Investigational Drug	Durvalumab (MEDI4736) and tremelimumab
Study Number	GETNE - T1812
Version Number	6.0
Date	05/12/2022

A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with progressive, refractory advanced thyroid carcinoma-The DUTHY trial

Sponsor:

[redacted]

Coordinating Investigator:

[redacted]

PROTOCOL SIGNATURE PAGE

Study title: A phase II study of **du**rvalumab (MEDI4736) plus **t**remelimumab for the treatment of patients with progressive, refractory advanced t**hy**roid carcinoma - **The DUTHY trial**
Study code: GETNE - T1812
Version number and date: 05/12/2022

PROTOCOL SYNOPSIS

Clinical Protocol GETNE -T1812

Study Title: A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with progressive, refractory advanced thyroid carcinoma-The DUTHY trial
Protocol Number: GETNE-T1812
EudraCT: 2018-001066-42
Clinical Phase: II
Study Duration: 42 months
Investigational Product(s) and Reference Therapy: Durvalumab (MEDI4736) will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL durvalumab for intravenous (IV) infusion after dilution. Tremelimumab is supplied as a sterile solution for IV infusion. Tremelimumab will be supplied in glass vials containing 400 mg or 25 mg of liquid solution at a concentration of 20 mg/mL for infusion after dilution.
Research Hypothesis First-line and second-line therapy with multikinase inhibitors (sorafenib/lenvatinib in DTC and vandetanib/cabozantinib in MTC) achieve a 6-month PFS rate of 70-80%. However, beyond second-line treatment with other MKIs out of clinical trial in both DTC and MTC median PFS achieve 6-7 months with no partial remissions reported[4]. The PFS-rate at 6 months of placebo arms in first and second-line in patients with documented disease progression in DTC and MTC is between 20-30%. Anaplastic thyroid cancer (ATC) has no standard therapy that demonstrates benefit in overall survival. Prognosis is very poor and median overall survival is 3-4 months. Our hypothesis is that Durvalumab plus Tremelimumab may improve PFS-rate at 6 months in advanced thyroid cancer from 25% up to 45% based on the initial report of early clinical trials with immune checkpoint inhibitors in advanced thyroid cancer. For ATC, we hypothesize that the combination therapy may improve overall survival rate at 6 months from 5% to 35%.
Objectives: **Primary Objectives:** 1. Progression-free survival (PFS) rate at 6 months for DTC and MTC cohorts

2. Overall survival (OS) rate at 6 months for ATC cohort

Secondary Objectives:

1. Overall response rate (ORR) by irRECIST and RECIST.
2. To assess the duration of response according to irRECIST/RECIST.
3. To assess the median progression-free survival time (PFS) according to RECIST.
4. To assess the safety profile of Durvalumab and Tremelimumab in subjects with advanced thyroid neoplasms.
5. To assess the median overall survival (OS) time.
6. To assess response status according to irRECIST/RECIST at 6 and 12 months after start of study treatment.

Exploratory objective(s)

1. To evaluate biochemical response (changes in thyroglobulin, calcitonin and CEA levels) and its association with response rate and progression-free survival.
2. To assess whether baseline tumor and blood biomarkers may be predictive of response to durvalumab and tremelimumab therapy (if feasible).
3. To explore additional hypotheses related to biomarkers and relationship to durvalumab and tremelimumab efficacy and/or toxicity and thyroid cancer evolution that may arise from internal or external research activities (if feasible).

Study Design:

Patients will be included following review of inclusion/exclusion criteria in a prospective, non-randomized, open label, single arm, three parallel cohorts (DTC, MTC and ATC) phase II study in a Simon-II stage design to receive durvalumab 1500 mg plus tremelimumab 75 mg every 4 weeks up to 4 cycles followed by durvalumab 1500 mg every 4 weeks until disease progression, unacceptable toxicity or patients' decision.

Number of Centres:

15

Number of Patients:

- 46 patients in stage I
  - 17 patients for cohort DTC
  - 17 patients for cohort MTC
  - 12 patients for cohort ATC
- 38 patients in stage II
  - 19 patients for cohort DTC
  - 19 patients for cohort MTC

Study Population:

Advanced, radioiodine-refractory differentiated thyroid carcinoma, including papillary, follicular, Hürtle Cell and poorly-differentiated thyroid carcinoma (DTC).

Advanced medullary thyroid carcinoma (MTC)

Advanced anaplastic thyroid cancer (ATC)

Inclusion Criteria:

- Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
- Age $\geq$ 18 years at time of study entry.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Body weight >30kg.
- Confirmed differentiated thyroid cancer (papillary, follicular, poorly differentiated and Hürtle cell), medullary thyroid cancer or anaplastic thyroid cancer.
- Available tumor and blood samples for translational research
- Patients should meet one of the following criteria:
    - Cohort 1: Patients with locally advanced or metastatic differentiated thyroid cancer (including the subtypes of papillary, follicular, poorly differentiated and Hürthle cell carcinoma) after disease progression on systemic therapy with MKIs. Patients could be recruited in the study after progression to Lenvatinib (regardless prior lines) or progression on at least two prior MKIs which may or not include Lenvatinib. No prior therapy with immune checkpoint inhibitors is allowed. Patients with intolerable toxicity to MKIs that meet the prior inclusion criteria and experience disease progression by RECIST v1.1 after stopping therapy may be included.
    - Cohort 2: Patients with locally advanced or metastatic medullary thyroid cancer after progression on systemic therapy with MKIs. Patients could be recruited in the study after progression to Vandetanib (regardless prior lines) or progression to at least two prior MKIs that may or not include Vandetanib. No prior therapy with immune checkpoint inhibitors is allowed. Patients with intolerable toxicity to MKIs that meet the prior inclusion criteria and experience disease progression by RECIST v1.1 after stopping therapy may be included.
    - Cohort 3: Patients with locally advanced or metastatic anaplastic thyroid cancer regardless of prior therapy. No prior therapy with immune checkpoint inhibitors is allowed.
- No limitation of number of prior therapies.
- Life expectancy >3 months

- Adequate normal organ and marrow function as defined below:
- Haemoglobin ≥9.0 g/dL.
- Absolute neutrophil count (ANC) ≥ 1500 per mm^3.
- Platelet count ≥100,000 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 their physician.
- AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN.
- Measured creatinine clearance (CL) >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 clearance:

  Males:

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

  Females:

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

- Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
  - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
  - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

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:

- Participation in another clinical study with an investigational product during the last 21 days (washing period < 21 days)
- 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.
- Any previous treatment with a PD1, PD-L1 or CTLA-4 inhibitor, including durvalumab and tremelimumab.
- Any previous treatment with immunotherapy, including combinations of immunotherapy and other anticancer or targeted agents.
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
- Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
    - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
- 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 only after consultation with the Study Physician.
- 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.
- History of allogenic organ transplantation.
- 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.

- Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
- History of another primary malignancy except for:
  - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated carcinoma in situ without evidence of disease.
- History of active primary immunodeficiency.
- Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), hepatitis C, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccines whilst receiving IP and up to 30 days after the last dose of IP.
- Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from

screening to 90 days after the last dose of durvalumab monotherapy and 180 days for combined treatment with durvalumab and tremelimumab.

- Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
- Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

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

Durvalumab 1500 mg plus tremelimumab 75 mg via IV infusion Q4W, starting on Week 0, for up to a maximum of 4 doses/cycles followed by durvalumab monotherapy 1500 mg via IV infusion Q4W, starting 4 weeks after the last infusion of the combination, until disease progression, unacceptable toxicity or patients' decision.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

The safety objective of this trial is to characterize the safety and tolerability of durvalumab in combination with tremelimumab in subjects with advanced thyroid cancer. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, v5.0 The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analysed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (iris) will be collected and designated as immune related events of clinical interest (ECIs).

Efficacy Assessments:

The primary efficacy objective of this study is to evaluate the anti-tumour activity of durvalumab in combination with tremelimumab in subjects with advanced thyroid cancer measured by the PFS rate at 6 months for the cohorts of DTC and MTC and overall survival for the cohort of ATC.

Pharmacodynamic/Pharmacokinetic Assessments (if applicable):

Correlative blood samples for pharmacodynamic studies will be obtained during the course of the trial.

Archival tumour tissue will be required at baseline.

Statistical Methods and Data Analysis:

Summary tables (descriptive statistics and frequency tables) will be provided for all baseline variables, efficacy variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (mean, standard deviation, range, and median).

Ninety-five (95) percent confidence highest probability density (HPD) confidence intervals (95% CI) may also be presented, as appropriate. Frequency counts and percentage of subjects within each category will be provided for categorical data.

The primary efficacy analysis will be performed using the binomial test procedure. Missing data will be treated using statistical multiple random imputation.

Secondary endpoints will be summarized with descriptive statistics. Continuous variables will be summarized with n, mean, standard deviation, and range, frequency counts and percentage of subjects within each category will be provided for categorical data. Multivariate regression models will be used to study relations between explanatory variables and primary endpoint.

Survival analysis will be performed to analyse DFS, Kaplan-Meier curves will be presented and possible comparisons will be tested using the log-rank test or the Cox proportional hazard model for multivariate analysis, hazard ratios (HR) and their 95% confidence interval (CI95%) will be provided. Patients who are lost to follow-up or who discontinued treatment will be included in the final analysis by ITT of primary endpoint if they have at least one tumour evaluation.

Sample Size Determination:

Simon-II design was applied for sample size estimation for DTC (cohort 1) and MTC (cohort 2).

For cohorts 1 and 2, we hypothesize that the experimental therapy will improve the probability of being progression free at 6 months, from 25% in historical cohorts up to 45% in the current study.

With 80% of power (β = 0.2) and unilateral alpha (0.05), 36 patients per arm are needed to demonstrate the primary hypothesis. The Simon-II design suggested to observe $\geq$ 5 patients free of disease progression or unacceptable toxicity at 6 months within the first 17 patients included in the first stage. If $\geq$ 5 out of 17 patients in each cohort (DTC and MTC) are free of disease progression or unacceptable toxicity at 6 months in the first stage, study will continue recruiting 19 additional patients up to 36 patients per cohort. If $\geq$13 pts out of a total of 36 patients are alive and progression-free at the final analysis, the study should be declared positive. If stage I is reached only in one cohort, recruitment will continue in the successful cohort and stop in the non-effective cohort.

For sample size estimation for cohort 3, we hypothesize that the experimental therapy will improve the probability of being alive at 6 months from 5% in historical cohorts up to 35% in the current study. With 80% of power (β = 0.2) and unilateral alpha (0.05), 12 patients are needed to demonstrate the primary hypothesis. Cohort 3 will include the 12 patients only in one stage. No second stage is planned in the current study. If the hypothesis is reached for cohort 3, the study should be considered positive and further confirmatory studies will be needed.

SCHEDULE OF STUDY ASSESSMENTS

	Screening	C1	C1 D15	C2	C2 D15	C3	C3 D15	C4	C5 to PD	End of Treatment	For details see Section
Week	**-4 to -1**	**0**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**								
Day	**-28 to -1**	**1[a]**	**Q28 days ±3 days unless dosing needs to be held for toxicity reasons**								
Informed Consent											
Informed consent: study procedures[b]	X										4.1 8.1.1
Consent: genetic sample and analysis (optional)	X										12.3
Study procedures											
Physical exam (full)	X										8.2.2
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	X	X	X	8.2.2
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	8.2.4
ECG[d]	X	As clinically indicated									8.2.3
Concomitant medications	<----------									---------->	7.2
Demography, including baseline characteristics and tobacco use	X										3.2
Eligibility criteria	X										4.1 4.2
Laboratory Assessments											
Clinical chemistry[e]	X	X[f]	X	X	X	X	X	X	X	X	8.2.5
Hematology[e]	X	X[f]	X	X	X	X	X	X	X	X	8.2.5
TSH[g], (reflex free T3 or free T4[h])	X	X	X	X	X	X	X	X	X	X	8.2.5
Hepatitis B and C and HIV	X										8.2.5
Pregnancy test[i]	X										8.2.5
Monitoring											
ECOG performance status	X	X	X	X	X	X	X	X	X	X	
AE/SAE assessment [l]		<----------								---------->	10.2

Patient follow up contact / Patient review for safety		Midway through Cycles 1, 2 and 3: days 14 of C1, 2 and 3									3.3
IP administration											
Durvalumab [m,n]		X		X		X		X	X		5.2.1
Tremelimumab [m,n]		X		X		X		X			5.2.1
Other assessments and assays											
Tumor biopsy (archival, if available)	X										8.3
Efficacy evaluations											
Tumor evaluation (CT or MRI) (RECIST 1.1) [o,p]	X	q12w ± 1w until confirmed objective disease progression/death (whichever comes first). The schedule of q12w ± 1 week MUST be followed regardless of any delays in dosing. In case of suspected pseudo progression, treatment should be continued until PD is confirmed in the following imaging.									9
Biomarkers	x			x						x	

[a] Every effort should be made to minimize the time between randomization and starting treatment. (i.e. within 1 day of randomization)

[b] Informed consent of study procedures may be obtained prior to the 28-day screening window. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization.

