinine clearance >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine CL:

Males:

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

Females:

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

11. Female patients must be either postmenopausal or, if premenopausal, must have a negative pregnancy test and agree to use 2 forms of contraception, if sexually active during their study participation.
    Male patients must be surgically sterile or, if sexually active and having a pre-menopausal female partner then, must be using an acceptable form of contraception.
    Adequate contraception allowed in this trial is as follows:
    - Hormonal contraceptives such as combined oral contraceptive pill
    - Intrauterine devices or the implantation of intrauterine system (IUS)
    - Blockage methods (spermicides and condoms/spermicides and vaginal diaphragm for contraception, vaginal sponges or cervical cap)
    - Sterilization surgery such as tubal ligation in females and vasectomy in males.
12. Evidence of postmenopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women <50 years of age would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    - Women ≥50 years of age would be considered postmenopausal if they have been amenorrhoeic 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.

Exclusion Criteria:

1. Eligible for potentially curative treatment (surgical resection, radiofrequency ablation or immediate liver transplantation).
2. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti- Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune pathways, including prior randomization or

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

3. History of organ transplantation or hematopoietic stem cell transplantation.
4. Any other concurrent malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, papillary thyroid cancer, early gastric cancer, or other cancer for which the patient has been disease-free for at least five years.
5. Evidence of extrahepatic metastasis, except for regional lymph node(s) involvement.
6. A history of a severe contrast allergy (i.e. anaphylaxis) not controlled with premedication.
7. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the investigational product (IP) or interpretation of patient safety or study results.
8. Participation in another clinical study with an IP during the last 8 weeks or 5 half-lives of the study drug, whichever is longer, prior to screening.
9. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
10. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) ≤1 cycle length or 14 days, whichever is longer, prior to the first dose of study drug. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as determined by the Investigator.
11. Any unresolved toxicity NCI-CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included at the discretion of the Investigator.
12. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
13. Prior hepatic radiation therapy including Total Body Irradiation (TBI) for HCC or other malignancy.
14. 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.
15. 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.]). The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with celiac disease controlled by diet alone
16. 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 adverse events (AEs) or compromise the ability of the patient to give written informed consent.

17. History of leptomeningeal carcinomatosis.
18. History of active primary immunodeficiency.
19. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), other than chronic infection of HBV or HCV.
20. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. 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., Computed tomography [CT] scan premedication)
21. 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.
22. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth from screening to 120 days after the last dose of durvalumab monotherapy.
23. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
24. 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.

Exclusion Criteria <u>Specific to</u> Radioembolization:

The screening angiogram and technetium-99m macroaggregated albumin (99mTc-MAA) scan (using Technescan or Pulmocis) are used to determine lobar liver volume from CT or MR images, to identify vascular shunting to the gastrointestinal (GI) tract requiring use of angiographic occlusion techniques and to determine the lung shunt fraction.

Patients who are ineligible to radioembolization meeting the following criteria will not be included in the study. <u>Additional patients will be screened to replace those patients.</u>

- Deposition of yttrium-90 microspheres to the GI tract that cannot be corrected by placement of the catheter distal to collateral vessels or the application of standard angiographic techniques, such as coil embolization to prevent deposition of yttrium-90 microspheres in the GI tract.
- Exposure of radiation to the lungs exceeds 30 Gray (Gy) for a single infusion or 50 Gy cumulative for all infusions of yttrium-90 microspheres.

Investigational Product, Dose and Mode of Administration:

The first 1500 mg IV dose of durvalumab will be administered 1−2 weeks (7 to 14 days) after the transarterial radioembolization (TARE) with yttrium-90 microspheres procedure.

Patients will receive 1500 mg durvalumab (MEDI4736) via IV infusion Q4W until confirmed PD, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

TARE with Yttrium-90 microspheres will be performed per standard practice, 2 weeks before the first dose of durvalumab is administered. Per Investigator decision, TC-99mMAA scan can be repeated after tumor biopsy and before TARE with Yttrium-90 microspheres. TARE may be repeated on-demand up

to 2 more times during the study (maximum of 3 doses). Considering potential overlapping toxicities, if additional TARE is performed, the interval between additional TARE treatments and administration of durvalumab should be at least 1 week.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

Targeted physical exam, vital signs, electrocardiogram (ECG) (as clinically indicated), clinical chemistry, hematology, prothrombin time (PT), thyroid-stimulating hormone (TSH) and ECOG performance status will be evaluated at each visit.

Efficacy Assessments:

Tumor evaluations (CT or MRI) will be performed at Week 8 ± 2 weeks and thereafter, every 8 weeks (Q8W ± 1 week) relative to date of enrolment until treatment discontinuation. This schedule of Q8W MUST be followed regardless of any delays in dosing.

Biomarker Exploration:

Evaluation of expression levels of PD-L1 and genomic analysis (tumor mutational burden) will be performed prior to treatment. Plasma samples will be collected prior to the treatment, at Week 8 ± 2 weeks and at the time of PD for future genomic analysis.

Statistical Methods and Data Analysis:

Demographic characteristics including age, gender, race, and ethnicity and other baseline characteristics including weight, height, ECOG performance, etc. will be summarized and listed.

Analyses will be performed using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and frequency and percentage for discrete variables. For the safety analysis, data will be presented for all patients.

The Kaplan-Meier method will be used to estimate survival times.

If statistical analysis is required, it will use SAS® v9.4 or higher (SAS Institute, Cary NC, USA) along with International Business Machines (IBM) Statistical Package for Social Sciences (SPSS), v24.0 or higher (SPSS Inc., Chicago, IL, USA) and R language, v3.4.2 or higher (R Foundation for Statistical Computing, Vienna, Austria).

Alternatively, statistical analysis can be managed by the institutional Medical Research Collaborating Center and/or other vendors.

Sample Size Determination:

No formal sample size calculations were performed. A pilot study of 24 patients, including initial 6 patients for safety assessment, will be conducted to obtain preliminary data on efficacy.

SCHEDULE OF STUDY ASSESSMENTS

Table 1: Schedule of assessments for combination treatment with durvalumab plus radioembolization with yttrium-90 microspheres

	Screening	W0	C1	C2	C3	C4	C5 to PD	End of Treatment (EoT) visit[q]	Safety Follow-Up	Survival Follow-Up[s]
Week	**-4 to -1**	**0**	**1 to 2**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**				**Week *X***		
Day	**-28 to -1**	**0**	**7 to 14[a]**	**Q28 days ±3 days unless dosing needs to be held for toxicity reasons**				**Day *X***	**30 days after last dose[r]**	**Every 3 months**
Informed Consent										
Informed consent: study procedures[b]	X									
Consent: genetic sample and analysis (optional)	X									
Study procedures										
Physical exam (full)	X								X	
Targeted physical exam (based on symptoms)			X	X	X	X	X	X		
Vital signs[c]	X		X	X	X	X	X	X	X	
ECG[d]	X		As clinically indicated					X	If clinically indicated	
Concomitant medications	X	<----------							---------->	

	Screening	W0	C1	C2	C3	C4	C5 to PD	End of Treatment (EoT) visit[q]	Safety Follow-Up	Survival Follow-Up[s]
Week	**-4 to -1**	**0**	**1 to 2**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**				**Week *X***		
Day	**-28 to -1**	**0**	**7 to 14[a]**	**Q28 days ±3 days unless dosing needs to be held for toxicity reasons**				**Day *X***	**30 days after last dose[r]**	**Every 3 months**
Demography, including baseline characteristics and tobacco use	X									
Eligibility criteria	X									
Laboratory Assessments										
Clinical chemistry[e]	X		X[f]	X	X	X	X	X	X[g]	
Hematology[e]	X		X[f]	X	X	X	X	X	X[g]	
Prothrombin Time (PT)	X		X	X	X	X	X	X	X[g]	
TSH[h], (reflex free T3 or free T4[i])	X		X	X	X	X	X	X	X[g]	
Hepatitis B and C and HIV	X									
Pregnancy test[j]	X		X	X	X	X	X	X		
Urinalysis	X								X[g]	
Monitoring										
ECOG performance status	X		X	X	X	X	X	X	X	
AE/SAE assessment [k]	X	←----------							X	
Follow-up contact for OS										Every 3 months

	Screening	W0	C1	C2	C3	C4	C5 to PD	End of Treatment (EoT) visit[q]	Safety Follow-Up	Survival Follow-Up[s]
Week	**-4 to -1**	**0**	**1 to 2**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**				**Week *X***		
Day	**-28 to -1**	**0**	**7 to 14[a]**	**Q28 days ±3 days unless dosing needs to be held for toxicity reasons**				**Day *X***	**30 days after last dose[r]**	**Every 3 months**
Treatment administration										
TARE with Yttrium-90 Microspheres[l]		X	Per Investigator discretion, on-demand up to 2 more times							
Durvalumab [m]			X	X	X	X	X			
Other assessments and assays										
Plasma sample collection	X				X (Week 8[n])		X (at time of PD)			
Plasma sample for disease-specific tumor markers	X		Tumor marker test will be done at every tumor assessment.							
Tumor biopsy (newly acquired or archival ≤3 years old)[a] (archival, if available, for patients who submit a newly acquired biopsy at screening for PD-L1 status and genomic analysis [tumor mutational burden])	X									
Efficacy evaluations										

	Screening	W0	C1	C2	C3	C4	C5 to PD	End of Treatment (EoT) visit[q]	Safety Follow-Up	Survival Follow-Up[s]
Week	**-4 to -1**	**0**	**1 to 2**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**				**Week *X***		
Day	**-28 to -1**	**0**	**7 to 14[a]**	**Q28 days ±3 days unless dosing needs to be held for toxicity reasons**				**Day *X***	**30 days after last dose[r]**	**Every 3 months**
Tumor evaluation (CT or MRI) (mRECIST) [o,p]	X		The first tumor evaluation will be conducted at Week 8 ± 2 weeks. Thereafter Q8W ± 1w (relative to the date of enrollment), until confirmed objective PD/death (whichever comes first) or treatment discontinuation.							