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

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

[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 haematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

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

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

[i] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug. 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

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

[m] During the combination portion of treatment, tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. If there are no clinically significant infusion reactions with the first cycle, and at the discretion of the investigator, then for all other cycles, the durvalumab can be given immediately after the tremelimumab infusion has finished.

[n] 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.

[o] RECIST assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the neck, chest, abdomen (including liver and adrenal glands) and pelvis. Pelvic imaging is

recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to and prior to the start of IP. The confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit.

[p] Patients will have scans done q12w until confirmed objective disease progression.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated. C Cycle; ECG Electrocardiogram; IM Intramuscular; LFT Liver function test; PGx Pharmacogenetics research; qXw Every X weeks; qXw Every X weeks; SNP Single nucleotide polymorphism; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

TABLE OF CONTENTS **PAGE**

PROTOCOL SYNOPSIS **2**

Exploratory objective(s) 4

ABBREVIATIONS AND DEFINITION OF TERMS **21**

1. INTRODUCTION **26**

1.1 Disease background 26

1.1.1. Immunotherapies 28

1.1.2. Durvalumab 29

1.1.3. Tremelimumab 30

1.1.4. Durvalumab in combination with tremelimumab 30

1.2. Research hypothesis 30

1.3. Rationale for conducting this study 31

1.3.1. Durvalumab + tremelimumab combination therapy dose rationale 32

1.3.2. Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy 34

1.4. Benefit-risk and ethical assessment 35

1.4.1. Potential benefits 35

1.4.1.1. Durvalumab + tremelimumab 35

1.4.1.2. Overall risks 36

1.4.1.3. Durvalumab 36

1.4.1.4. Tremelimumab 38

1.4.2. Durvalumab + tremelimumab 39

1.4.3. Overall benefit-risk 41

2. STUDY OBJECTIVE **42**

2.1. Primary objective(s) 42

2.2. Secondary objective(s) 42

2.3. Exploratory objective(s) 42

3. STUDY DESIGN 43

3.1. Overview of study design 43

3.2. Study schema 43

Screening phase 43

Follow-up phase 44

3.3. Study oversight for safety evaluation 45

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL 46

4.1. Inclusion criteria 46

4.2. Exclusion criteria 48

4.3. Withdrawal of patients from study treatment and/or study 50

4.4. Replacement of patients 51

5. INVESTIGATIONAL PRODUCT(S) 52

5.1. Durvalumab and tremelimumab 52

5.1.1. Formulation/packaging/storage 52

5.2. Dose and treatment regimens 52

5.2.1. Treatment regimens 52

5.2.2. Duration of treatment and criteria for retreatment 53

5.2.3. Study drug preparation of durvalumab and tremelimumab 54

5.2.4. Monitoring of dose administration 55

5.2.5. Accountability and dispensation 56

5.2.6. Disposition of unused investigational study drug 56

6. TREATMENT PLAN 58

6.1. Patient enrolment and allocation 58

6.1.1. Procedures for allocation 58

6.1.2. Procedures for handling patients incorrectly enrolled 58

6.2. Dose modification and toxicity management 58

6.2.1. Durvalumab and tremelimumab 58

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S) 60

7.1. Restrictions during the study 60

7.2. Concomitant treatment(s) 61

7.2.1. Permitted concomitant medications 62

7.2.2. Excluded concomitant medications 62

8. STUDY PROCEDURES 64

8.1. Schedule of study procedures 64

8.1.1. Screening phase 64

8.1.2. Treatment phase 65

8.1.3. End of treatment 67

8.2. Description of study procedures 68

8.2.1. Medical history and physical examination, electrocardiogram, weight and vital signs 68

8.2.2. Physical examination 68

8.2.3. Electrocardiograms 68

8.2.4. Vital signs 68

8.2.5. Clinical laboratory tests 69

8.3. Biological sampling procedures 72

8.3.1. Biomarker/pharmacodynamics sampling and evaluation methods 73

8.3.2. Estimate of volume of blood to be collected for biomarkers studies 76

8.3.3. Archival tumor samples use beyond PD-L1 76

8.3.3.1. Archival tumor samples 76

8.3.4. Withdrawal of informed consent for donated biological samples 76

9. DISEASE EVALUATION AND METHODS 77

9.1. Efficacy variable 77

10. ASSESSMENT OF SAFETY 79

10.1. Safety parameters 79

10.1.1. Definition of adverse events 79

10.1.2. Definition of serious adverse events 79

10.1.3. Durvalumab + tremelimumab adverse events of special interest 79

10.2. Assessment of safety parameters 81

10.2.1. Assessment of severity 81

10.2.2. Assessment of relationship 82

10.3. Recording of adverse events and serious adverse events 82

10.3.1. Study recording period and follow-up for adverse events and serious adverse events 83

10.3.2. Causality collection 84

10.3.3. Relationship to protocol procedures 84

10.3.4. Adverse events based on signs and symptoms 84

10.3.5. Adverse events based on examinations and tests 84

10.3.6. Hy's Law 85

10.3.7. Disease progression 85

10.3.8. New cancers 85

10.3.9. Deaths 85

10.3.10. Reporting of serious adverse events 86

10.3.10.1. Reporting of deaths 86

10.3.11. Other events requiring reporting 87

10.3.11.1. Overdose 87

10.3.11.2. Pregnancy 87

10.3.12. Maternal exposure 87

10.3.13. Paternal exposure 88

10.4. Medication error 88

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION 90

11.1. Description of analysis sets 90

11.2. Methods of statistical analyses 91

11.2.1. Safety analyses 91

11.2.2. Efficacy analyses 91

11.2.3. Secondary objective(s) 92

11.2.4. Exploratory objective(s) 92

11.2.5. Interim analyses 92

11.3. Determination of sample size 93

12. ETHICAL AND REGULATORY REQUIREMENTS 94

12.1. Ethical conduct of the study 94

12.2. Ethics and regulatory review 94

12.3. Informed consent 94

12.4. Changes to the protocol and informed consent form 95

12.5. Audits and inspections 95

12.6. Confidentiality 95

12.7. Insurance 96

12.8. Publications 96

13. STUDY MANAGEMENT 98

13.1. Training of study site personnel 98

13.2. Monitoring of the study 98

13.2.1. Source data 98

13.3. Retention of Records 98

13.4. Quality assurance 99

13.5. Study timetable and end of study 99

14. DATA MANAGEMENT **100**

14.1. Study governance and oversight 100

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS **101**

15.1. Identity of investigational product(s) 101

16. LIST OF REFERENCES **102**

APPENDICES **106**

Appendix 1. 106

List of Abbreviations 153

Appendix 2. Schedule of study procedures: follow-up for patients who have completed durvalumab and tremelimumab treatment and achieved disease control (until confirmed progression of disease) and patients who have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progression of disease 155

Appendix 3. Schedule of study procedures: follow-up for patients who have discontinue durvalumab and tremelimumab treatment due to confirmed progression of disease at the investigator discretion 157

Appendix 4. Durvalumab dose volume calculations 159

Appendix 5. Tremelimumab dose volume calculations 160

Appendix 6. Contact details 161

Appendix 7. Sites and Investigators Participants 162

Appendix 8. Drug shipment form 163

LIST OF TABLES

Table 1. Highly effective methods of contraception (<1% failure rate) 62
Table 2. Supportive medications 63
Table 3. Prohibited concomitant medications 63
Table 4. Clinical chemistry 71
Table 5. Hematology 72
Table 6. Urinalysis 72
Table 7. List of investigational products for this study 104

ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
ATC	Anaplastic thyroid carcinoma
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report

CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
DTC	Differentiated thyroid carcinoma
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G

IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
L-T4	Levothyroxine
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MKIs	Multi kinase inhibitors
MRI	Magnetic resonance imaging
MTC	Medullary Thyroid Carcinoma
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease

PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Frederica's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, although it is a relatively rare tumor, representing less than 1% of all human malignancies. The incidence of thyroid cancer has been increasing in many countries over the last 30 years but without notable increase in mortality. The age and gender-adjusted incidence of thyroid cancer has increased faster than that of any other malignancy in recent years, with the increased incidence seen in both genders and all ethnic backgrounds. In Europe, according to GLOBOCAN in 2012 there were almost 53000 new cases of thyroid cancer, with more than 6300 deaths. The increasing incidence reflects better detection of subclinical disease with an increased detection of small papillary cancers, but an analysis of the National Cancer Institute's SEER database found an increase in detection of differentiated thyroid cancer of all sizes, including tumors greater than 4 cm, that may be also related to improved screening.
Thyroid cancer is a heterogeneous disease that is classified into: differentiated thyroid cancer (this category includes papillary, follicular, poorly differentiated histologic and Hürthle cell types), anaplastic thyroid carcinoma and medullary thyroid carcinoma. Differentiated carcinomas (DTC) are by far the most common type (approximately 90%: papillary 80%, follicular 10%; poorly differentiated <5%) medullary thyroid cancer (MTC) accounts for 5-10% of cases and anaplastic carcinomas for less than 5%.

1.1 Disease background

For patients with early stage disease, thyroidectomy represents the backbone of treatment. Radioiodine treatment is undertaken post-operatively in patients with documented persistent disease or at high risk of persistent or recurrent disease (according to the surgeon’s and pathologist’s report). Recurrent disease occurs in 10–15% of cases, mostly in patients with extensive disease (with large thyroid tumors, extension beyond the thyroid capsule, and lymph node metastases) and in those with an aggressive histologic type. In the majority of cases, recurrent disease is confined in the neck only, in lymph nodes, or in the thyroid bed. Patients with persistent or recurrent disease should be treated with l-T4 at doses high enough to suppress TSH because increased serum TSH level may enhance tumor growth. For these patients with neck recurrence treatment includes surgery, radioiodine, and in some patients external radiation therapy. Complete remission is achieved in more than two-thirds of patients with recurrent disease in lymph nodes, but recurrences in the thyroid bed or in soft tissues are often associated with a poorer prognosis.
Less than 10% of DTC patients will develop distant metastases, with half of them being detected at presentation. Usually these metastases are located in the lungs (50%), bones (25%), lungs and bones (20%), or rarely at other sites (5%). Treatment includes l-T4 treatment at doses that suppress TSH, local treatment modalities (such as surgery, radiation therapy, and radiofrequency ablation), and radioiodine in the two-thirds of patients who demonstrate significant radioiodine uptake in their metastases. Unfortunately, these methods provide a complete remission in only one-third of patients with distant metastases. The other patients have radioiodine refractory disease (defined as having at least one target lesion without radioiodine uptake or that has progressed within a year following radioiodine treatment or with persistent disease after the administration of a cumulative activity of more than 22 GBq (600 mCi) radioiodine). These tumors may remain stable with time or show a slow progression, and in such patients, follow-up with imaging every 6 months is recommended. However, in case of progression and significant tumor burden, systemic treatment may become indicated.

For these patients systemic cytotoxic chemotherapy offers limited benefit. The most widely tested cytotoxic agent in DTC is doxorubicin, either as single agent or in combination with cisplatin. However response rate is low (0-20%) and short lasting and toxicity is high.
As in many other tumors, tyrosine kinases play a crucial role in thyroid tumor proliferation, angiogenesis, invasion, metastasis, and avoidance of apoptosis. Small molecule tyrosine kinase inhibitors (TKIs) targeting signalling tyrosine kinases have been tested in patients with advanced differentiated thyroid cancer, given the oncogenic roles of mutations described above (BRAF, RET, RAS, as well as the VEGFR pathway). Several different tyrosine kinase inhibitors (TKIs) such as sorafenib, sunitinib, axitinib, pazopanib, and lenvatinib have been tested in patients with DTC in the context of phase II trials. Based on the results of two phase III trials, sorafenib and lenvatinib are approved in this setting (Brose M, et al. Lancet 2014; Schlumberger M, et al. N Engl J Med 2015). The phase III trial of sorafenib included patients with refractory DTC in first-line therapy. However, the lenvatinib phase III study included patients in both first and second-line therapy. Based on data available from phase III trials, lenvatinib has showed efficacy after a prior TKIs but no evidence of efficacy of sorafenib after TKIs therapy is available.

The primary treatment of both hereditary and sporadic forms of MTC is total thyroidectomy and removal of all neoplastic tissue present in the neck. Total thyroidectomy is preferred because up to 30% of patients with sporadic MTC and all patients with inherited MTC have bilateral or multifocal disease. MTC usually spreads to neck nodes and therefore routine dissection of the adjacent nodal tissue is recommended. After surgery T4 treatment is given with the objective to maintain the TSH level within the normal range and the patients are followed-up with serum calcitonin (and CEA) measurements. Patients who have undetectable serum calcitonin values are considered biochemically cured. On the contrary if basal serum calcitonin remains detectable then the patient is not cured and must be evaluated for residual disease. Postoperative radiation therapy may be indicated in patients who underwent an incomplete resection, have microscopic positive margins or even in patients with detectable postoperative serum calcitonin in the absence of distant metastases because this will decrease the risk of local recurrence.
Surgery is the main treatment for local and regional recurrences whenever feasible.
Patients with progressive or symptomatic metastatic disease who cannot be treated by surgery or radiotherapy should be considered candidates for systemic therapy. Treatment with traditional cytotoxic agents offers limited benefit and increased toxicity. The most commonly used agents were dacarbazine, doxorubicin and 5-FU (either in combination or single agent). Partial responses are reported in approximately in 10 percent of patients, but long-term responses are uncommon and no benefit on PFS has been demonstrated.
Similarly to DTC, because of the RET activating mutations observed in MTC several TKIs have been tested. Vandetanib and cabozantinib have demonstrated benefit on PFS in two phase III placebo-controlled clinical trials (Wells SA, et al. J Clin Oncol 2012; Elisei R, et al. J Clin Oncol 2013). Vandetanib is widely approved in this setting. However, the percentage of grade 3-4 toxicity reported in the phase III study of cabozantinib has limited its approval in most of countries.

Despite the significant advances in the management of refractory DTC and advanced MTC it should be noted that unfortunately, in the majority of patients, the disease eventually progresses, highlighting the need for new effective therapies as second and beyond treatment lines.

The history of anaplastic thyroid cancer (ATC) is completely different. ATC is one of the most aggressive solid tumors in humans. No standard therapy has demonstrated survival benefit in this setting. For localized disease, surgery and local radiotherapy is the standard of care, but for locally advanced disease or metastatic setting, the usefulness of chemotherapy and radiotherapy is controversial, and best supportive care is mandatory.

1.1.1. Immunotherapies

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

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

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

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

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al. 2012; Hirano et al. 2005; Iwai et al. 2002; Okudaira et al. 2009; Topalian et al. 2012; Zhang et al. 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al. 2014; Rizvi et al. 2015; Segal et al. 2015). In addition, high mutational burden e.g., in bladder carcinoma (Alexandrov et al. 2013) may contribute to the responses seen with immune therapy.

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

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

1.1.2. Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

As of the data cut-off (DCO) date (12 July 2017), across the entire clinical development program over than 8000 patients, an estimated 4067 patients have been exposed to 1 or more doses of durvalumab in ongoing AstraZeneca-sponsored Phase I to III studies, either as monotherapy or in combination, and 5911 patients where the treatment arm is blinded. Additionally, approximately 4000 patients have been exposed to 1 or more doses of durvalumab in externally sponsored/investigator-initiated clinical trials (ESR/IITs). Details on the safety profile of durvalumab monotherapy are summarized in Section 6.5. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.3. Tremelimumab

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

To date tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.4. Durvalumab in combination with tremelimumab

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

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue. In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date more than 1000 patients have received the combination, using a number of doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in Sections 1.4.2. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

1.2. Research hypothesis

The treatment options for patients with DTC and MTC who have progressed on one line of therapy are limited and there is no treatment that is generally considered as standard of care. No clinically meaningful benefit has yet been demonstrated with cytotoxic chemotherapy. On the other hand patients are still in good general condition and may still benefit from treatment and experience survival prolongation.

First-line and second-line therapy with TKIs (sorafenib/lenvatinib in DTC and vandetanib/cabozantinib in MTC) achieve a 6-month PFS rate of 70-80%. However, beyond second-line treatment with other MKIs out of clinical trial in both DTC and MTC median PFS achieve 6-7 months with no partial remissions

reported (Massicotte MH, et al. Eur J of Endocr 2014). The PFS-rate at 6 months of placebo arms in first and second-line in patients with documented disease progression in DTC and MTC is between 20-30%.

Anaplastic thyroid cancer has no standard therapy that demonstrated benefit in overall survival. Prognosis is very poor and median overall survival is 3-4 months.

Following the knowledge of increased tumor-specific antigens with the presence of more mutational load, dedifferentiation process and treatments previously received we hypothesize that immunotherapy could have a higher effect in the setting of refractory neuroendocrine neoplasms, when tumor behaviour is more aggressive and the probability of immune escape process is higher.

Our hypothesis is that Durvalumab plus Tremelimumab may improve PFS-rate at 6 months in advanced thyroid cancer from 25% up to 45% based on the initial report of early clinical trials with immune check point inhibitors in advanced thyroid cancer.

For ATC, we hypothesize that the combination therapy may improve overall survival rate at 6 months from 5% to 35%.

1.3. Rationale for conducting this study

The treatment of advanced DTC and MTC has evolved dramatically during the last 5 years with the arrival of TKIs that have changed the natural history of these diseases. However, when tumors became resistant to TKIs, no additional therapies have showed activity in these settings. The initial good prognosis of DTC and MTC changes completely when these diseases progress to TKIs therapy with a higher aggressiveness and poor outcome. The ATC evolution is even worse, being refractory to chemotherapy upfront and with no real options to control the disease.

The scientific rationale for the use of immunotherapy in advanced thyroid cancer includes:

1. The presence of an inflammatory infiltrate in a large percentage of tumors (in particular DTC).
2. The presence of a driver mutation in most DTCs and MTC. However, the number of mutations per tumor is rather low in classical thyroid cancers but is significantly higher in refractory thyroid cancers.
3. Anaplastic thyroid cancer is characterized for carrying a high mutational tumor load that increases the probability of neoantigens and the usefulness of immunotherapy in this setting.
4. Positive immunohistochemistry with antibodies directed against PDL1 has been reported between 50-80% in different series, correlated with worse prognosis.
5. Microsatellite instability has been reported in up to 50% of DTC. This microsatellite instability has been correlated with a higher mutational tumor load.

The evidence of efficacy of immune checkpoint inhibitors in thyroid cancer is still very preliminary, including initial data from phase I/Ib clinical trials. The data currently reported from the KEYNOTE-028 showed a 9% of partial responses by RECIST, tumor shrinkage in almost 50% of patients and mPFS of 6.8 months in refractory setting, including long responders (Mehnert JM, et al. ASCO 2016).

Tremelimumab and Durvalumab would be the first immune combination agents showing efficacy in advanced thyroid cancer including all the histologies (DTC, MTC and ATC).

As an antibody that blocks the interaction between PD-L1 and its receptors, durvalumab may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile and responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. Additionally, the rationale for combining durvalumab and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity**.** In fact, combining immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy.

1.3.1. Durvalumab + tremelimumab combination therapy dose rationale

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

Pharmacokinetics/Pharmacodynamics data

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of durvalumab in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included to align with the Q4W dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in PDx activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented PDx activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Clinical data

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to 20 mg/kg. Tremelimumab was

given on a Q4W schedule whilst durvalumab was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes the benefit-risk profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab.

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to another dose combinations. Of the 14 patients in this cohort, there were 4 patients (29%) with PR, 4 patients (29%) with SD, and 2 patients (14%) with PD. Two patients were not evaluable for response.

Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

Refer to the current durvalumab Investigator’s Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

1.3.2. Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy

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

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. (For further information on PK observations in Study 006, please see the current IB).

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen.

The durvalumab + tremelimumab combination regimen will be administered for 4 doses Q4W followed by durvalumab monotherapy Q4W until disease progression.

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 or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK exposures (AUC_{ss},0-28, $Cmax_{,ss}$, and $Cmin_{,ss}$) using the population PK model. A fixed dose of 750 mg Q2W was selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (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 (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) regimens yield similar median steady state Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W.
Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses=0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) (Wang et al. 2014). Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 kg to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al. 2006; Wang et al. 2009; Zhang et al. 2012; Narwal et al. 2013). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and

body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al. 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters (Zhang et al. 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and a fixed dose of 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

1.4. Benefit-risk and ethical assessment

Natural history of advanced DTC and MTC is usually prolonged. Well differentiated thyroid cancers are slowing growing tumors that require continued therapy to control tumor growth, increasing the risk of long-term side effects. The prolonged effect of immunotherapy could be of especial interest in this setting, reducing the risk of chronic toxicity and maintaining the long-term benefit. The arrival of TKIs have changed the management of refractory disease. However, the toxicity profile of these drugs, the need for prolonged treatments and the lack of efficacy in overall survival have limited the expanded use of these therapies, otherwise being the only treatment option in advanced stages.

In ATC, the lack of approved therapies with impact in OS, PFS or even response rate, urgently increases the need for effectives therapies that could change the very poor prognosis of this disease.

1.4.1. Potential benefits

1.4.1.1. Durvalumab + tremelimumab

Available data suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma. Of the 102 subjects with advanced NSCLC treated with durvalumab in combination with tremelimumab in Study D4190C00006, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of PR, 14 (22%) had SD, 22 (35%) had PD, and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed CR or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.

Current experience with single-agent immune checkpoint inhibitor studies suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich the patient population by selecting patients likely to respond to therapy. To date, no assay has been established or validated, and no single approach has proven accurate, for patient enrichment for immune checkpoint inhibitors, especially for drug combination. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumor cells and/or tumor infiltrating cells may be associated with greater clinical benefit.

Data from ongoing studies with durvalumab and other agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (e.g., NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious (in terms of ORR) in patients who are PD-L1-positive.

Given these findings, a number of ongoing studies are assessing the activity of agents in patients with PD-L1–positive tumors. There is also an unmet medical need in patients with PD-L1–negative tumors that needs to be addressed. Data from the combination of tremelimumab to durvalumab, the ORR can be increased in patients with PD-L1 negative NSCLC.

In the particular case of thyroid cancers, the expression of PD-L1 has been described between 50-80%, and the combination of durvalumab plus tremelimumab could offer benefit to the whole refractory population. Data from anti PD-L1/PD-1 monotherapy has reported <10% of partial remissions in DTC, that could also be increased with the combination of durvalumab and tremelimumab.

1.4.1.2. Overall risks

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

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

1.4.1.3. Durvalumab

Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/interstitial lung disease (ILD), endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus (which may present with diabetic ketoacidosis), and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid, myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, encephalitis serious infections, subcutaneous injection site reaction, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis).

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

In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetite. Approximately 10% of participants discontinued the drug due to an AE.

Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 5 events reported across the durvalumab program.