Abbreviations: AE: adverse event; CT: computed tomography; ctDNA: circulating tumor deoxyribonucleic acid; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EoT: End of Treatment; HIV: human immunodeficiency virus; LFT: liver function test; MRI: magnetic resonance imaging; OS: overall survival; PD: progressive disease; PD-L1: programmed death-ligand 1; Q28days: every 28 days; Q4W: every 4 weeks; Q8W: every 8 weeks; mRECIST: modified response evaluation criteria in solid tumors; SAE: serious adverse event; TARE: transarterial radioembolization; TSH: thyroid-stimulating hormone.

[a] Every effort should be made to minimize the time between enrollment and starting treatment. (i.e. within 1 day of enrollment). Fresh tumor biopsy will be required, subject to patient consent, if no archival tissue is available. Instances where a patient does not provide consent and a fresh tumor sample or biopsy is not taken, will not be considered a protocol deviation.

[b] Informed consent of study procedures may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to initiating study procedures. The collection of tumor biopsies at the time of progression prior to retreatment is required (subject to patient consent); the Investigator must consult with the Study Physician if such sampling is not feasible. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of enrollment.

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

[d] Any clinically significant abnormalities detected (including QTcF >470 ms) require triplicate ECG results. Patient must be in supine position for at least 5 minutes prior to ECG recording.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[f] If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

[g] For safety follow-up, clinical laboratory tests are to be performed as per clinical opinion.

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

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

[j] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then Q4W. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

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

[l] TARE may be repeated on-demand up to 2 more times during the study (total of 3 procedures). Interval between additional TARE treatments and administration of durvalumab should be at least 1 week.

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

[n] Week 8 plasma sample collection to be conducted within ± 2 weeks of Week 8.

[o] mRECIST assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of enrollment and, ideally, should be performed as close as possible to and prior to the start of IP. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

[p] Patients will have scans done Q8W (relative to the date of enrollment) until treatment discontinuation.

[q] Refer to Section 3 for details of treatment and study discontinuation criteria. If the date of confirmation of progression is over 30 days after the last dose, procedures performed at the Safety Follow-Up visit should be performed at the EoT visit.

[r] 30 days after radioembolization with yttrium-90 microspheres or the last dose of durvalumab.

[s] All patients will be followed up for OS telephonically until study is complete, as determined by the Investigator.

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

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ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACTH	Adrenocorticotropic hormone
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
AUCss	Area Under the Concentration-Time Curve At Steady State
BCLC	Barcelona Clinic Liver Cancer staging
CD80	Cluster of Differentiation 80
CI	Confidence Interval
C_{max}	Peak Concentration
CR	Complete Response
CRF	Case Report Forms
CT	Computed Tomography
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DC	Disease Control
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCC	Hepatocellular Carcinoma
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IgG1	Immunoglobulin G1
IgG1κ	Immunoglobulin G1 Kappa Subclass
IgG2	Immunoglobulin G2
IGSF	Immunoglobulin Superfamily
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
imAE	Immune-Mediated Adverse Event
I-O	Immuno-oncology
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent-to-treat
IUS	Intrauterine System
IV	Intravenous(ly)

Abbreviation or special term	Explanation
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic Acid
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OLT	Orthotopic Liver Transplantation
OR	Objective Response
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
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PP	Per-protocol
PR	Partial Response
PRS	Post-Radioembolization Syndrome
PVC	Polyvinyl Chloride
PT	Prothrombin time
Q2W	Every 2 Weeks
Q3M	Every 3 Months
Q3W	Every 3 Weeks

Abbreviation or special term	**Explanation**
Q4W	Every 4 Weeks
Q8W	Every 8 Weeks
Q12W	Every 12 Weeks
QoL	Quality of Life
QTc	Time between the start of the Q wave and the end of the T wave Corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
sPD-L1	Soluble Programmed Cell Death-Ligand 1
SOP	Standard Operating Procedure
SPO_2	Saturation of peripheral oxygen
SPSS	Statistical Package for Social Sciences
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	Half-Life
TACE	Transarterial Chemoembolization
TARE	Transarterial Radioembolization
TBL	Total bilirubin
Tc-99m MAA	Technetium ^{99m}Tc Macro Aggregated Albumin
TEAE	Treatment-Emergent Adverse Event
TIL	Tumor Infiltrating Lymphocyte
T_{max}	Time to Peak Concentration
$T_{max,ss}$	Time to Peak Concentration at Steady State

Abbreviation or special term	**Explanation**
TNF-α	Tumor Necrosis Factor Alpha
TSH	Thyroid-Stimulating Hormone
TTP	Time to Progression
ULN	Upper Limit of Normal
USA	United States of America
WT	Body Weight

1. INTRODUCTION

Durvalumab, an anti-programmed cell death-ligand 1 (anti-PD-L1) antibody, is being developed as a potential anticancer therapy for patients with solid tumors and hematological malignancies. On May 1, 2017, the United States (US) Food and Drug Administration (FDA) granted accelerated approval to durvalumab (IMFINZI, AstraZeneca UK Limited) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (FDA, 2017). Durvalumab is a human immunoglobulin G1 (IgG1) kappa subclass (IgG1κ) monoclonal antibody (mAb) selected from a panel of hybridomas secreting human antibodies recognizing human PD-L1. Durvalumab is composed of two identical heavy chains and two identical light chains, with an overall molecular weight of approximately 149 kilodalton. The antibody-coding deoxyribonucleic acid (DNA) sequence was recovered from a selected hybridoma and engineered by recombinant DNA technology to introduce a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein complement component 1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function (Oganesyan et al. 2008). Functional binding properties of the modified antibody were confirmed. An expression plasmid was prepared for durvalumab production in Chinese hamster ovary cells. Durvalumab is selective for human PD-L1 and blocks the binding of human PD-L1 to the human programmed cell death 1 (PD-1) and cluster of differentiation 80 (CD80) (B7.1) receptors.

1.1 Disease Background

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy and is a leading cause of cancer-related death worldwide. Despite advances in prevention techniques, screening, and new technologies in both diagnosis and treatment, incidence and mortality continue to rise. Cirrhosis remains the most important risk factor for the development of HCC regardless of etiology. Diagnosis is confirmed without pathologic confirmation. Screening includes both radiologic tests, such as ultrasound, computerized tomography, and magnetic resonance imaging, and serological markers such as α-fetoprotein at 6-month intervals. Multiple treatment modalities exist; however, only orthotopic liver transplantation (OLT) or surgical resection is curative. Additional treatment modalities include transarterial chemoembolization (TACE), radiofrequency ablation, microwave ablation, percutaneous ethanol injection, cryoablation, radiation therapy, systemic chemotherapy, and molecularly targeted therapies. Selection of a treatment modality is based on tumor size, location, extrahepatic spread, and underlying liver function. HCC is an aggressive cancer that occurs in the setting of cirrhosis and commonly presents in advanced stages. Continued improvement in both surgical and nonsurgical approaches has demonstrated significant benefits in overall survival (OS). While OLT remains the only curative surgical procedure, the shortage of available organs precludes this therapy for many patients with HCC (Balogh J, et al. 2016).

The implementation of surveillance programs for HCC in high-risk populations has increased early detection of HCC and the chance of curative treatment. However, the majority of patients is still diagnosed at an unresectable stage of disease and is not candidate for surgical interventions. Sorafenib, a multikinase inhibitor, is the first effective systemic therapy and the only approved treatment as first-line therapy for advanced HCC, with median survival ranging from 6.5 to 10.7 months (Figure 1). Although sorafenib was shown to improve OS and time to progression (TTP), patients treated with sorafenib suffer from various adverse events (AEs) and the therapeutic benefit is limited. While several targeted agents including brivanib and linifanib were tested in clinical trials, those failed to verify the superiority or non-inferiority to sorafenib (Johnson et al. 2013 and Cainap et al. 2015).

1.2 Durvalumab Background/Non-Clinical and Clinical Experience

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure (IB, 2017).

Durvalumab is a human mAb of the IgG1κ that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al. 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al. 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

Durvalumab is approved for the treatment of patients with unresectable stage 3 non-small cell lung cancer following concurrent platinum-containing chemotherapy and radiation therapy, and patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy (FDA, 2017). The total post-marketing exposure to durvalumab from May 2017 to the 12 July 2017 was estimated to be approximately 1.46 patient-years. To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 5 and Section 6.5 of the current durvalumab IB (IB, 2017). Refer to the current durvalumab for a

complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics (IB, 2017).

1.3 Research Hypothesis

The aim of the present Phase 1/2a pilot study is to assess the safety and to analyze the tumor response of patients with locally advanced and unresectable HCC receiving combination treatment with durvalumab plus radioembolization with yttrium-90 microspheres.

1.4 Rationale for Conducting this Study

1.4.1 Durvalumab Monotherapy Dose Rationale

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

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W and 15 mg/kg Q3W (dose-escalation), 10mg/kgQ2W (dose-expansion), and 20 mg/kg Q4W (dose-exploration), durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (for further information on immunogenicity, please see the IB, 2017).

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

exposure in case of anti-drug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab for a complete summary of clinical information at the 20mg/kg Q4W regimen (IB, 2017).