Serious adverse reactions for durvalumab monotherapy considering expected;

Table 34 Serious Adverse Reactions for Durvalumab Monotherapy Considered Expected for Safety Reporting Purposes, DCO: 12 July 2022

MedDRA (v25.0) SOC	PT	Number (%) of subjects exposed (N=5208)		
		Suspected SARs n (%) [a]	Occurrence of life-threatening suspected SARs n (%) [b]	Occurrence of fatal suspected SARs n (%) [b]
Respiratory, thoracic, and mediastinal disorders	Pneumonitis	43 (0.8)	0	0
	Interstitial lung disease	10 (0.2)	0	0
Injury, poisoning, and procedural complications	Infusion related reaction	7 (0.1)	0	0
Infections and infestations	Pneumonia	16 (0.3)	0	0
	Pneumocystis jirovecii pneumonia	2 (<0.1)	0	0
Gastrointestinal disorders	Colitis	12 (0.2)	0	0
	Diarrhoea	13 (0.2)	0	0
	Abdominal pain	3 (<0.1)	0	0
	Enterocolitis	3 (<0.1)	0	0
	Pancreatitis	2 (<0.1)	0	0
	Proctitis	2 (<0.1)	0	0
Endocrine disorders	Adrenal insufficiency	6 (0.1)	0	0
	Hyperthyroidism	3 (<0.1)	0	0
	Hypopituitarism	3 (<0.1)	0	0
	Hypothyroidism	3 (<0.1)	0	0
Hepatobiliary disorders	Hepatitis	5 (<0.1)	0	0
	Autoimmune hepatitis	3 (<0.1)	0	0
Renal and urinary disorders	Nephritis	3 (<0.1)	0	0
	Blood creatinine increased	2 (<0.1)	0	0

Table 34 Serious Adverse Reactions for Durvalumab Monotherapy Considered Expected for Safety Reporting Purposes, DCO: 12 July 2022

MedDRA (v25.0) SOC	PT	Number (%) of subjects exposed (N=5208)		
		Suspected SARs n (%) [a]	Occurrence of life-threatening suspected SARs n (%) [b]	Occurrence of fatal suspected SARs n (%) [b]
Investigations	AST increased	6 (0.1)	0	0
	ALT increased	5 (<0.1)	0	0
	Hepatic enzyme increased	2 (<0.1)	0	0
	Transaminases increased	2 (<0.1)	0	0
General disorders and administration site conditions	Pyrexia	5 (<0.1)	0	0
Musculoskeletal and connective tissue disorders	Myositis	4 (<0.1)	0	0
Skin and subcutaneous tissue disorders	Rash	4 (<0.1)	0	0
Blood and lymphatic system disorders	Immune thrombocytopenia	2 (<0.1)	0	0
Metabolism and nutrition disorders	Type 1 diabetes mellitus	2 (<0.1)	0	0
Nervous system disorders	Myasthenia gravis	2 (<0.1)	0	0

[a] n = number of patients who have experienced the SAR.

[b] All fatal and all life-threatening events for durvalumab monotherapy are considered unexpected for reporting purposes and are excluded from this table.

Pooled dataset from studies CD-ON-MEDI4736-1108, ATLANTIC, MYSTIC, EAGLE, ARCTIC, CONDOR, HAWK, PACIFIC, D4190C00002, BISCAY, STRONG, PACIFIC 6, DANUBE, HIMALAYA, KESTREL, NeoCOAST, D4190C00007, D4190C00021, D4190C00022, and D4198C00001.

Only patients exposed to 10 mg/kg Q2W or 20 mg/kg Q4W durvalumab, or equivalent fixed dosing of durvalumab 750 mg Q2W or 1500 mg Q4W schedule, are included.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DCO = data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; Q2W = every 2 weeks; Q4W = every 4 weeks; SAR = serious adverse reaction; SOC = system organ class.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (please see Appendix 1)

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

1.4.1.4. Tremelimumab

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

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

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

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

Serious adverse reactions for tremelimumab monotherapy considering expected;

MedDRA (v22.0) SOC	PT	Number (%) of subjects exposed Tremelimumab RSI pool (N=1665)		
		Suspected SARs [a] n (%)	Occurrence of life-threatening suspected SARs [b] n (%)	Occurrence of fatal suspected SARs [b] n (%)
Endocrine disorders	Hypophysitis	13 (0.8)	0	0
	Adrenal insufficiency	7 (0.4)	0	0
	Hyperthyroidism	5 (0.3)	0	0
	Hypothyroidism	4 (0.2)	0	0
	Lipase increased	2 (0.1)	0	0
Gastrointestinal disorders	Diarrhoea	183 (11.0)	0	0
	Colitis	68 (4.1)	0	0
	Enterocolitis	4 (0.2)	0	0
Hepatobiliary disorders	Autoimmune hepatitis	2 (0.1)	0	0
Skin and subcutaneous tissue disorders	Rash	8 (0.5)	0	0
	Pruritus	2 (0.1)	0	0

Includes legacy studies (A3671002, A3671008, A3671009, A3671022, A3671001, A3671011, A3671014, A3671015) and D4880C00003, D4880C00010, D4881C00024, D4884C00001, D4193C00003, D4190C00022 and D4191C00004. n = Number of subjects who have experienced the SAR.

[a] n = number of subjects who have experienced the SAR.

[b] All fatal and all life-threatening events for tremelimumab monotherapy are considered unexpected for reporting purposes.

ADR Adverse drug reaction; DCO Data cut-off; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term; RSI Reference safety information; SAR Serious adverse reaction; SOC System organ class.

1.4.2. Durvalumab + tremelimumab

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and is being studied in a number of other ongoing clinical trials, in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab and tremelimumab (based on an equivalent durvalumab dose of 20 mg/kg and a tremelimumab dose of 1 mg/kg) are similar to those for durvalumab monotherapy with additional risks of amylase increased, lipase increased, intestinal perforation and large intestinal perforation, pulmonary embolism which are unique risks for the durvalumab and tremelimumab combination.

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

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20 mg/kg and tremelimumab 1 mg/kg AEs (all grades) reported very commonly (≥ 10% of patients) are cough/productive cough, alteration of hepatic enzymes ALT/AST, diarrhoea, abdominal pain, hypothyroidism, rash, pruritus, pyrexia, peripheral oedema, and upper respiratory tract infections.

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

Serious adverse reactions for durvalumab plus tremelimumab combination considered expected.

Table 35 Serious Adverse Reactions for Durvalumab Plus Tremelimumab Combination Considered Expected for Safety Reporting Purposes, DCO: 12 July 2022

MedDRA (v25.0) SOC	PT	Number (%) of subjects exposed (N=3595)		
		Suspected SARs n (%) [a]	Occurrence of life-threatening suspected SARs n (%) [b]	Occurrence of fatal suspected SARs n (%) [b]
Gastrointestinal disorders [c]	Colitis	55 (1.5)	0	0
	Diarrhoea	85 (2.4)	0	0
	Autoimmune colitis	7 (0.2)	0	0
	Abdominal pain	5 (0.1)	0	0
	Enterocolitis	11 (0.3)	0	0
	Autoimmune pancreatitis	3 (<0.1)	0	0
	Enteritis	2 (<0.1)	0	0
	Immune-mediated enterocolitis	2 (<0.1)	0	0
	Pancreatitis	10 (0.3)	0	0
	Pancreatitis acute [d]	2 (0.4)	0	0
Respiratory, thoracic, and mediastinal disorders	Pneumonitis	49 (1.4)	0	0
	Interstitial lung disease	17 (0.5)	0	0
Endocrine disorders	Adrenal insufficiency	18 (0.5)	0	0
	Hyperthyroidism	7 (0.2)	0	0
	Hypopituitarism	10 (0.3)	0	0
	Hypophysitis	7 (0.2)	0	0
	Hypothyroidism	4 (0.1)	0	0
	Thyroiditis	3 (<0.1)	0	0
General disorders and administration site conditions	Pyrexia	22 (0.6)	0	0
	Oedema peripheral	2 (<0.1)	0	0

Table 35 Serious Adverse Reactions for Durvalumab Plus Tremelimumab Combination Considered Expected for Safety Reporting Purposes, DCO: 12 July 2022

MedDRA (v25.0) SOC	PT	Number (%) of subjects exposed (N=3595)		
		Suspected SARs n (%) [a]	Occurrence of life-threatening suspected SARs n (%) [b]	Occurrence of fatal suspected SARs n (%) [b]
Hepatobiliary disorders	Autoimmune hepatitis	8 (0.2)	0	0
	Hepatitis	12 (0.3)	0	0
	Hepatotoxicity	3 (<0.1)	0	0
	Immune-mediated hepatitis	6 (0.2)	0	0
Infections and infestations	Pneumonia	18 (0.5)	0	0
Cardiac disorders	Myocarditis	3 (<0.1)	0	0
Injury, poisoning, and procedural complications	Infusion related reaction	4 (0.1)	0	0
Renal and urinary disorders	Nephritis	3 (<0.1)	0	0
Skin and subcutaneous tissue disorders	Pemphigoid	3 (<0.1)	0	0
	Pruritus	2 (<0.1)	0	0
	Rash	5 (0.1)	0	0
	Rash maculo-papular	4 (0.1)	0	0
Musculoskeletal and connective tissue disorders	Myositis	4 (0.1)	0	0
	Polymyositis	2 (<0.1)	0	0
Investigations [e]	ALT increased	3 (<0.1)	0	0
	Amylase increased	5 (0.1)	0	0
	AST increased	6 (0.2)	0	0
	Lipase increased	9 (0.3)	0	0
Nervous system disorders	Myasthenic syndrome	2 (<0.1)	0	0

[a] n = number of subjects who have experienced the SAR.
[b] All fatal and all life-threatening events for durvalumab + tremelimumab are considered unexpected for reporting purposes and are excluded from this table.
[c] At the time of the DCO (12 July 2022), one patient had an AE of large intestine perforation reclassified from non-life-threatening to life-threatening; therefore, this event is no longer considered expected for safety reporting purposes and has been excluded from this table.
[d] For this PT, only occurrence in subjects exposed to the tremelimumab 300 mg x one dose + durvalumab 1500 mg Q4W schedule from studies D4190C00022 and HIMALAYA (N=463) has been included.
[e] One patient had an AE of transaminases increased as per MedDRA Version 22.0 that codes to hypertransaminasaemia as per MedDRA Version 25.0; therefore, this event has been excluded from this table.

Pooled dataset from studies D4190C00002, D4190C00006, D4190C00010, D4190C00011, D4190C00021, D4190C00022, D4190C00007, D4190C00023, D4198C00001, D419AC00006, D4880C00010, D4884C00001, ARCTIC, EAGLE, MYSTIC, CONDOR, DANUBE, NEPTUNE, KESTREL, HIMALAYA, and BALTIC.

Patients exposed to 20 mg/kg durvalumab plus 1 mg/kg Q4W tremelimumab, or equivalent durvalumab 1500 mg + tremelimumab 75 mg fixed dose Q4W (T75+D), and tremelimumab 300 mg x one dose +durvalumab 1500 mg Q4W (T300+D) are included.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DCO = data cut-off; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; Q4W = every 4 weeks; SAR = serious adverse reaction; SOC = system organ class; T75+D = 20 mg/kg durvalumab plus 1 mg/kg tremelimumab, or equivalent durvalumab 1500 mg + tremelimumab 75 mg fixed dose; T300+D = tremelimumab 300 mg x one dose plus durvalumab 1500 mg Q4W.

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

1.4.3. Overall benefit-risk

Considering the refractory setting of the design of the current study and the safety profile of the combination of durvalumab and tremelimumab, the overall benefit-risk of the treatment combination of this trial is expected to be favourable.

2. STUDY OBJECTIVE

2.1. Primary objective(s)

The study will include patients with advanced thyroid cancer in three different cohorts with the following primary endpoints:

Primary endpoint for cohorts 1 and 2 (DTC and MTC):

6-months progression-free survival by Response Evaluation Criteria in Solid Tumors (RECIST), which is defined as the percentage of patients achieving complete response, partial response (PR), or stable disease (SD) at 24 weeks after durvalumab plus tremelimumab was started without observing disease progression or death at this time point.

Primary endpoint for cohort 3 (ATC):

6-months overall survival rate, which is defined as the percentage of patients alive at 24 weeks after durvalumab plus tremelimumab was started.

2.2. Secondary objective(s)

1. Overall response rate (ORR) by irRECIST and RECIST.
2. To assess the duration of response according to irRECIST/RECIST.
3. To assess the median progression-free survival time (PFS) according to RECIST.
4. To assess the safety profile of Durvalumab and Tremelimumab in subjects with advanced thyroid neoplasms.
5. To assess the median overall survival (OS) time.
6. To assess response status according to irRECIST/RECIST at 6 and 12 months after start of study treatment.

2.3. Exploratory objective(s)

1. To evaluate biochemical response (changes in thyroglobulin, calcitonin and CEA levels) and its association with response rate and progression-free survival.
2. To assess whether baseline tumor and blood biomarkers may be predictive of response to durvalumab and tremelimumab therapy.
3. To explore additional hypotheses related to biomarkers and relationship to durvalumab and tremelimumab efficacy and/or toxicity and thyroid cancer evolution that may arise from internal or external research activities.

3. STUDY DESIGN

3.1. Overview of study design

This is a prospective, multi-centre, open label, stratified, exploratory phase II study evaluating the efficacy and safety of durvalumab plus tremelimumab in different cohorts of patients with thyroid cancers.

The study will include patients in three different cohorts:

- Cohort 1: Patients with locally advanced or metastatic differentiated thyroid cancer (including the subtypes of papillary, follicular, poorly differentiated and Hürthle cell carcinoma) after progression to systemic therapy with MKIs. Patients could be recruited in the study after progression to Lenvatinib (regardless prior lines) or progression to at least two prior MKIs that could or not include Lenvatinib. No prior therapy with immune checkpoint inhibitors is allowed.

- Cohort 2: Patients with locally advanced or metastatic medullary thyroid cancer after progression to systemic therapy with MKIs. Patients could be recruited in the study after progression to Vandetanib (regardless prior lines) or progression to at least two prior MKIs that could or not include Vandetanib. No prior therapy with immune checkpoint inhibitors is allowed.

- Cohort 3: Patients with locally advanced or metastatic anaplastic thyroid cancer regardless of prior therapy.

The study includes a Simon-II design to assess efficacy and rule out futility. The first stage will include 17 patients per cohort 1 and 2 and 12 patients per cohort 3. The patient recruitment period of the study for this first stage will last approximately 18 months. The maximum treatment period for each subject on study is anticipated to be approximately 24 months (based on long responders of preliminary data of current trials with immune checkpoint inhibitors in this setting). However, subjects will continue on active treatment until disease progression or unacceptable toxicity and also active follow-up to determine secondary endpoints of duration of response, median progression-free survival, median overall survival and safety profile. The second stage will be assessed after completion of first stage and only in the cohort that reached the specified clinical benefit. For stage II, study will continue recruiting 19 additional patients up to 36 patients per cohort. Stage II only may apply to cohort 1 and 2.

This study will be conducted in 3 phases: a screening phase, a treatment phase stratified by tumor origin (three different cohort) and a follow up phase.

3.2. Study schema

Screening phase

Screening will occur between Day -28 and Day -1. The purpose of the screening period is to establish protocol eligibility. Informed consent will be obtained up to 4 weeks prior to Cycle 1 Day 1 and after the

study has been fully explained to each subject and prior to the conduct of any screening procedures or assessments.

The purpose of the baseline visit is to establish disease characteristics prior to allocation and treatment and to confirm protocol eligibility as specified in the inclusion/exclusion criteria. Results of baseline assessments must be obtained prior to the first dose of study drug (Cycle 1/Day 1). Baseline assessments may be performed on Day -1 or on Cycle 1/Day 1 prior to dosing. Clinical laboratory tests including pregnancy test (where applicable) can be performed within 72 hours of the first dose of study drug. Subjects who complete the baseline visit and continue to meet the criteria for inclusion/exclusion will begin the treatment phase of this study.

Treatment phase

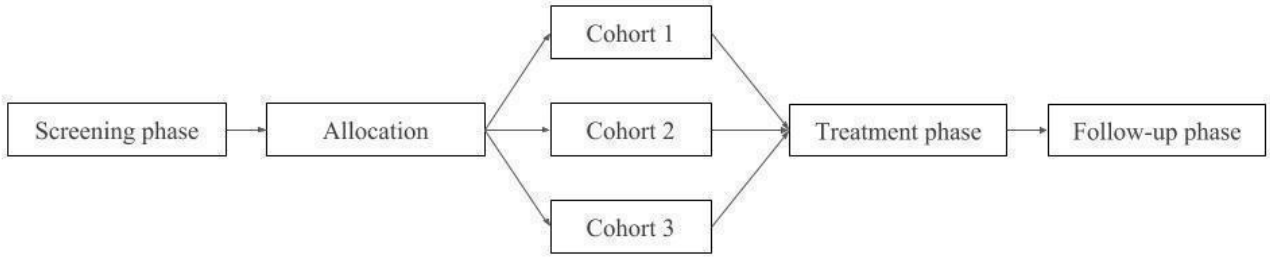
The treatment phase will begin at the time of allocation of the first patient and will consist of the study treatment cycles. The treatment phase will end when the last patient discontinues the study drug.

Subjects will be allocated in each primary tumor cohort to receive durvalumab 1500 mg Q4W plus tremelimumab 75 mg Q4W for up to 4 doses during the first 4 cycles of combined therapy. After the first 4 cycles (or before is tremelimumab is stopped due to toxicity), patients will continue to receive durvalumab 1500 mg Q4W until disease progression or unacceptable toxicity. Cycles are defined by 4 weeks or 28 days. Subjects will undergo safety and efficacy assessment as defined per protocol.

If a toxicity pause occurs, cycles not administered for that toxicity can be delayed for a maximum of 4 weeks, after that time that cycle will be considered lost and the next cycle will be administered.
Remember no restarts are allowed after a delay of more than 12 weeks due to toxicity or more than 4 weeks of delay if **the reason is different from toxicity** without consulting the Coordinating Investigator.

Follow-up phase

Patients will finish the treatment phase after disease progression during the treatment phase or if they present unacceptable toxicity. For patients that complete the scheduled treatment, the follow-up phase will begin to determine survival endpoints. Tumor assessments will continue every 12 weeks or clinically indicated following local protocol assessments.



3.3. Study oversight for safety evaluation

A subject may elect to discontinue study drug at any time for safety, medical, or personal reasons. Patients who choose to discontinue study drug prior to disease progression will be followed in the post study treatment follow up period and continue to undergo regularly scheduled disease assessment until documentation of disease progression or start of an alternative anticancer treatment. All subjects who discontinue study drug will be followed for overall survival and all post progression cancer treatments administered will be recorded. Subjects may at any time withdraw consent for further study participation. No further data will be collected on subjects once consent has been withdrawn. The investigator will promptly explain to the subject involved that the study drug will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means as much as possible to gather information such as the reason for failure to return and the status of treatment compliance, presence or absence of adverse events, and clinical courses of signs and symptoms, and the information will be recorded in the CRF.

Subjects who discontinue early from the study or treatment will be discontinued for 1 of these primary reasons: adverse event(s), lost to follow-up, subject choice, progressive disease, or administrative/other. In addition to the primary reason, the subject may have indicated 1 or more of these reasons as secondary reasons for discontinuation. Study disposition information will be collected on the appropriate CRF. A subject removed from the study for any reason may not be replaced.

Safety will be assessed by monitoring and recording all AEs including all CTCAE grades (for both increasing and decreasing severity) and serious adverse events (SAEs); regular monitoring of hematology and clinical chemistry; physical examinations; and regular measurement of vital signs, and electrocardiograms (ECGs) as detailed in the schedule of visits and procedures.

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

Approximately 46 patients will be enrolled and allocated in a balanced manner into either the three cohorts of patients at approximately 15 sites in Spain during the first stage of the trial (Simon-II design). Each patient must meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study. Under no circumstances, will there be exceptions to this rule.

In a second stage, 38 additional patients may be included in cohorts 1 and 2 (19 in each cohort respectively) if they meet the efficacy endpoint.

4.1. Inclusion criteria

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

1. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
2. Age ≥ 18 years at time of study entry.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Body weight >30kg.
5. Confirmed differentiated thyroid cancer (papillary, follicular, poorly differentiated and Hürtle cell), medullary thyroid cancer and anaplastic thyroid cancer.
6. Available tumor and blood samples for translational research
7. Patients should meet one of the following criteria:
    a. Cohort 1: Patients with locally advanced or metastatic differentiated thyroid cancer (including the subtypes of papillary, follicular, poorly differentiated and Hürthle cell carcinoma) after disease progression on systemic therapy with MKIs. Patients could be recruited in the study after progression to Lenvatinib (regardless prior lines) or progression on at least two prior MKIs which may or not include Lenvatinib. No prior therapy with immune checkpoint inhibitors is allowed. Patients with intolerable toxicity to MKIs that meet the prior inclusion criteria and experience disease progression by RECIST v1.1 after stopping therapy may be included.
    b. Cohort 2: Patients with locally advanced or metastatic medullary thyroid cancer after progression on systemic therapy with MKIs. Patients could be recruited in the study after progression to Vandetanib (regardless prior lines) or progression to at least two prior MKIs that may or not include Vandetanib. No prior therapy with immune checkpoint inhibitors is allowed. Patients with intolerable toxicity to MKIs that meet the prior inclusion criteria and experience disease progression by RECIST v1.1 after stopping therapy may be included.

c. Cohort 3: Patients with locally advanced or metastatic anaplastic thyroid cancer regardless of prior therapy. No prior therapy with immune checkpoint inhibitors is allowed.

8. No limitation of number of prior therapies.
9. Life expectancy >3 months
10. Adequate normal organ and marrow function as defined below:
    a. Haemoglobin ≥9.0 g/dL.
    b. Absolute neutrophil count (ANC) ≥ 1500 per mm^3.
    c. Platelet count ≥100,000 per mm^3.
    d. 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 their physician.
    e. AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x U
    f. Measured creatinine clearance (CL) >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 clearance:

       Males:

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

       Females:

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

11. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    a. Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

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

12. 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. Participation in another clinical study with an investigational product during the last 21 days.(washing period < 21days)
2. 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.
3. Any previous treatment with a PD1, PD-L1 or CTLA-4 inhibitor, including durvalumab and tremelimumab.
4. Any previous treatment with immunotherapy, including combinations of immunotherapy and other anticancer or targeted agents.
5. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
6. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection).
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
7. 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:
    a. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
    b. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.

8. 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.
9. History of allogenic organ transplantation.
10. 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:
    a. Patients with vitiligo or alopecia.
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.
    c. Any chronic skin condition that does not require systemic therapy.
    d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician.
    e. Patients with celiac disease controlled by diet alone.
11. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
12. History of another primary malignancy except for:
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    c. Adequately treated carcinoma in situ without evidence of disease.
13. History of active primary immunodeficiency.
14. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), hepatitis C, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

15. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccines whilst receiving IP and up to 30 days after the last dose of IP.
16. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ highly effective birth control from screening to 90 days after the last dose of durvalumab monotherapy and 180 days for combined treatment with durvalumab and tremelimumab
17. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
18. 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.

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

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

4.3. Withdrawal of patients from study treatment and/or study

Permanent discontinuation of study treatment

An individual patient will not receive any further investigational product if any of the following occur in the patient in question and will enter in the follow-up phase:

1. An individual patient will not receive any further durvalumab + tremelimumab combination therapy or durvalumab monotherapy if their weight falls to 30 kg or less.
2. Withdrawal of consent or lost to follow-up
3. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
4. 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
5. Pregnancy or intent to become pregnant
6. Any AE that meets criteria for discontinuation as defined in Section 0.
7. Grade ≥3 infusion reaction
8. Patient noncompliance that, in the opinion of the investigator or sponsor, 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 + tremelimumab or durvalumab monotherapy. Patients who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment

11. Patients who are permanently discontinued from receiving investigational product will be followed for safety per Section 10 and Appendix 2 or Appendix 3, 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.

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.

Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (Appendix 1)

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

- all further participation in the study including any further follow up (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

4.4. Replacement of patients

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

5. INVESTIGATIONAL PRODUCT(S)

5.1. Durvalumab and tremelimumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab and tremelimumab to the sponsor as a solution for infusion after dilution. It is the sponsor's responsibility to provide the sites with the study drug.

5.1.1. Formulation/packaging/storage

Durvalumab (MEDI4736)

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. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca either as a 400-mg or a 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal fill volume is 20.0 mL for the 400-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged light exposure.