1.4.2 Rationale for Fixed Dosing

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

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

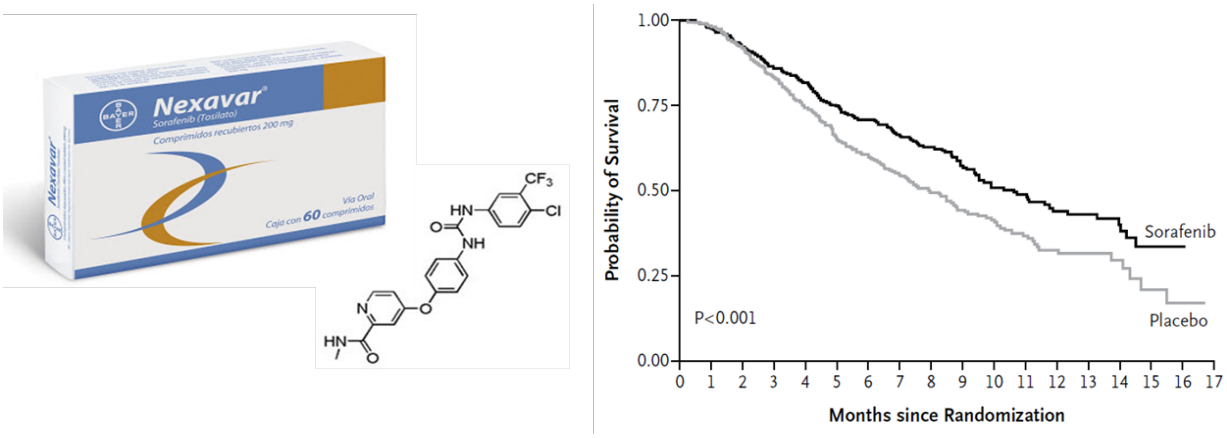
A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500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

1.4.3 Unmet Clinical Needs in the Treatment of Advanced HCC

The implementation of surveillance programs for HCC in high-risk populations has increased early detection of HCC and the chance of curative treatment. However, the majority of patients is still

diagnosed at an unresectable stage of disease and is not candidate for surgical interventions. Sorafenib, a multikinase inhibitor, is the first effective systemic therapy and had been the only approved treatment as first-line therapy for advanced HCC before approval of lenvatinib, with median survival ranging from 6.5 to 10.7 months (Figure 1). Although sorafenib was shown to improve OS and TTP, patients treated with sorafenib suffer from various AEs and the therapeutic benefit is limited. While several targeted agents including brivanib and linifanib were tested in clinical trials, those failed to verify the superiority or non-inferiority to sorafenib (Johnson et al. 2013 and Cainap et al. 2015).

Figure 1 Sorafenib response in advanced HCC

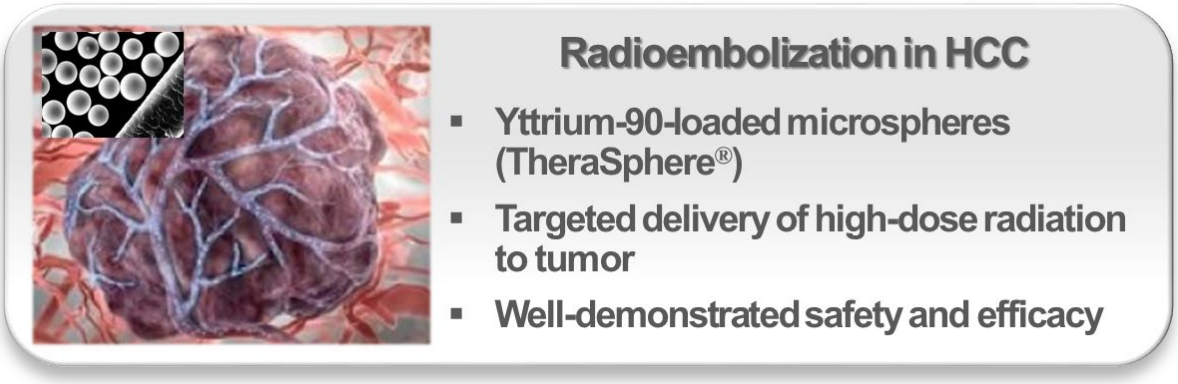


Sorafenib showed survival benefit in advanced HCC patients; however, the survival gain was limited (Llovet and Ricci et al. 2008).

Recently, immunotherapy using immune checkpoint blockade has emerged as the most promising treatment for advanced HCC. Treatment with nivolumab, an anti-PD-1 mAb, elicited promising objective response rate (ORR) of 20% and disease control rate (DCR) of 64% in patients with advanced HCC (El-Khoueiry et al, 2017). Although the response rates were better compared to sorafenib, the tumor response is still unsatisfactory. To improve the therapeutic effect, combination therapy with locoregional treatment plus immune checkpoint inhibitor is worthy of investigation.

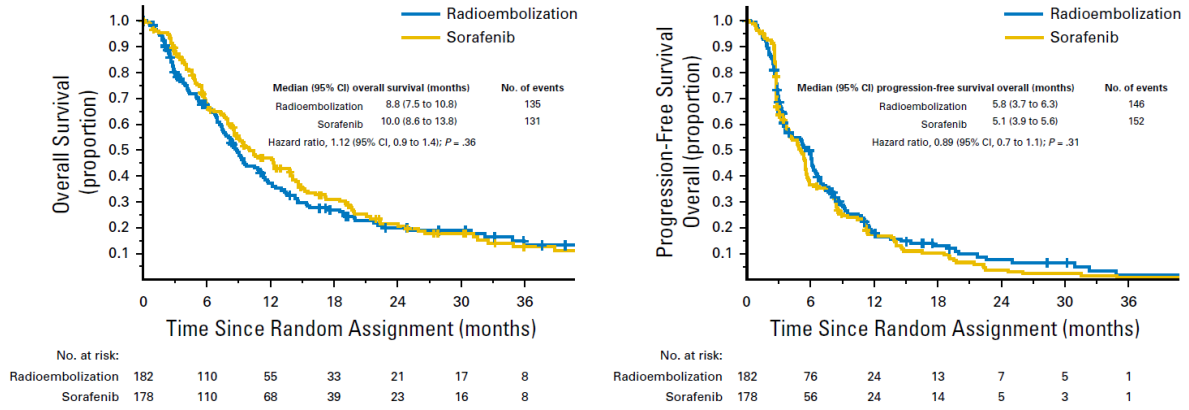
Radioembolization with yttrium-90 is preferred to conventional TACE (cTACE) especially in locally advanced HCC patients with portal vein thrombosis (Figure 2). Radioembolization with yttrium-90 is a therapeutic procedure applied via the hepatic artery, allowing targeted delivery of high-dose radiation to liver tumors. The small size of the microspheres loaded with yttrium-90 together with the short penetration of radiation into tissues increases tumor targeting while sparing the liver parenchyma. Growing evidence supports the efficacy of radioembolization in intermediate-stage and advanced-stage HCC.

Figure 2 Strengths of Radioembolization with Yttrium-90 in HCC



Recently, radioembolization with yttrium-90 showed non-inferior OS compared to sorafenib in patients with locally advanced HCC (Figure 3). Although 30.8% of patients in the radioembolization group of the study were accompanied by portal vein thrombosis, significantly fewer patients in the radioembolization than sorafenib group had Grade ≥3 AEs.

Figure 3 Radioembolization with Yttrium-90 and Sorafenib in locally advanced HCC



Chow et al. 2018

The aim of our study is to evaluate the efficacy and safety of combination treatment with durvalumab plus radioembolization with yttrium-90 microspheres in patients with locally advanced and unresectable HCC.

1.5 Benefit/Risk and Ethical Assessment

Monoclonal antibodies (mAbs) directed against immune checkpoint proteins, such as programmed cell death-ligand 1 (PD-L1) as well as those directed against PD-1 or cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

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

Risks associated with transarterial radioembolization (TARE) include post-radioembolization syndrome (PRS) which includes fatigue, nausea/vomiting, abdominal pain/discomfort, and/or cachexia. Other complications may result from improper microsphere deposition or radioactivity to surrounding structures. PRS is less severe than that observed after embolic therapies. Incidence of PRS ranges from 20 to 70% (Riaz et al. 2014). A 2-week post-radioembolization telephone call is recommended to inquire for symptoms of PRS. A visit to the clinic 1 month following treatment is recommended to clinically assess the patient (Riaz et al. 2014).

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

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, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced an SAE that was considered to be related to durvalumab by the 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 as described in Appendix 1 Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy or in Combination with other Products.

Durvalumab is currently being investigated in clinical trials in HCC patients. The potential benefits of durvalumab is based on the aforementioned study involving nivolumab which showed ORR of 20% and DCR of 64% in patients with advanced HCC (El-Khoueiry et al, 2017).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB (IB, 2017).

2. OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate time to progression (TTP) from enrolment using modified response evaluation criteria in solid tumors (mRECIST).

2.2 Secondary Objective

The secondary objectives include evaluation of:

- Overall Survival (OS) from first dose of study drug until the time of data-cutoff, as determined by the Investigator.

- The objective response rate (ORR) of the target lesion(s) and non-target lesion(s) at Week 8 and thereafter, every 8 weeks following radioembolization as evaluated by mRECIST.

- The safety of durvalumab until 30 days after radioembolization with yttrium-90 microspheres or the last dose of durvalumab, regardless of causality.

2.3 Exploratory Objectives – Biomarker Exploration

- Tumor tissues: Expression levels of PD-L1 and genomic analysis (tumor mutational burden) prior to treatment

- Plasma sample collection for future genomic analysis: Prior to the start of treatment, at Week 8 and at the time of progressive disease (PD)

3. STUDY DESIGN

3.1 Overview of Study Design

This is a single-arm, open-label safety and efficacy study to be implemented at a single site in Korea.

The aim of this study is to analyze the tumor response of patients with locally advanced and unresectable HCC receiving combination treatment of durvalumab plus radioembolization with yttrium-90 microspheres by mRECIST.

Transarterial radioembolization (TARE) with yttrium-90 microspheres will be employed in combination with an intravenous (IV) dose of 1500 mg durvalumab every 4 weeks (Q4W) until PD. TARE will be performed 1–2 weeks (7 to 14 days) before the first dose of durvalumab and a maximum of 2 more times during the treatment period, per Investigator discretion. If additional TARE is performed, the interval between additional TARE treatments and administration of durvalumab should be at least 1 week.

Clinical response assessments will be completed at Week 8 ± 2 weeks and thereafter, every 8 weeks ± 1 week until PD.

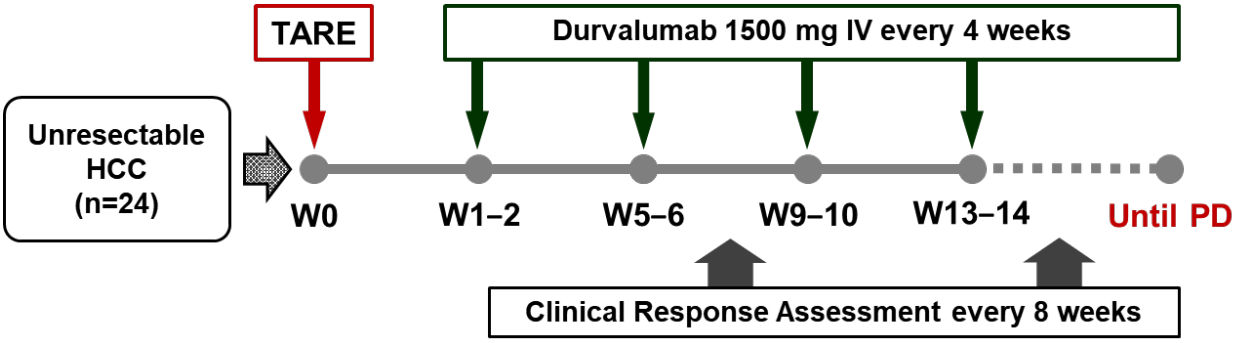
Safety will be assessed by Investigators initially in a cohort of 6 patients, followed by additional recruitment of 18 patients for safety and preliminary efficacy assessment. The safety run-in cohort will consist of the first 6 enrolled patients. Prior to the 2nd dose of durvalumab at Week 5–6, if any event which satisfies treatment discontinuation criteria (as stated in Section 3.3.1, except for PD per mRECIST) occurs in more than 2 patients within the safety run-in cohort, no further enrollment will proceed, and the study will be terminated.

- If more than 2 patients experience any event satisfying the treatment discontinuation criteria (except for PD per mRECIST), then stop the trial.
- If less than or equal to 2 patients experience any event satisfying the treatment discontinuation criteria (except for PD per mRECIST), then continue the trial.

Exploratory biomarker testing will be done on tumor tissues prior to treatment and plasma samples prior to treatment and at the time of PD.

3.2 Study Schema

Figure 4 Study Schema



3.3 Study Oversight for Safety Evaluation

Refer to established treatment guidelines as described in Appendix 1.

3.3.1 Treatment Discontinuation Criteria

Durvalumab treatment will be discontinued if any of the following criteria are met:

- PD per mRECIST.
- Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the retreatment period or requires systemic treatment.
- Any Grade 3 non-skin, drug-related AE lasting >7 days or recurs.
- Any Grade 4 drug-related AE or laboratory abnormality.
- Any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the Investigator, indicates that continued participation in the study is not in the best interest of the patient.

3.3.2 Treatment Interruption or Delay Criteria

Durvalumab and TARE will be interrupted or delayed, based on the treatment guidelines described in Appendix 1.

3.4 Withdrawal of Patients from Study Treatment and/or Study

3.4.1 Permanent Discontinuation of Durvalumab

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

1. Withdrawal of consent or lost to follow-up
2. AE that, in the opinion of the Investigator, contraindicates further dosing
3. 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
4. Pregnancy or intent to become pregnant
5. AE related to TARE, with the exception of toxicities that do not meet the criteria for discontinuation as defined in Section 3.3.1
6. Dose-limiting toxicity (DLT)* *if applicable*
7. Grade ≥3 infusion reaction
8. Patient noncompliance that, in the opinion of the Investigator, warrants withdrawal; e.g., refusal to adhere to scheduled visits
9. Initiation of alternative anticancer therapy including another investigational agent
10. Confirmation of PD and Investigator determination that the patient is no longer benefiting from treatment with durvalumab
11. Patients who are permanently discontinued from receiving IP will be followed for safety, 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. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

* Dose-limiting toxicity is defined according to Common Terminology Criteria for Adverse Events (CTCAE) classification and includes all Grade 3 or higher toxicities with the exception of Grade 3 nonfebrile neutropenia and alopecia. Additionally, DLTs may include some prior untreatable or irreversible Grade 2 toxicities (eg, neurotoxicity, ocular toxicities, or cardiac toxicities) and prolonged Grade 2 toxicities (i.e., Grade 2 toxicities lasting longer than a certain period).

3.4.2 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.

3.5 End of Study

The data cut-off will be determined by the Investigator as the clinical trial proceeds. All patients still in the study at this time will be assessed according to the End of Treatment (EoT) Visit schedule (see Table 1 Schedule of Study Assessments).

3.6 Survival Follow-Up

In order to collect OS data, patients whose disease has progressed, or whose study treatment has been terminated for any reason will be followed for survival every 3 months until the study is complete, as determined by the Investigator.

The below checklist will be followed to capture survival follow-up information:

Survival follow-up (period to be defined as per Investigator)		
Date of Follow-up	Mode of follow-up	Any active therapy
	☐ Unscheduled visit per protocol ☐ Telephonic	☐ Yes ☐ No If yes, Provide details:

4. PATIENT SELECTION

4.1 Inclusion Criteria

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

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations

2. Male or female, aged ≥19 years at time of study entry

3. Diagnosed with unequivocal HCC confirmed histologically or diagnosed radiologically according to American Association for the Study of Liver Diseases practice guideline

4. Locally advanced HCC, defined as Barcelona clinic liver cancer (BCLC) staging intermediate (B) stage or BCLC advanced stage (C) without extrahepatic metastasis

5. Must have at least 1 untreated measurable disease (untreated target lesion i.e. a viable lesion that has never been treated with locoregional treatment [TACE, TARE, percutaneous ethanol injection therapy, or radiofrequency ablation])

6. Child-Pugh score ≤7 points

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

8. Life expectancy of ≥12 weeks

9. Body weight >30 kg

10. Adequate normal organ and marrow function as defined below:

    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count (ANC) ≥1500 per mm^3
    - Platelet count ≥75,000 per mm^3
    - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). (This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis

or hepatic pathology), who will be allowed only in consultation with the Investigator)

- Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase [SGOT])/ alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase [SGPT]) ≤5 x institutional upper limit of normal

- Measured creatinine clearance >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine CL:

Males:

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

Females:

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

11. Female patients must be either postmenopausal or, if premenopausal, must have a negative pregnancy test and agree to use 2 forms of contraception, if sexually active during their study participation

    Male patients must be surgically sterile, or if sexually active and having a premenopausal female partner then must be using an acceptable form of contraception.

    Adequate contraception allowed in this trial is as follows:
    - Hormonal contraceptives such as combined oral contraceptive pill
    - Intrauterine devices or the implantation of intrauterine system (IUS)
    - Blockage methods (spermicides and condoms/spermicides and vaginal diaphragm for contraception, vaginal sponges or cervical cap)
    - Sterilization surgery such as tubal ligation in females and vasectomy in males

12. Evidence of postmenopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women <50 years of age would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone

levels in the postmenopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy)

- Women ≥50 years of age would be considered postmenopausal if they have been amenorrhoeic 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.

4.2 Exclusion Criteria

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

1. Eligible for potentially curative treatment (surgical resection, radiofrequency ablation or immediate liver transplantation)

2. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment

3. History of organ transplantation, or allogeneic or hematopoietic stem cell transplantation

4. Any other concurrent malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, papillary thyroid cancer, early gastric cancer, or other cancer for which the patient has been disease-free for at least five years

5. Evidence of extrahepatic metastasi(e)s, except for regional lymph node(s) involvement

6. A history of a severe contrast allergy (i.e. anaphylaxis) not controlled with premedication

7. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the IP or interpretation of patient safety or study results

8. Participation in another clinical study with an IP during the last 8 weeks or 5 half-lives of the study drug, whichever is longer, prior to screening

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

10. Receipt of the last dose of anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, mAbs) ≤ one cycle length or 14 days, whichever is longer, prior to the first dose of study drug. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as determined by the Investigator

11. Any unresolved toxicity NCI-CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

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

    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included at the discretion of the Investigator.

12. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable

13. Prior hepatic radiation therapy including Total Body Irradiation (TBI) for HCC or other malignancy

14. 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

15. 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.]). The following are exceptions to this criterion:

    - Patients with vitiligo or alopecia

    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

    - Any chronic skin condition that does not require systemic therapy

    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician

    - Patients with celiac disease controlled by diet alone

16. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, serious chronic 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

17. History of leptomeningeal carcinomatosis

18. History of active primary immunodeficiency

19. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), other than chronic infection of HBV or HCV

20. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. 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., Computed tomography [CT] scan premedication)

21. 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.

22. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth from screening to 120 days after the last dose of durvalumab monotherapy.

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

24. 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.

Exclusion Criteria <u>Specific to</u> Radioembolization:

The screening angiogram and technetium-99m macroaggregated albumin (99mTc-MAA) scan (using Technescan or Pulmocis) are used to determine lobar liver volume from CT or MR

images, to identify vascular shunting to the GI tract requiring use of angiographic occlusion techniques and to determine the lung shunt fraction.

Patients who are ineligible to radioembolization meeting the following criteria will not be included in the study. Additional patients will be screened to replace these patients.

- Deposition of yttrium-90 microspheres to the GI tract that cannot be corrected by placement of the catheter distal to collateral vessels or the application of standard angiographic techniques, such as coil embolization to prevent deposition of yttrium-90 microspheres in the GI tract.

- Exposure of radiation to the lungs exceeds 30 Gray (Gy) for a single infusion or 50 Gy cumulative for all infusions of yttrium-90 microspheres.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 3.4.

4.3 Replacement of Patients

There will be no replacement of patients.