5.2. Dose and treatment regimens

5.2.1. Treatment regimens

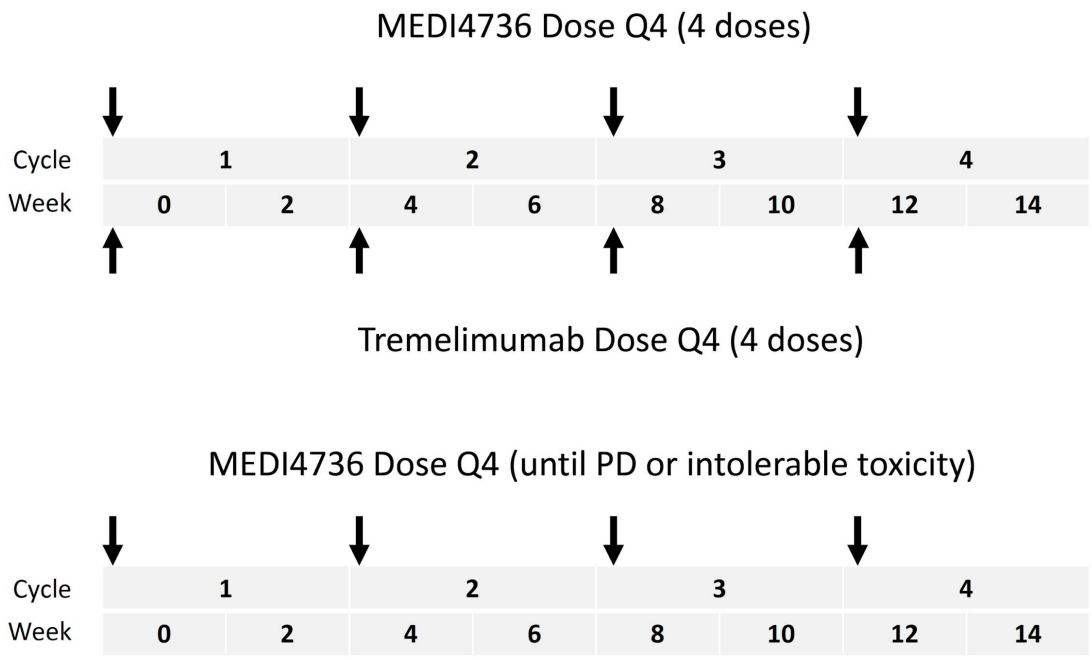
Durvalumab + tremelimumab combination therapy followed by durvalumab monotherapy

Patients will receive durvalumab (MEDI4736) (1500 mg Q4W) in combination with tremelimumab (75 mg IV Q4W) for up to 4 doses/cycles each, followed by durvalumab (MEDI4736) 1500 mg Q4W until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. The first durvalumab (MEDI4736) monotherapy dose at 1500 mg Q4W will be 4 weeks after the final dose of durvalumab (MEDI4736) in combination with tremelimumab. See Figure 2. (N.B An individual patient will not receive any further durvalumab + tremelimumab combination therapy or durvalumab monotherapy if their weight falls to 30 kg or less).

Tremelimumab will be administered first; the durvalumab (MEDI4736) infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. Standard infusion time for each is 1 hour. In the event that there are interruptions during infusion, the total allowed time should not exceed

8 hours at room temperature per infusion. If there are no clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of durvalumab (MEDI4736) can be given immediately after the tremelimumab infusion has finished.

Figure 1. Durvalumab (MEDI4736) + tremelimumab combination therapy dosing schedule



The trial medication (i.e., Durvalumab and Tremelimumab) and its packaging will be labelled in accordance with annex 13 of EU to Good Manufacturing Practice. Storage will be done according IB and labelling specifications.

5.2.2. Duration of treatment and criteria for retreatment

All treatment will be administered beginning on Day 1 until confirmed PD unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible for continuing durvalumab (MEDI4736) ± tremelimumab.

For all patients who are treated through progression, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing would not further benefit the patient.

Patients who the sponsor and the Investigator determine may not continue treatment after PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic

deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed disease progression and for survival.

5.2.3. Study drug preparation of durvalumab and tremelimumab

Based on average body WT of 75 kg, 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

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

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 1500 mg (for patients >30kg 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 in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 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.

An individual patient will not receive any further durvalumab + tremelimumab combination therapy or durvalumab monotherapy if their weight falls to 30 kg or less.

Standard infusion time 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 and document if the line was not flushed.

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

Preparation of tremelimumab doses for administration with an IV bag

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

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

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

A dose of 75 mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 3.8 mL (i.e.75 mg of tremelimumab, with the dose volume rounded to the nearest tenth mL) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

An individual patient will not receive any further durvalumab + tremelimumab combination therapy or durvalumab monotherapy if their weight falls to 30 kg or less.

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 and document if the line was not flushed.

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

5.2.4. Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

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

management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in 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.

5.2.5. Accountability and dispensation

The trial medication will be sent to the investigator's site pharmacy preceded by the Regulatory Green Light. The medication is to be used exclusively in the clinical trial according to the instructions of this trial protocol.

When a drug shipment is received, the Investigator or designee will check the amount and condition of the delivery, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed or emailed to the CRO (see appendix 8). The original form will preliminarily be retained at the site and will be collected at the next monitoring visit by the monitor and stored in the Trial Master File at CRO. A copy remains in the Investigator File at the site. In case of shipment problems the Investigator or designee shall contact the CRA as soon as possible.

An Investigational Product Accountability Log will be provided for the trial medication. The record must be continuously updated and contain the dates, quantities and compounds of drugs received, medication identification number(s), the patient identification number to whom the trial medication was dispensed, date and quantity of medication dispense and the initials of the dispenser.

5.2.6. Disposition of unused investigational study drug

Trial medication will be monitored by the CRA at the respective hospital pharmacy prior to destruction after having completed a final inventory. Study drug will be destroyed at local hospital pharmacy and not returned to the promoter/sponsor. Local or institutional regulations may require immediate destruction of the study drug used for safety reasons, e.g., cytotoxicity or to maintain the storage capacity and functionality of the storage at the site. In these cases, it may be acceptable to destroy it by the research staff, including partially used and empty vials, dispensed before a monitoring inspection, if the verification of original documents of empty boxes that indicate the information of batch number and dispensing date to the patient on the label. This documentation will be verified against the quantity shipped, dispensed, returned and destroyed.

Prior to the destruction a final trial medication reconciliation statement must be completed. Drug supplies will be destroyed according to the legal requirements in Spain.

All trial medication inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

6. TREATMENT PLAN

6.1. Patient enrolment and allocation

6.1.1. Procedures for allocation

Patients will be allocated in one of the following cohorts regarding primary tumour site:

1. Cohort 1: Patients with locally advanced or metastatic differentiated thyroid cancer (including the subtypes of papillary, follicular, poorly differentiated and Hürthle cell carcinoma) after progression to systemic therapy with MKIs. Patients could be recruited in the study after progression to Lenvatinib (regardless prior lines) or progression to at least two prior MKIs that may or not include Lenvatinib. No prior therapy with immune checkpoint inhibitors is allowed.
2. Cohort 2: Patients with locally advanced or metastatic medullary thyroid cancer after progression to systemic therapy with MKIs. Patients could be recruited in the study after progression to Vandetanib (regardless prior lines) or progression to at least two prior MKIs that may or not include Vandetanib. No prior therapy with immune checkpoint inhibitors is allowed.
3. Cohort 3: Patients with locally advanced or metastatic anaplastic thyroid cancer regardless of prior therapy. No prior therapy with immune checkpoint inhibitors is allowed.

6.1.2. Procedures for handling patients incorrectly enrolled

Patients incorrectly enrolled in the trial will be considered as protocol deviations. If investigator considerer that the patient is obtaining benefit of the investigational treatment, patients could continue on therapy. They will not be considered for the primary endpoint of the trial, neither for efficacy nor biomarker secondary and exploratory analyses. Patients incorrectly enrolled that continue on treatment can be assessed for safety profile endpoint.

6.2. Dose modification and toxicity management

6.2.1. Durvalumab and tremelimumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the durvalumab/tremelimumab Toxicity Management Guidelines (TMGs). Please see Appendix 1. The most current version of the TMGs is also available through the following link: https://tmg.azirae.com.

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

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 4.3 of this protocol and the Dosing Modification and Toxicity Management Guidelines in Appendix 1.

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in Appendix 1**.** These guidelines have been prepared to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

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

All toxicities will be graded according to NCI CTCAE, Version 5.0.

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

7.1. Restrictions during the study

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

Female patient of child-bearing potential

- 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 1) from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). Non-sterilised 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 washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 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 1).

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

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

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

Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced

menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

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

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

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

[a] This is also considered a hormonal method

Blood donation

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab or 180 days after last infusion of tremelimumab, whichever occurs longest.

7.2. Concomitant treatment(s)

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

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.2 for guidance on management of IP-related toxicities.

7.2.1. Permitted concomitant medications

Table 2. **Supportive medications**

Supportive medication/class of drug	Usage
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed 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 3. **Prohibited concomitant medications**

Prohibited medication/class of drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding <<10 mg/day>> of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	*Should not be given concomitantly or used for premedication prior to the I-O infusions. The following are allowed exceptions:* ● *Use of immunosuppressive medications for the management of IP-related AEs,* ● *Use in patients with contrast allergies.* ● *In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.*

	A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by *the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).*
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

8. STUDY PROCEDURES

8.1. Schedule of study procedures

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

For all treatment periods (durvalumab-tremelimumab combination and durvalumab monotherapy)

- PRO and tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of inclusion (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.

For durvalumab monotherapy or durvalumab + tremelimumab combination period

- Patients may delay dosing under certain circumstances.

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

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

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

8.1.1. Screening phase

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

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Archival tumor sample
- Review of prior/concomitant medications
- Imaging by CT/MRI
- Clinical laboratory tests for:
    - Clinical chemistry (see Table 4)
    - Hematology (see Table 5)
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis serology
    - Disease-specific tumor markers (thyroglobulin for DTC, calcitonin and CEA for MTC)
    - Collect blood samples for biomarker analyses

8.1.2. Treatment phase

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

Efforts should be made to conduct study visits on the day scheduled (± 1 day). Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures. Results of the laboratory assessments should be reviewed always prior each cycle dose administration. Whenever possible, subjects should be evaluated at approximately the same time of the day (e.g., morning or afternoon) at each visit, and reasonable efforts should be made to conduct all evaluations in the same test order at each visit.

Cycle 1/Day 1

- Obtain vital signs (resting BP, HR, RR, body temperature) and weight.
- Evaluate ECOG performance status.
- Physical examination is not mandatory if performed at baseline (day -1) however a symptom-directed physical examination will be performed on Cycle 1/Day 1 and at any time during the study, as clinically indicated.
- Administer study drug:

- Record all concomitant medication use.
- Record any AEs or SAEs.

Cycle 1/Day 15

- Obtain vital signs (resting BP, HR, RR, body temperature) and weight.
- Evaluate ECOG performance status.
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated.
- Biochemistry and hematology up to 72 hours prior the visit.
- Record all concomitant medication use.
- Record any AEs or SAEs.

Cycle 2/Day 1

- Evaluate ECOG performance status.
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight.
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated.
- Collect blood samples for biochemistry and hematology analyses (up to 72 hours before), including TSH, fT3 and fT4.
- Administer study drug.
- Collect blood samples for biomarker analysis.
- Record all concomitant medication use.
- Record any AEs or SAEs.
- Record survival data.

Cycle 2/Day 15

- Evaluate ECOG performance status.
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight.
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated.
- Collect blood samples for biochemistry and hematology analyses.
- Record all concomitant medication use.
- Record any AEs or SAEs.

Cycle 3/Day 1

- Evaluate ECOG performance status.
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight.

- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated.
- Collect blood samples for biochemistry and hematology analyses, including TSH, fT3 and fT4.
- Administer study drugs.
- Record all concomitant medication use.
- Record any AEs or SAEs.

Cycle 3/Day 15

- Evaluate ECOG performance status.
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight.
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated.
- Collect blood samples for biochemistry and hematology analyses.
- Record all concomitant medication use.
- Record any AEs or SAEs.