5. INVESTIGATIONAL PRODUCT

5.1 Identity of Investigational Product(s)

Table 2 Investigational Product and Concomitant Therapy for This Study

Investigational product	**Dosage form and strength**	**Manufacturer**
Durvalumab	50 mg/mL solution for infusion after dilution	AstraZeneca/MedImmune
Concomitant therapy	**Dosage form and strength**	**Manufacturer**
Transarterial radioembolism (TARE) (Yttrium-90 microspheres, TheraSphere®)	Refer to the ® package insert	BTG International

5.2 Durvalumab

5.2.1 Formulation/packaging/storage

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

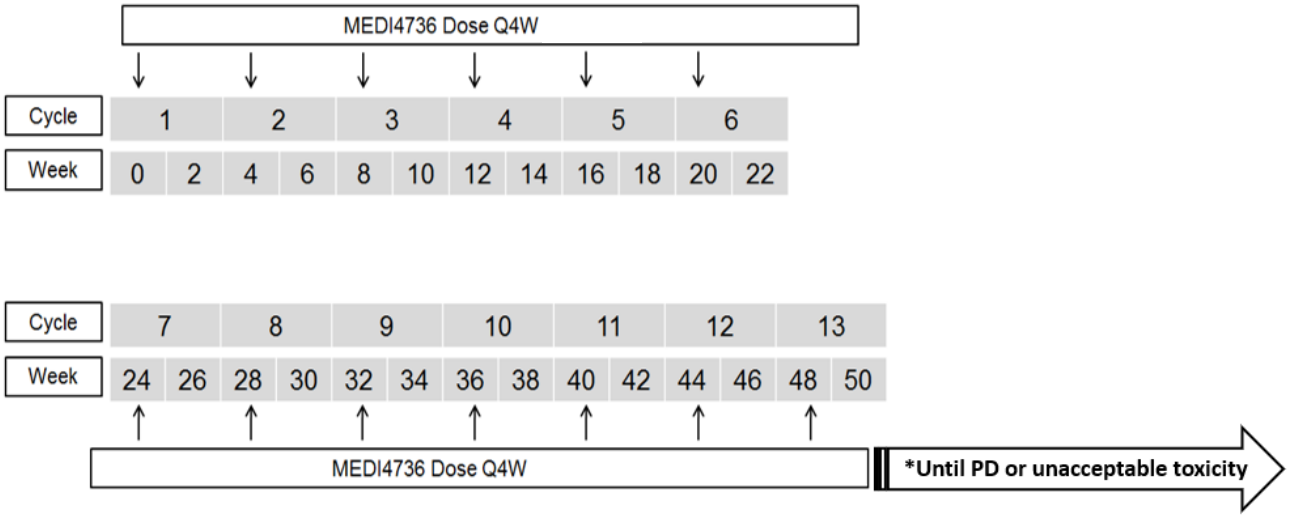
5.2.2 Durvalumab Doses and Treatment Regimens

The first 1500 mg IV dose of durvalumab will be administered 1‑2 weeks after the transarterial radioembolization (TARE) with yttrium-90 microspheres procedure.

Patients will receive 1500 mg durvalumab (MEDI4736) via IV infusion Q4W until confirmed PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

If a patient's weight falls to ≤30 kg, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the body weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W) (see Figure 5).

Figure 5. Durvalumab (MEDI4736) Dosing Schedule



*Durvalumab (MEDI4736) administration will be continued until PD or unacceptable toxicity

5.2.3 Preparation of Durvalumab Doses for Administration With an IV Bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

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

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (MEDI4736) (i.e., 1500 mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Standard infusion time is 1 hour. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered or complete the infusion according to institutional policy to ensure the full dose is administered.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

5.3 Yttrium-90 Microspheres Administered with TransArterial Radioembolization (TARE)

Refer to the TheraSphere® (yttrium-90 Microspheres) Package Insert for additional product details (TheraSphere® PI 2018).

5.3.1 Packaging and Storage

Yttrium-90 microspheres are packaged in single-use preassembled administration sets. Accessory kits contain reusable components, acrylic box and beta shield.

Each dose vial contains one of 6 available doses of yttrium-90. The vials should be kept in the acrylic container, in the lead shield, to avoid exposure.

Dose vials, administration sets, and accessory kits should be stored at room temperature. The requirements of the applicable regulatory agency for safe handling and storage of radioactive materials should be consulted and must be followed.

5.3.2 Doses and treatment regimens

TheraSphere® is available in six dose sizes: 3 GBq (81 mCi), 5 GBq (135 mCi), 7 GBq (189 mCi), 10 GBq (270 mCi), 15 GBq (405 mCi) and 20 GBq (540 mCi). Custom dose sizes available in 0.5 GBq increments between 3 and 20 GBq. The dose is supplied in 0.6 mL of sterile, pyrogen-free water in a 1.0 mL vee-bottom vial sealed within a clear acrylic vial shield.

5.3.3 Product preparation

Follow the package insert directions for dose vial preparation.

5.3.4 Dose administration

Patients should undergo hepatic arterial catheterization using balloon catheterization or other appropriate angiographic techniques to prevent extrahepatic shunting, prior to administration of TheraSphere®.

The recommended dose to the liver is between 80 Gy to 150 Gy (8,000 rad to 15,000 rad). The amount of radioactivity required to deliver the desired dose to the liver can be calculated as follows:

$$\text{Activity Required (GBq)} = \frac{(\text{Desired dose [Gy]})\,(\text{Liver mass [kg]})}{50}$$

The liver volume and corresponding liver mass may be determined using CT or ultrasound scans. The entire contents of the dose vial are administered to the patient.

Follow TheraSphere® Package Insert instructions for infusion to ensure complete delivery of the calculated dose (TheraSphere® PI 2018).

5.4 Management and Accountability of Study Drugs

5.4.1 Monitoring of Dose Administration

Durvalumab

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

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. The total allowed infusion time should not exceed 8 hours at room temperature. For patients with a ≤Grade 2 infusion-related reaction,

subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the Investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued.

The standard infusion time is one hour, however if the infusion is interrupted, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature, with maximum total time at room temperature not exceeding 8 hours (otherwise a new infusion preparation is required).

Infusion site reactions will be managed per Investigator's standard practice and established treatment guidelines as described in the Appendix 1.

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

TheraSphere®

Refer to the TheraSphere® Package Insert for precautions and warnings regarding dose administration (TheraSphere® PI 2018).

5.4.2 Accountability and Dispensation

The PI or appropriately trained designee will maintain an accurate record of the receipt of the product, including the date and quantity received. In addition, an accurate drug disposition record will be kept that specifies the amount administered to each patient and the date of administration. This inventory record must be available for inspection at any time.

Durvalumab: Empty or partially used vials of study drug will be destroyed at the study center per study center procedures and documentation of destruction will be kept by the site personnel.

TheraSpehere®: Empty or partially used vials of TheraSphere® will be destroyed per study center and radiation control procedures, and documentation of destruction will be kept by the site personnel.

5.4.3 Disposition of Unused Product

The site will account for all unused investigation study drug and TheraSphere®.

6. TREATMENT PLAN

6.1 Patient Enrolment

Sequential screening numbers will be assigned to patients at the time of informed consent signing. As they are enrolled into the study, patients will be assigned to a unique study number. Study numbers are consecutive. After the enrolment of the first 6 patients, Investigators will review safety data. If no safety concerns are identified, the remaining 18 patients will be enrolled to complete a total of 24 patients in the study.

The safety run-in cohort will consist of the first 6 enrolled patients. Prior to the 2nd dose of durvalumab at Week 5−6, if any event which satisfies treatment discontinuation criteria (as stated in Section 3.3.1, except for PD per mRECIST) occurs in more than 2 patients within the safety run-in cohort, no further enrollment will proceed, and the study will be terminated.

- If more than 2 patients experience any event satisfying the treatment discontinuation criteria (except for PD per mRECIST), then stop the trial.
- If less than or equal to 2 patients experience any event satisfying the treatment discontinuation criteria (except for PD per mRECIST), then continue the trial.

6.2 Dosage and Administration

The first 1500 mg IV dose of durvalumab will be administered 1 to 2 weeks (7 to 14 days) after the transarterial radioembolization with yttrium-90 microspheres procedure.

Subsequent doses of durvalumab (1500 mg, IV) will be administered Q4W until PD as evaluated by mRECIST or until treatment discontinuation criteria are met.

Treatment will continue to be provided after data cut-off for patients who do not progress or have serious drug toxicities.

Refer to Sections 5.2.2 and 5.4.1 for the administration, dose modification in case of weight dropping ≤30 kg and monitoring of durvalumab.

6.3 Toxicity Management Guidelines

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the established treatment guidelines as described in Appendix 1.

Adverse events related to TARE will be managed as per standard of care.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune-mediated adverse event (imAE). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 3.3.1 of this protocol).

All toxicities will be graded according to Investigator's discretion or defined criteria (e.g. NCI-CTCAE, Version 5.0), if necessary.

7. RESTRICTIONS 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

- Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 3) from the time of screening throughout the total duration of the drug treatment and the drug wash-out period (90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, 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 male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug wash-out period (90 days after the last dose of durvalumab monotherapy). However, periodic 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 3).

N.B. Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or postmenopausal.

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

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

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

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Section 4.1. 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 3 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

[a] This is also considered a hormonal method

Blood donation

Patients should not donate blood while participating in this study or for at least 90 days after receipt of the final dose of durvalumab.

7.2 Concomitant Treatment(s)

7.2.1 Permitted Concomitant Medications

Table 4 Supportive Medications

Supportive medication/class of drug	Usage
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator

Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

7.2.2 Excluded Concomitant Medications

Table 5 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])

Prohibited medication/class of drug	Usage
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 • Short-term premedication for patients receiving combination agent where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions • 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.).
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 assessed by the Investigator to be safe.

Abbreviations: AE: adverse event; CTLA-4: cytotoxic T-lymphocyte-associated antigen-4; EGFR: epidermal growth factor receptor; IP: investigational product; PD-1: programmed cell death 1; PD-L1: programmed cell death-ligand 1; SoC: standard of care; TKI: tyrosine kinase inhibitor.

8. STUDY PROCEDURES

Refer to Table 1 Schedule of Assessments for details of 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 Schedule of Assessment during the screening and treatment period is provided following the Protocol Synopsis.

Please consider following:

- Tumor efficacy (mRECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of enrollment (not the date of therapy).
- 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 durvalumab 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.
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (mRECIST). Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-life of durvalumab (see current Investigator's Brochure 2017 for durvalumab).