Cycle 4 through Last Cycle/Day 1

- Evaluate ECOG performance status.
- Obtain vital signs (supine BP, HR, RR, body temperature) and weight.
- Perform a comprehensive physical examination (including a neurological evaluation). A symptom-directed physical examination will be performed at any time during the study, as clinically indicated.
- Collect blood samples for biochemistry and hematology analyses (see Table 5for the tests to be performed), including TSH, fT3 and fT4.
- Administer study drugs.
- Perform tumor assessments at time points indicated in the Schedule of Visits and Procedures.
- Record all concomitant medication use.
- Record any AEs or SAEs.
- Record survival data.

If a toxicities pause occurs, cycles not administered for that toxicity can be delayed for a maximum of 4 weeks, after that time that cycle will be considered lost and the next cycle will be administered.
Remember no restarts are allowed after a delay of more than 12 weeks due to toxicity or more than 4 weeks of delay if **the reason is different from toxicity** without consulting the Coordinating Investigator.

8.1.3. End of treatment

End of treatment is defined as the last visit where the decision is made to discontinue treatment. All required procedures of the Final Visit schedule may be completed within ±7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for patients who have completed durvalumab and tremelimumab treatment and achieved disease control, or have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progressive disease are provided in Appendix 2.

Assessments for patients who have discontinued durvalumab or tremelimumab treatment due to confirmed PD are presented in Appendix 3.

All patients will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

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 the Schedule of Assessments.

8.2.2. Physical examination

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 10.

8.2.3. Electrocardiograms

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.

Situations in which ECG results should be reported as AEs are described in Section 10.3.1

8.2.4. Vital signs

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

First infusion

On the first infusion day, patients in the durvalumab + tremelimumab combination therapy schema <<and the durvalumab monotherapy group>> will be monitored and vital signs collected/recorded in eCRF prior to, during and after infusion of IP as presented in the bulleted list below.

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

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

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

Subsequent infusions

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

8.2.5. Clinical laboratory tests

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 2 through Table 5).

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

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

The laboratory variables to be measured are presented in Table 4 (clinical chemistry), Table 5 (hematology), and Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory haematology assessments are performed within 3 days prior to Day 0), and as clinically indicated.

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

The following laboratory variables will be measured:

Table 4. Clinical chemistry

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

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.
[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.
[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated.
[d] Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).
[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.
ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid Stimulating Hormone.

Table 5. Hematology

Basophils	Mean corpuscular volume
Eosinophils	Neutrophils
Absolute neutrophil count	Platelet count
Absolute lymphocyte count	Red blood cell count
Hematocrit	Total white cell count[a]
Hemoglobin	Mean corpuscular hemoglobin
Lymphocytes	Mean corpuscular hemoglobin concentration

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory haematology assessments are performed within 3 days prior to Day 0), and as clinically indicated.
[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

Table 6. Urinalysis

Urinalysis should be done at baseline (screening) and then as clinically indicated	
Bilirubin	Ketones
Blood	pH
Colour and appearance	Protein
Glucose	Specific gravity

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

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

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

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 10.3.5.

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

8.3. Biological sampling procedures

Blood samples and plasma for the development of exploratory predictive biomarkers will be collected from all subjects prior to the first dose of study drug, on Cycle 2/Day 1 and at end-of treatment visit or after documented disease progression, whichever occurs first. Biomarker discovery and validation will be performed to identify blood or tumor biomarkers which may be useful to predict subject response, as determined by evaluation of primary or secondary efficacy endpoints. Plasma samples from study subjects will undergo global proteomic and/or enzyme-linked immunosorbent assay (ELISA)-based analyses or multiplex bead-based immunoassay in an effort to identify protein biomarkers. In addition, DNA and RNA analyses will be performed in search of predictive or prognostic biomarkers and also biomarkers identified in other durvalumab and tremelimumab clinical studies may also be assessed in samples collected from subjects enrolled in this study.

Archived, fixed tumor tissue will be collected for all subjects for confirmation of histology (if needed) and assessment of somatic mutations of genes which may be important in the development and progression of thyroid cancers. Gene-expression profiling (GEP), proteomic, or immunohistochemical (IHC) analysis will be performed based on the amount of tumor tissue available for analysis. All analyses will be limited to correlations relevant to thyroid tumors and clinical outcomes related to treatment with durvalumab and tremelimumab.

Blood and tumor samples collected during the study will be stored at the study sites until the initial primary efficacy and safety analyses of the study will be completed and results will be available. Then, the study promoter will decide whether to perform all or part of the pharmacogenetics/pharmacogenomics assessments.

Data obtained will only be used for research, to assist in developing safer and more effective treatments, and will not be used to change the diagnosis of the subject or alter the therapy of the subject. Any DNA derived from the sample may be stored for up to 15 years to assist in any research scientific questions related to durvalumab or tremelimumab. Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

8.3.1. Biomarker/pharmacodynamics sampling and evaluation methods

PD-L1 Testing

To ensure comparability of data across all studies of durvalumab and/or tremelimumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the Ventana SP263 assay. Testing should be restricted to the Ventana SP263 assay and should be performed 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 (NSCLC), and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm. In other cancer types (pancreatic, gastric, hepatocellular, triple negative breast, ovarian, oesophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma and cervical HPV + cancers), the Ventana SP263 assay has only limited clinical performance data.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status 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.
- In AstraZeneca studies, the preferred sample for PD-L1 testing was less than or equal to 3 months old. In cases where a sample a less than 3-month-old was not available, patients were asked to undergo a new biopsy if considered clinically appropriate by their treating physician.
- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e., >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.
- 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, the age of the sample/date of collection should be captured.
- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Sample data collection for PD-L1 testing

The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (ecode or unique identifier)
- Specimen identifier (written on the specimen)
- Site identifier
- Specimen collection date

- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival of fresh tumor
- Tumor type
- Primary tumor location
- Metastatic tumor location (if applicable)
- Fixative

The following fields of data should be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

The Ventana SP263 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist, they should be retrieved from the Biobank storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.
- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.
- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended.

Storage of tumor blocks for PD-L1 testing

- FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for PD-L1 testing

- Tissue should be assessed by the site pathologist prior to PD-L1 testing.
- Each sample should be reviewed for:
    - Adequate fixation.
    - Good preservation of morphology.
    - Presence of tumor tissue.
    - Histopathology consistent with indication.
    - Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

If indicated, shipping samples to a PD-L1 testing laboratory

- When submitting sample to for PD-L1 testing the recommendation is to ship the block in order for sectioning to occur at the laboratory. Blocks should be shipped - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4 microns thick) to be used for PD-L1 testing.

Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for PD-L1 testing, unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:
    - A minimum of 5-10 x 4 micron (μm) thick, unstained sections should be provided for PD-L1 testing.

- A new disposable microtome blade must be used for each block to prevent contamination between patient samples.
- Slides are stable under these conditions for 6 months.
- Apply one section per slide to positively-charged Superfrost glass slides.
- The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.

Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status.

8.3.2. Estimate of volume of blood to be collected for biomarkers studies

The total of two blood and two plasma samples will be drawn from each subject in this study (at baseline, C2D1, end of treatment/progression) for biomarkers analyses and will be managed according the laboratory manual and stored -80ºC (-20ºC if not available) in the investigators centres. At the end of the study treatment period and follow-up up, and regarding results obtained, the sponsor and investigators will decide if biomarker analyses will be performed.

8.3.3. Archival tumor samples use beyond PD-L1

8.3.3.1. Archival tumor samples

Archival tumor samples in formalin-fixed paraffin-embedded tissue block will be identified at screening period. Samples will only be used at the end of the study treatment and always regarding results obtained with the investigational drugs.

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.

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.

9. DISEASE EVALUATION AND METHODS

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino et al 2013):

- Response to immunotherapy may be delayed.
- Response to immunotherapy may occur after PD by conventional criteria.
- The appearance of new lesions may not represent PD with immunotherapy.
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anticancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anticancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with durvalumab + tremelimumab would continue between the initial assessment of progression and confirmation for progression.
- In addition, patients may continue to receive durvalumab + tremelimumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab + tremelimumab and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anticancer therapy other than durvalumab + tremelimumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

9.1. Efficacy variable

RECIST v1.1 and irRECIST 1.1 criteria will be used to assess patient response to treatment by determining progression-free survival rates at 6, 9 and 12 months, median progression-free survival, overall response rate and median overall survival using Investigator assessments. The management of patients will be based in part upon the results of the RECIST v1.1 but always considering the irRECIST 1.1 assessment (secondary endpoint) conducted by the Investigator.

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions

- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or 2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

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

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

NOTE: In order to have confirmed objective disease progression, there should be two consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

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

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

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

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

10. ASSESSMENT OF SAFETY

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

10.1. Safety parameters

10.1.1. Definition of adverse events

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

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

10.1.2. Definition of serious adverse events

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- 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

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

10.1.3. Durvalumab + tremelimumab adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring An AESI may be serious or non-serious, however an expedited report is required using the SAE form, indicating an event of special interest.

AESIs for durvalumab ±tremelimumab include but are not limited to events with a potential inflammatory immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressant and/or hormone replacement therapy. “These AESIs may require close monitoring in clinical studies with durvalumab monotherapy and durvalumab combination therapy.” An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and

is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

AESIs observed with durvalumab ±tremelimumab include:

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

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

Events with an inflammatory or immune mediated mechanism could occur in nearly all organs. Potential risks with an immune-mediated aetiology that are rare or less frequent include, but are not limited to, Guillain-Barre Syndrome, myasthenia gravis, pericarditis, sarcoidosis, uveitis, and other events involving the eye (eg, keratitis and optic neuritis), skin (eg, scleroderma, vitiligo and pemphigoid), haematological (eg, haemolytic anaemia and immune thrombocytopenic purpura), rheumatological events (polymyalgia rheumatic and autoimmune arthritis), vasculitis, non-infectious meningitis and non-infectious encephalitis.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

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

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

Additional Clinical chemistry: CRP, LDH

10.2. Assessment of safety parameters

10.2.1. Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v5.0. The determination of severity for all other events not listed in the CTCAE should be made by
the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as
defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc.).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.2.1. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2. Assessment of relationship

Relationship of adverse events with study drugs will be assessed by investigators based on toxicity profile described for each study drug (see investigator brochure).

10.3. Recording of adverse events and serious adverse events

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

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

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

The following variables will be collected for each AE:

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

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 6.3.4.
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

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

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

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

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

10.3.2. Causality collection

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

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

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

10.3.3. Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (i.e., SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

10.3.4. Adverse events based on signs and symptoms

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

10.3.5. Adverse events based on examinations and tests

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

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

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

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

10.3.6. 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. Please refer to Appendix 1. Toxicity Management Guidelines for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.3.7. Disease progression

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

10.3.8. 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.

10.3.9. Deaths

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

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result

of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

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

10.3.10. Reporting of serious adverse events

SAE report and accompanying cover page will be sent by the investigator to the sponsor representative, by way of email to

[redacted]

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The Sponsor is responsible for reporting to the Regulatory Authorities of the SAE as per local requirements. A copy of the report must be sent by email to AstraZeneca Patient Safety data entry site at the time the event is reported to the Competent Authorities. It is the responsibility of the investigator to compile all necessary information and ensure that the Competent Authorities receives a report according to the regulatory agencies and competent authorities reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany report indicating the following:
• External Scientific Research
• The IND number assigned by the regulatory agencies and competent authorities
• The Sponsor's name and address
• The trial name/title and AstraZeneca ESR reference number
***** Investigative site 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.

[redacted]

10.3.10.1. Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab + tremelimumab safety follow-up period must be reported as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to appropriate CRO representatives as a SAE within **24 hours** (see Section 10.3.2 for further

details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as a SAE.

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

10.3.11. Other events requiring reporting

10.3.11.1. Overdose

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

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

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

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

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

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

10.3.11.2. Pregnancy

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

- Pregnancy discovered before the study patient has received any study drugs.
- Pregnancy of a female partner of male patient, providing there is no restriction of male patient fathering a child.

10.3.12. Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects

and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

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

The designated sponsor representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

10.3.13. Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period should, if possible, be followed up and documented.

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

10.4. Medication error

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

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

Medication error includes situations where an error.