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 Institutional Review Board (IRB) / independent Ethics Committee (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.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Consent for genetic sample and analysis (optional)
- Complete physical exam including weight and height
- Vitals signs
- 12-lead electrocardiogram (ECG) (in triplicate [2-5 minutes apart])
- Review of prior/concomitant medications
- Medical history and demographics, including baseline characteristics and tobacco use
- Review of eligibility criteria
- AE/SAE assessment
- ECOG Performance Status
- Plasma sample collection for future genomic analysis
- Plasma sample for disease-specific tumor markers (see Table 9)
- Tumor biopsy, of newly acquired or archival ≤3 years old
- Tumor biopsy, of archival, if available, for patients who submit a newly acquired biopsy at screening for PD-L1 status and genomic analysis
- Tumor evaluation (CT/MRI)
- TC-99mMAA scan (Per Investigator decision, TC-99mMAA scan can be repeated after tumor biopsy and before TARE with Yttrium-90 microspheres.)
- Clinical laboratory tests for:
    - Hematology
    - Prothrombin Time (PT) to determine Child-Pugh score
    - Clinical chemistry
    - Thyroid-Stimulating Hormone (TSH)
    - Serum/Urine pregnancy test (for women of childbearing potential only)
    - Hepatitis B, C and HIV
    - Urinalysis

8.1.2 Treatment Phase

Procedures to be conducted during the treatment phase (Week 0 through C5/PD) of the study are presented in Table 1 Schedule of Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

Transarterial radioembolization (TARE) procedure with yttrium-90 microspheres will be performed on Week 0/Day 0. Treatment with durvalumab (1500 mg IV) will begin 2 weeks (14 days) after the TARE procedure.

TARE may be repeated on-demand up to 2 more times during the study (for a total of 3 procedures), at Investigator's discretion.

The following assessments/procedures will be performed during each Treatment Visit (except Week 0), Q4W (Q28 days ±3 days unless dosing needs to be held for toxicity reasons):

- Targeted physical examination (based on symptoms) including body weight
- Vital signs
- ECG (*as clinically indicated)*
- Review of prior/concomitant medications
- ECOG Performance Status
- AE/SAE assessment
- Clinical laboratory tests for:
    - Hematology
    - PT
    - Clinical chemistry
    - TSH
    - Pregnancy test (urine or serum)
- Durvalumab infusion
- Tumor Evaluation: A Clinical Response Assessment (CT/MRI) will be performed at Week 8 ± 2 weeks, and then every 8 weeks ± 1 week until confirmed PD
- Plasma sample collection for future genomic analysis at Week 8 ± 2 weeks
- Plasma sample for disease-specific tumor markers will be collected at the time of tumor assessment for all patients.

8.1.3 End of Treatment

For patients who discontinue durvalumab prior to PD, EoT is considered the last visit, where the decision is made to discontinue treatment. All required procedures may be completed within ±7 days of the EoT visit. Repeat disease assessment is not required if performed within 28 days prior to the EoT visit.

The following assessments/procedures will be performed during the EoT Visit:

- Targeted physical examination (based on symptoms) including weight
- Vital signs
- ECG

- Review of prior/concomitant medications
- ECOG Performance Status
- AE/SAE assessment
- Clinical laboratory tests for:
    - Hematology
    - PT
    - Clinical chemistry
    - TSH
    - Pregnancy test (urine or serum)
- Tumor Evaluation, unless performed within 28 days/weeks
- Plasma sample collection for future genomic analysis at the time of PD
- If tumor evaluation is performed at EoT visit, a plasma sample for disease-specific tumor markers will also be collected.

8.1.4 Safety Follow-up

A Safety Follow-Up Visit will be performed 30 days after radioembolism with yttrium-90 microspheres, or after the last dose of durvalumab.

The following safety assessments/procedures will be performed during the Safety Follow-Up Visit:

- Full physical examination including weight
- Vital signs
- ECOG Performance Status
- AE/SAE assessment
- ECG *(as clinically indicated)*
- Clinical laboratory tests will be performed as per clinical opinion.

In addition, all patients will be telephonically followed up every 3 months, for OS until study completion.

8.1.5 Survival Follow-up

All patients will be contacted telephonically for OS assessment every 3 months until the study is complete, as determined by the Investigator.

8.2 Description of Study Procedures

8.2.1 Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs

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 Table 1 Schedule of Assessments.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

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

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. Height is measured at Screening only.

TARE Procedure

TARE with yttrium-90 microspheres will be performed per standard practice at Week 0/Day 0. Refer to TheraSphere® package insert for details (TheraSphere® PI 2018).

First infusion

On the first infusion day (Week 1−2/Day 7−14), patients will be monitored, and vital signs collected/recorded on a paper case report form (CRF) prior to, during and after infusion of IP as presented in the bulleted list below.

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

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent infusions

BP, pulse and other vital signs should be measured, collected/recorded in the CRF 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 abnormal vital signs should be repeated as clinically indicated and recorded on the CRF.

8.2.2 Clinical Laboratory Tests

The following clinical laboratory tests will be performed according to the Schedule of Assessments:

Table 6 Hematology Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	Prothrombin time

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

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

Table 7 Clinical Chemistry (Serum or Plasma) Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase[b]
Amylase[b]	Magnesium[c]
Aspartate aminotransferase	Potassium
Bicarbonate[c]	Sodium
Calcium	Total bilirubin[a]
Chloride[c]	Total protein
Creatinine[c,d]	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyl transferase[c]	Uric acid

Hepatitis B and C and HIV	TSH (reflex free T3 or free T4)[e]

Abbreviations: AE: adverse event; HIV: human immunodeficiency virus; TSH: thyroid stimulating hormone.

[a] Tests for alanine aminotransferase, aspartate aminotransferase, 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. In case only 1 of these parameters is routinely measured, then either lipase or amylase is acceptable.

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

[d] Creatinine clearance will be calculated by data management using Cockcroft-Gault (using actual bodyweight).

[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 1. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

Table 8 Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Color and appearance

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

Table 9 Disease-Specific Tumor Markers

Alpha-fetoprotein
Protein Induced by Vitamin K Absence or antagonist-II

For a patient showing an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, 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 fulfil any of the SAE criteria.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the CRF.

8.2.3 Estimated Volume of Blood to Be Collected

Blood volume collection will follow local collection and storage guidelines.

8.3 Biological Sampling Procedures for Biomarker Exploration

8.3.1 Plasma Sampling and Evaluation Methods

Blood samples for genotyping of circulating tumor DNA (ctDNA) in plasma, as a potential biomarker predicting treatment response will be collected in samples taken according to the schedule presented in the Schedule of Assessments and detailed in the text below.

A single blood sample (25 mL) will be drawn prior to first cycle of durvalumab, at the time of the first clinical response assessment (Week 8 ± 2 weeks) and again at time of PD or EoT Visit. In case of no PD, sampling will occur at the last visit. These samples will be processed and stored as per local guidelines.

Unless already available, a tumor biopsy will be performed at screening (subject to patient consent), to obtain a sample for PD-L1 status confirmation and genomic analysis (tumor mutational burden). Instances where a patient does not provide consent and a fresh tumor sample or biopsy is not taken, will not be considered a protocol deviation.

See below sections for details of sample collection.

8.3.2 Archival Tumor Samples and Fresh Tumor Biopsies Use Beyond PD-L1

Archival or fresh tumor samples may be retained for use beyond PD-L1 testing; this will only be done for patients who have provided consent to use these samples.

8.3.3 Archival or Fresh Tumor Samples

PD-L1 testing

To ensure comparability of data across all studies of durvalumab and to gain real world experience on the performance of this assay, PD-L1 testing will utilize the Ventana SP263 assay, in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer and squamous cell carcinoma of the head and neck. For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma and cervical HPV+ cancers), the Ventana SP263 assay has only limited clinical performance data.

Genomic analysis: tumor mutational burden

Tumor heterogeneity may affect the efficacy of TARE with yttrium-90 microspheres followed by durvalumab administration. Tumor mutational burden prior to the treatment, which is a potential biomarker of the investigational treatment, will be analyzed by whole exome sequencing (WES) methods. Blood sample (4 mL) collected as above will be utilized for normal WES.

Sample collection for PD-L1 testing and genomic analysis

- The preferred tumor sample for the determination of a patient's PD-L1 status and genomic analysis is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.

- The preferred sample for PD-L1 testing and genomic analysis is less than or equal to 3 months old. In cases where a sample a less than 3 months old is not available, patients will be asked to undergo a new biopsy if considered clinically appropriate by their treating physician.

- When the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than 3 years of age. When archival samples are used to assess PD-L1 status and tumor mutational burden, the age of the sample/date of collection should be captured.

8.3.4 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. As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

• Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented

• Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented, and the signed document returned to the study site

• Ensures that the patient is informed about the sample disposal.

8.3.5 Storage and disposal of collected samples

The human-derived material collected in this study will be stored and disposed of according to the retention period selected by the research subject in the human-derived material research agreement, whether or not it is provided for other research purposes, and the processing of personal information when provided. Collected human-derived materials may be used for purposes other than this trial. Collected human-derived material will be managed under the supervision of the Principal Investigator. Each human-derived material control number will be coded during the entire sample storage period and will be managed separately from personally identifiable information. Personal identification codes are managed so that only the research team can access them. Collected human-derived material will be stored and analyzed in the laboratory of the Investigator and then disposed of according to the standards of the laboratory. Human-derived materials, including blood from this clinical study, may be stored permanently with the subject's consent after the study is over, and may be stored for as long as the subject specifies the storage period. Subjects may withdraw their consent for their samples to be retained for the study and the human material will be discarded.

9. DISEASE EVALUATION AND METHODS

9.1 Efficacy Variables

9.1.1 Time to Progression (TTP)

TTP is defined as the time from the first study treatment administration until the first confirmed tumor progression (PD) based on the mRECIST assessment.

9.1.2 Objective Response Rate (ORR) of Target Lesion(s) and Non-Target Lesion(s)

The ORR is defined as the percentage of patient that had a best overall response of CR or PR during the study, based on the mRECIST assessment.

9.2 Methods

The first tumor evaluation will be conducted at Week 8 ± 2 weeks and thereafter Q8W ± 1 week (relative to the date of enrollment) until confirmed objective PD/death (whichever comes first). The schedule of Q8W ± 1 week MUST be followed regardless of any delays in dosing.

Tumor response will be evaluated by mRECIST criteria (Lencioni and Llovet, 2010).

The Investigator will evaluate all tumor assessments.

9.2.1 mRECIST Criteria/Definitions

Table 10: Assessment of Target Lesion(s)

Response Category	mRECIST Criteria
CR	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the 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 PR or PD
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

Abbreviations: CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table 11: Assessment of Non-Target Lesion(s)

Response Category	mRECIST Criteria
CR	Disappearance of any intratumoral arterial enhancement in all non-target lesions
IR/SD	Persistence of intratumoral arterial enhancement in one or more non-target lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Abbreviations: CR: complete response; SD: stable disease; PD: progressive disease; IR: incomplete response.

Assessment of New Lesion(s)

A newly detected hepatic nodule will be classified as HCC—and therefore will be declared as evidence of progression—when its longest diameter is at least 1 cm and the nodule shows the

typical vascular pattern of HCC on dynamic imaging, that is, hypervascularization in the arterial phase with wash-out in the portal venous or late venous phase.

Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm-interval growth in subsequent scans.

An individual radiologic event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing (Lencioni and Llovet, 2010).

10. SAFETY ASSESSMENT

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

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

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

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

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

10.1.2 Definition of Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect in offspring of the patient
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

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

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

10.1.3 Definition of Adverse Events of Special Interest

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

AESIs observed with durvalumab include:

- Diarrhea/Colitis and intestinal perforation
- Pneumonitis/ILD
- Hepatitis/transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash/Dermatitis
- Nephritis/Blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis/Polymyositis
- Neuropathy/neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure (IB, 2017).

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.
- SpO_2
  - Saturation of peripheral oxygen (SpO_2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    (ii) Tumor markers: Particular tumor markers which are related to PD.

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. The determination of severity should be made by the Investigator based upon medical judgment and/or the defined severity categories as applicable.

10.2.2 Assessment of Relationship

The Investigator will assess causal relationship between the IPs (durvalumab and TheraSphere®) and each AE.

10.3 Recording of AEs and SAEs

AEs and SAEs will be collected from the time of the patient signing the informed consent form (ICF) until the follow-up period is completed (30 days after the last dose of durvalumab and/or TARE). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study drug, then it should be reported as an AE or SAE as applicable.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against IP (yes or no) and/or comparator / combination drug (yes/no)
- Action taken with regard to IP / comparator / combination agent
- Outcome

The following variables will be collected for SAEs as applicable:

- AstraZeneca tracking number
- Sponsor/Sponsor-Investigator study number
- Patient identification
- Age
- Sex
- IP(s) dose, start & stop date
- Event term as reported by the Investigator
- SAE onset & stop date
- Investigator's assessment of seriousness, according to ICH definitions
- Date of death (if applicable)
- Causality assessment in relation to IP
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to additional study drug (if applicable)
- SAE outcome

10.3.1 Progressive Disease

PD 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 PD and not an AE. Events that are unequivocally due to PD should not be reported as an AE during the study.

10.3.2 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.

10.3.3 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.

10.3.4 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined 30-day post last dose of durvalumab and/or TARE safety follow-up period, must be reported as follows:

- Death clearly resulting from PD should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the CRF. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within **24 hours** (see Section 10.3.7 for further details). It should also be documented in the CRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the CRF. A post mortem may be helpful in the assessment of the cause of death.

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 CRF. 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.

10.3.5 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. After 30 days, only patients with ongoing IP-related SAEs will continue to be followed for safety.

10.3.6 Post-study Events

After the patient has been permanently withdrawn from the study, there is no obligation for the Investigator to actively report information on new AE or SAEs occurring in former study patients

after the 30-day safety follow-up period for patients treated with durvalumab. However, if an Investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the Investigator should report the event.

10.3.7 Reporting of Serious Adverse Events

All SAEs will be reported, whether or not considered causally related to the IP, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 30 days after the last dose of durvalumab and/or TARE or until the initiation of alternative anticancer therapy. The Investigator is responsible for informing the IRB/IEC of the SAE as per local requirements.

The Investigator and/or Sponsor must report Suspected Unexpected Serious Adverse Reactions (SUSARs) to AstraZeneca as individual case reports as they occur and in parallel to reporting to the Regulatory Authority.

SAEs that do not require expedited reporting to the Regulatory Authority still need to be reported to AstraZeneca preferably using the MedDRA coding language for SAEs. This information can be reported on a monthly basis.

A cover page and a copy of the SAE report written in English must be sent to AstraZeneca at the time the event is reported to the Regulatory Authority. To meet data privacy and confidentiality requirements AE information (both individual case reports and listings) must be sent from the Investigator and/or Sponsor to AstraZeneca by **secure email**, if secure email is not available AE information must be sent by fax. For methods of achieving secure email data exchange, via encrypted email or password-protected attachment.

*** AstraZeneca's contact details for AE reporting**

- Designated mailbox: **AEMailboxClinicalTrialTCS@astrazeneca.com**

- Fax: +1 302 886 4114

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the Regulatory Authority.

A cover page should accompany the AE report form indicating the following:

- Notification from an Investigator Sponsored Study
- The Investigator's name and address

- The trial name/title and AstraZeneca ESR reference number (ESR-18-13764)

The Investigator and/or 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.

10.4 Events Related to TARE (Therasphere®)

A product malfunction is defined as a failure of the device to meet its performance specifications, essential function or otherwise perform as intended. Performance specifications include all claims made in the labelling for the device. The essential function of a device refers not only to the device's labelled use, but for any use widely prescribed within the practice of medicine.

10.4.1 Reporting of Adverse Events, Serious Adverse Events and Device Malfunctions

TARE-related events occurring after TARE procedure *and prior to* Duvalumab dosing must be reported to BTG only.

TARE-related events occurring after TARE and Duvalumab must be reported to **both** BTG and AstraZeneca.

All adverse events will be documented by the Sponsor-Investigator within the study records (e,g CRF) and reported within the final study report and/or publication.

The Institution and/or the Sponsor-Investigator shall report all and any SAEs related to the device or procedure, product malfunctions or quality complaints that they become aware of in relation to TheraSphere® (BTG device) and/or the procedure associated with the device within the study to BTG.

All reports will be exchanged in English and Sponsor-Investigator will also provide BTG with such information and reasonable assistance as may be requested by BTG to allow BTG to comply with their obligations.

The Institution and/or the Sponsor-Investigator shall report all SAEs and incidents impacting patient safety to **vigilance@btgplc.com**.

10.4.2 SAEs

The Sponsor-Investigator will report SAEs within **one business day** to enable BTG to comply with their obligations as the device manufacturer, under applicable laws and regulations.

All reports will contain the following, if available:

Study title and name of the Sponsor-Investigator.

Patient number
Adverse event number
Date of event occurrence/date notified
Product details
Product name/ part number
Size / dose
Batch / lot number
Adverse event details along with comprehensive event description
Action(s) taken to treat or resolve the event
Outcome
Investigators opinion of causality of event i.e. related to
Drug
Device
Procedure
Product returned to BTG if applicable

10.4.3 Device Malfunctions

The Institution and/or the Sponsor-Investigator shall report all device malfunctions and/or quality complaints to **qualityottawa@btgplc.com** within one business day of becoming aware of the issue.

10.5 Other Events Requiring Reporting

10.5.1 Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

The Investigator will use clinical judgment to treat any overdose.

Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the Sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab.

10.5.2 Hepatic Function Abnormality

Hepatic function abnormality that fulfils the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the Investigator and AstraZeneca Patient Safety using the designated Safety e-mailbox, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to IP has been confirmed. The criteria for a potential Hy's Law case are AST or ALT ≥3x ULN together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to IP, the decision to continue dosing of the study patient will be based on the clinical judgment of the Investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the Investigator and AstraZeneca/MedImmune.

10.5.3 Pregnancy and Maternal Exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately, and the Investigator or other site personnel should report it within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it to the Investigator and AstraZeneca Patient Safety using the designated Safety e-mailbox.

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. The same timelines apply when outcome information is available.

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. The same timelines apply when outcome information is available.

10.5.4 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 + any drug 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 + any drug 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. The same timelines apply when outcome information is available.

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.

10.5.5 Other Safety Information

The Investigator should inform AstraZeneca within 24 hours of knowledge of any emerging safety issue, unanticipated problem or actions that the Investigator and/or Sponsor is considering as a result of a safety signal with the IP. This includes but is not limited to:

- Urgent safety measures to be implemented in the study
- Safety amendments to protocol/patient information & informed consent
- Interactions with Regulatory Authorities (RAs)/Ethics Committees (ECs)

The Investigator and/or Sponsor should inform AstraZeneca on an ongoing basis of any new safety trends or signals observed during routine safety surveillance activities.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

Demographic characteristics including age, gender, race, and ethnicity and other baseline characteristics including weight, height, ECOG performance, etc. will be summarized and listed.

Analyses will be performed using descriptive statistics. If statistical analysis is required, it will use SAS® v9.4 or higher (SAS Institute, Cary NC, USA) along with International Business Machines (IBM) Statistical Package for Social Sciences (SPSS), v24.0 or higher (SPSS Inc., Chicago, IL, USA) and R language, v3.4.2 or higher (R Foundation for Statistical Computing, Vienna, Austria).

Alternatively, statistical analysis can be managed by the institutional Medical Research Collaborating Center and/or other vendors.

No formal sample size calculations were performed.

A total of 24 patients will be enrolled to assess the safety and efficacy of radioembolization with yttrium-90 microspheres in combination with durvalumab in this population.

11.1 Description of Analysis Sets

11.1.1 Safety Analysis Set

The safety analysis set will include all patients who were enrolled into the study and who received at least one administration of study treatment (radioembolization with yttrium-90 microspheres or durvalumab) during the study.

11.1.2 Intent-to Treat (ITT) Analysis Set

The ITT analysis set will include all patients who were enrolled into the study.

11.1.3 Methods of Statistical Analyses

Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and frequency and percentage for discrete variables. Confidence intervals (95% Cis) will be presented where appropriate. For the safety analysis, data will be presented for all patients.

The Kaplan-Meier method will be used to estimate survival times. Survival time estimates (quartiles) and their corresponding 95% Cis will be presented. Survival times will also be presented graphically using Kaplan-Meier plots.

11.1.4 Sample Size Calculation

No formal sample size calculations were performed. A pilot study of 24 patients, including initial 6 patients for safety assessment, will be conducted to obtain preliminary data on efficacy.

11.1.5 Safety Review

There will be a safety run-in cohort of the first 6 enrolled patients. Data from these first 6 patients will be reviewed by Investigators to confirm safety before recruitment of the remaining 18 patients.

Prior to the 2nd dose of durvalumab at Week 5−6, if any event which satisfies treatment discontinuation criteria (as stated in Section 3.3.1, except for PD per mRECIST) occurs in more than 2 patients within the safety run-in cohort, no further enrollment will proceed, and the study will be terminated.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the Declaration of Helsinki, the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), and all applicable local regulatory requirements.

Ethics and regulatory review

The study protocol, ICF, information sheet advertisements (if any), and amendments (if any) will be reviewed by an IRB/IEC in conformance with ICH GCP. During the study, the Investigator or designee will provide timely and accurate reports to the IRB/IEC on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. Investigator or designee will notify the IRB/IEC of SAEs or other important safety findings.

12.2 Informed Consent

The Investigator must submit an ICF to the IRB/IEC for their review and approval before enrolling study patients. Informed consent must be obtained from each study patient in accordance with the ICH document “Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance”, before initiation of protocol-specified Screening procedures and enrolment into the study. A written informed consent must be obtained from each subject for the use or disclosure of protected medical information before any test specific procedures for the party are performed. The subject reads the agreement after the explanation of this study in a separate space. Prior to signing the agreement, the subject will be given opportunity and time to discuss the content of the agreement with the researchers. If the agreement is not obtained at the day, the Investigator will provide a copy of the agreement so that the subject can make a decision at home and sign the participation. The Investigator also informs the subject that, at any time and for any reason, the consent may be withdrawn. Explain to the subject that the reason for withdrawal of consent may be inquired by the Investigator, but the reason is not necessary.

12.3 Audits and Inspections

The study may be audited by the IRB/IEC per institutional guideline and/or Standard Operating Procedure (SOP).

12.4 Personal Information Protection Scheme for Whole Exome Sequencing

① Whether to include or anonymize personally identifiable information and how to process personal information (whether or not to replace all or part of personally identifiable information with a unique identifier).

In this study, personal identification information cannot be completely excluded because WES analysis results, clinical data such as demographic information, cancer treatment history, and cancer progression of the subjects will be obtained and matched and analyzed. Human derived control numbers collected for WES are coded during the analysis and are managed separately from personally identifiable information. The personal identification code is stored in a password-protected laboratory and stored in a password-protected laboratory where only the research team can access it under the supervisor's supervision.

② Clinical information will be included.

③ There is no possibility of identifying specific individuals and families due to genetic information.

④ Research information is stored in a separate file with a password under the supervisor's supervision, and stored and managed in a locked laboratory so that only the research team, such as the Investigator, co-researcher, and researcher, can access it.

⑤ The family tree will not be surveyed.

⑥ Genetic information will not be used secondarily except for the purpose of this study.

⑦ Genetic information of individuals found through WES will not be provided to any subject.

13. DATA MANAGEMENT

Data collection will involve the use of paper CRF which will be maintained by the site personnel. Data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of CRFs, regulatory documents, etc.) will be retained at the study center, along with adequate source documentation, according to regulatory and ICH requirements.

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APPENDIX 1

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy or in Combination with other Products – 14 October 2020

General Considerations regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support Investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. Refer to the section of the table titled “Other Immune-Mediated Reactions” for general guidance on imAEs not noted in the “Specific Immune-Mediated Reactions” section.

Early identification and management of immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the Investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI-CTCAE version in the applicable study protocol.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; ESMO European Society for Medical Oncology;NCI National Cancer Institute; NCCN National Comprehensive Cancer Network.

Pediatric Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** of starting corticosteroids.	− All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. − The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. − The recommendations for IVIG and plasmapheresis use provided for adult patients may be considered for pediatric patients. − The infliximab 5 mg/kg IV one-time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. − For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. − With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging, and other infectious and disease-related aetiologies excluded and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. –
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks.

		regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	– If no improvement within 2 to 3 days, additional work-up should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider, discussing with study physician as needed. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days, additional work-up should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – **WHEN SYMPTOMS OR EVALUATION INDICATE A PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN**

		ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY. – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a GI specialist for consideration of further work-up, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation.

		– If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressant agents such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days.
Grade 3 or 4	**Grade 3** • For patient treated with PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. • Permanently discontinue study drug for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade of intestinal perforation in any patient treated with ICI.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 to 3 days, promptly add further immunosuppressants (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.

		Grade 4 Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade** **(Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)**	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1	• No dose modifications. If it worsens, then treat as Grade 2.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2	• Hold study drug/study regimen dose until resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN) without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until LFT elevations improve or resolve. – If no resolution to ≤Grade 1 in 1 to 2 days, consider discussing with study physician as needed. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

Grade 3	For elevations in transaminases ≤8×ULN, or elevations in TB ≤5×ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline. • Resume study drug/study regimen if elevations downgrade to Grade≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade≤1 or baseline within 14 days.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an immunosuppressant therapy (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal work-up, and imaging as appropriate.
Grade 4	For elevations in transaminases >8×ULN or elevations in bilirubin >5×ULN, permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg. – For HCV+ patients: evaluate quantitative HCV viral load.

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients			– Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with HBcAb+: Evaluate for both HBV and HCV as above.
See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline**	• No dose modifications. • If ALT/AST elevations represents significant worsening based on Investigator assessment, then treat as described for elevations in the row below. For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician.

	Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline	drug/study regimen after completion of steroid taper. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– If event is persistent (>2 to 3 days) or worsens, and Investigator suspects toxicity to be imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work-up. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of IV methylprednisolone, consider additional abdominal work-up (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressants (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days.	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless Investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with study physician as needed. – If Investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an immunosuppressive therapy (mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**

	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise** - **For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** − Consult a nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections. recent IV contrast, medications, fluid status). − Consider using steroids in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Grade 1	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to >1 to 1.5 × baseline, consider following recommendations in this row.
Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional work-up. – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

			– If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional work-up and prompt treatment with an immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (Refer to NCI-CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emolient lotion or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy. – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate-strength topical steroid, consider discussing with study physician, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If >30% body surface area is involved, consider initiation of systemic steroids promptly.

			– Consider skin biopsy if the event persistent for >1 week or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. • If toxicity worsens, then treat as Grade 4. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider discussing with study physician as needed. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections).

		− Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). − If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the Investigator should send a blood sample for appropriate autoimmune antibody testing. − Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
Grade 1	No dose modifications.	**For Grade 1** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consultating an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). − If TSH <0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2, 3, or 4	For Grade 2-4 endocrinopathies other than hypothyroidism and Type 1 diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve.	**For Grade 2, 3, or 4** − Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. − For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or type 1 diabetes mellitus (DM), and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to

		Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen patient is clinically stable as per Investigator or treating physician's clinical judgement. If toxicity worsens, then treat based on severity.	2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated type 1 DM may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic work-up is positive for diabetic ketoacidosis.** – For patients with normal endocrine work-up (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)		– For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis. – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT). – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase. – If evidence of pancreatitis, manage according to pancreatitis recommendations.
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4:** In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade**	**General Guidance**	**For Any Grade:**

	(Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)		Consider Gastroenterology referral
	Grade 1	No dose modifications.	**For Grade 1:** – IV hydration – Manage as per amylase/lipase increased (asymptomatic)
	Grade 2, 3, or 4	**For Grade 2:** Hold study drug/study regimen dose until resolution to Grade ≤1. **For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 2, 3, or 4:** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration.
Neurotoxicity (To include but not be limited to non-infectious meningitis, non-infectious encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate. – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**
	Grade 1	No dose modifications.	**For Grade 1:** – See “Any Grade” recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia).

	Grade 2	− For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. − For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. − Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. − If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2:** − Consider, as necessary, discussing with the study physician. − Obtain Neurology consult. − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). − Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional work-up and promptly treat with an additional immunosuppressive therapy (e.g., IV IG or other immunosuppressant depending on the specific imAE).
	Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Consider, as necessary, discussing with study physician. − Obtain Neurology consult. − Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 2 to 3 days despite IV corticosteroids, consider additional work-up and promptly treat with an additional immunosuppressant (e.g., IV IG or other immunosuppressant depending on the specific imAE). − Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes	**Any Grade** (Refer to NCI-CTCAE applicable version in	**General Guidance**	**For Any Grade:** − The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute

(such as Guillain-Barre and myasthenia gravis)	study protocol for defining the CTC grade/severity)		decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurology consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Consider discussing with the study physician as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a Neurologist.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2:** – Consider discussing with the study physician as needed.

	Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	– Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a Neurologist – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**For Grade 3:**	**For Grade 3 or 4:**

		Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consider discussing with study physician as needed. – Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade** (Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the study physician as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary

		toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early to promptly assess whether and when to complete a cardiac biopsy, or any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1:** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4	- If Grade 2 – Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and

		taper. If toxicity does not rapidly improve, permanently. Discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/Polymyositis	**Any Grade** (Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a

		rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the

			discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult. – Consider discussing with the study physician as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
[c]NCCN Clinical Practice Guidelines in Oncology ″Management of Immunotherapy-Related Toxicities″ Version 1.2020 – December 2019

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune-mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– The study physician may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated.
Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. • Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper.	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO).
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of the Investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the Investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI-CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.