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

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

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

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

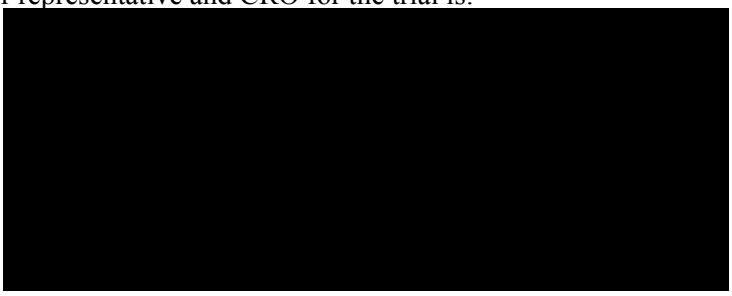
- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate sponsor representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 10.3.10) and within 30 days for all other medication errors.

The designated sponsor representative and CRO for the trial is:



11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses described in this section will be performed as further outlined in the Statistical Analysis Plan, which will be included in the clinical study report for this protocol.

11.1. Description of analysis sets

The analysis sets will be defined as follows:

- **Full Analysis Set** will include all allocated subjects. This will be primary analysis set for the efficacy endpoints.
- **Per Protocol Analysis Set** will include those subjects who were allocated and received at least one dose of the assigned study drug and had no major protocol deviations. The subjects will complete both baseline and at least one post-baseline tumor assessments (week 12).
- **Safety Analysis Set** will include all subjects who were allocated and received at least one dose of the study drug and had at least one post-baseline safety evaluation (week 12). This will be the analysis set for all safety evaluations.
- **Pharmacodynamic Analysis Set**: All the subjects who have received at least one dose of study drug and have evaluable pharmacodynamic data.

Demographic and other baseline characteristics
Demographic and other baseline characteristics will be summarized and listed. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as n, number of not available data (NA), mean, standard deviation, median, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

Prior and concomitant medications
Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class.

Efficacy Analyses
All efficacy analyses will be based primarily on the Full Analysis Set and secondarily on the Per Protocol Analysis Set.

Analysis of primary efficacy variable
The analysis of progression-free survival rate and overall survival rate will be performed independently for each study cohort when the last patient included in the corresponding cohort of the study will arrived to 6 months after start of first infusion of study treatment or have progressed. The primary objective of the study will be based on the investigator assessment.

11.2. Methods of statistical analyses

Strategic decisions about future development of immune therapy in thyroid tumors will be available after the results of this trial.

Summary tables (descriptive statistics and frequency tables) will be provided for all baseline variables, efficacy variables, and safety variables, as appropriate. Continuous variables will be summarized with descriptive statistics (mean, standard deviation, range, and median). Ninety-five percent confidence intervals (95% CI) may also be presented, as appropriate. Frequency counts and percentage of subjects within each category will be provided for categorical data.

The primary efficacy analysis will be performed using the binomial test procedure. Missing data will be treated using statistical multiple random imputation.

Secondary endpoints will be summarized with descriptive statistics. Continuous variables will be summarized with n, mean, standard deviation, and range, frequency counts and percentage of subjects within each category will be provided for categorical data. Multivariate regression models will be used to study relations between exploratory variables and primary endpoint. Survival analysis will be performed to analyse PFS, Kaplan-Meier curves will be presented and possible comparisons will be tested using the log-rank test or the Cox proportional hazard model for multivariate analysis, hazard ratios (HR) and their 95% confidence interval (CI95%) will be provided. In the per protocol analysis set, patients with loss of follow-up or treatment discontinuation will be included in the final analysis of primary endpoint if they have at least one tumor evaluation and considered as censored data for survival endpoints.

R software version 3.2.1 will be used for all analysis.

11.2.1. Safety analyses

Safety analyses will be based on the Safety Analysis Set. All safety analyses will be summarized separately by cohort. Adverse events and serious adverse events, laboratory test results, physical examination findings and vital signs, and their changes from baseline will be summarized using descriptive statistics. Abnormal values will be flagged.

Toxicity profile (short and long-term) will be described per patient to show all the AE information about grade, relationship to study treatment and severity. Toxicity will be evaluated according NCI CTCAE vs 5.0 criteria.

11.2.2. Efficacy analyses

- Primary endpoint for cohorts 1 and 2 (DTC and MTC):

6-months progression-free survival by Response Evaluation Criteria In Solid Tumors (RECIST), which is defined as the percentage of patients achieving complete response, partial response (PR), or stable disease (SD) at month 6 after durvalumab plus tremelimumab was started without observing disease progression or death at this timepoint.

- Primary endpoint for cohort 3 (ATC):

6-months overall survival rate, which is defined as the percentage of patients alive at 6 months after durvalumab plus tremelimumab was started.

11.2.3. Secondary objective(s)

1. *Overall response rate (ORR) by irRECIST and RECIST.*

ORR includes patients with partial (PR) and complete response (CR) as best response by RECIST v 1.1 and irRECIST.

2. *To assess the duration of response according to irRECIST/RECIST.*

Patients with PR and/or CR will be followed to determine the duration of the response. Patients with stable disease (SD) will also be followed to assess the duration of the SD to be able to define the clinical benefit rate (PR, CR and SD) as best responses of treatment.

3. *To assess the median progression-free survival time (PFS) according to RECIST.*

Together with the primary endpoints of PFS rate and overall survival rate at 6 months, patients will be followed by imaging with the same periods (every 12 weeks) to assess the median PFS.

4. *To assess the safety profile of Durvalumab and Tremelimumab in subjects with advanced thyroid neoplasms.*

Toxicity will be evaluated according NCI CTCAE v 5.0 criteria.

5. *To assess the median overall survival (OS) time.*

Patients will be followed after completion of the study treatment period to assess the median OS.

6. *To assess response status according to irRECIST/RECIST at 6 and 12 months after start of study treatment.*

11.2.4. Exploratory objective(s)

1. To evaluate biochemical response (changes in thyroglobulin, calcitonin and CEA levels) and its association with response rate and progression-free survival.
2. To assess whether baseline tumor and blood biomarkers may be predictive of response to durvalumab and tremelimumab therapy.
3. To explore additional hypotheses related to biomarkers and relationship to durvalumab and tremelimumab efficacy and/or toxicity and thyroid cancer evolution that may arise from internal or external research activities.

11.2.5. Interim analyses

The trial is designed following a Simon-II strategy. The first stage will include 17 patients in cohorts 1 and 2. If 5 out of 17 patients in each cohort (DTC and MTC) are free of disease progression or unacceptable toxicity at 6 months in the first stage, study will continue recruiting 19 additional patients up to 36 patients per cohort. **≥13** pts out of a total of 36 patients have to be alive and progression-free at the final analysis to declare a positive study. If stage I is reached only in one cohort, recruitment will continue in the successful cohort and stop in the non-effective cohort.

No interim analysis is planned for cohort 3. All 12 patients will be included in one stage.

11.3. Determination of sample size

Simon-II design was applied for sample size estimation for DTC and MTC cohorts.

For cohorts 1 and 2 (DTC and MTC, respectively), we hypothesize that the experimental therapy will improve the probability of being progression free at 6 months, from 25% in historical cohorts up to 45% in the current study.

With 80% of power ($\beta = 0.2$) and unilateral alpha (0.05), 36 patients per arm are needed to demonstrate the primary hypothesis. The Simon-II design suggested to observe 5 patients free of disease progression or unacceptable toxicity at 6 months within the first 17 patients included in the first stage. If 5 out of 17 patients in each cohort (DTC and MTC) are free of disease progression or unacceptable toxicity at 6 months in the first stage, study will continue recruiting 19 additional patients up to 36 patients per cohort. If stage I is reached only in one cohort, recruitment will continue in the successful cohort and stop in the non-effective cohort. If ≥13 pts out of a total of 36 patients are alive and progression-free at the final analysis the study will be considered positive.

For sample size estimation for cohort 3, we hypothesize that the experimental therapy will improve the probability of being alive at 6 months from 5% in historical cohorts up to 35% in the current study. With 80% of power ($\beta = 0.2$) and unilateral alpha (0.05), 12 patients are needed to demonstrate the primary hypothesis. Cohort 3 will include the 12 patients in one stage. To consider the study positive, 4 patients should be alive at 6 months after the first drug infusion.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1. Ethical conduct of the study

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

12.2. Ethics and regulatory review

The protocol, ICF, and appropriate related documents must be reviewed and approved by an EC constituted and functioning in accordance with ICH E6, Section 3, and any local regulations.
Any protocol amendment and/or revision to the ICF will be resubmitted to the EC for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change in CRA[s] or change of telephone number[s]). Documentation of EC compliance with ICH and any local regulations regarding constitution and review conduct will be provided to the sponsor.
A signed letter of study approval from the EC Chairman must be obtained prior to study start and the release of any study drug to the site by the sponsor or its designee. If the EC decides to suspend or terminate the study, the sponsor will immediately send the notice of study suspension or termination by the EC to the investigators. Study progress is to be reported to the EC annually (or as required) by the sponsor. If the investigator is required to report to the EC, he/she will forward a copy to the sponsor at the time of each periodic report. The sponsor will submit periodic reports and inform the EC of any reportable adverse events according to local legislation. Upon completion of the study, the investigator will provide the EC and the regulatory authorities with a brief report of the outcome of the study.

12.3. Informed consent

As part of administering the informed consent document, the investigator must explain to each subject (or guardian/legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an informed consent at the Screening Visit prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. An unsigned copy of an EC and sponsor-approved written informed consent must be prepared in accordance with ICH E 6, Section 4, and all applicable local regulations and provided to the sponsor. Each subject must sign an

approved informed consent prior to study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file, according to local procedure, at the study centre.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

12.4. Changes to the protocol and informed consent form

There are to be no changes to the protocol without written approval from the sponsor. Protocols will be followed as written. Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to Health Authorities as well as additional approval by the EC. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the investigator to be necessary for safety reasons, the sponsor's appropriate study team member must be notified promptly and the EC for the site must be informed immediately. A protocol change intended to eliminate an immediate hazard may be implemented immediately, provided that the Health Authorities and EC are subsequently notified by protocol amendment.

Changes affecting only administrative aspects of the study do not require formal protocol amendments or EC approval, but the EC (if regionally required, the heads of the medical institutions) must be kept informed of such changes. In these cases, the sponsor will send a letter to the EC (if regionally required, the heads of the medical institutions) detailing such changes.

12.5. Audits and inspections

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's Standard Operating Procedures (SOPs) to evaluate compliance with the principles of ICH GCP and all applicable local regulations. A government regulatory authority may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

The investigators and institutions will allow the monitoring, auditing and inspection activities related to this clinical trial including direct access to source data and documents.

12.6. Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the investigator, the investigator's staff, and the EC and will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the sponsor. No data collected as part of this study will be utilized in any written work, including publications, without the written consent of the sponsor. These obligations of

confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the sponsor and the investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in the Confidentiality Agreement between the investigator and sponsor (provided by the sponsor).

All laboratory specimens, evaluation forms, reports, and other records will be identified with patient code (clinical trial number) to maintain subject confidentiality throughout the trial. Each Investigator will ensure that all site personnel involved will respect the confidentiality of any information about trial subjects. Management of personal data from subjects participating in the trial, particularly as regards consent, will comply with the EEA General Data Protection Regulation (GDPR) 2016/679 and the Spanish implementation

At each site, all records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject. Subject identity is confidential and may only be known by the Investigator, trial personnel, appointed auditors and monitors, and Health Authorities.

Each Investigator and all employees and co-workers involved with this trial may not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the sponsor or its designee must be collected for the disclosure of any said confidential information to other parties.

12.7. Insurance

The sponsor has contracted an insurance policy to cover the responsibilities of the investigator and other parties participating in the study, according to the applicable Spanish legislation.

- Insurance company: CHUBB
- Policy Number: ESLC234638

12.8. Publications

The sponsor led by the principal investigator commits to responsible publication of both the positive and negative results from its clinical trials as required by all governing regulatory and health authorities.

Investigators will not publish the global study results (all sites) unless the sponsor has not done so in a suitable time period after the clinical study report (CSR) has been available. Should the Investigator(s) independently seek to publish results of this study which occur at their study site(s), they must inform the study sponsor of any/all drafts (including, but not limited to papers, manuscripts or abstracts) at least 60 days before submission to the congress, meeting or journal. The sponsor and Investigator(s) will agree with all aspects related to any proposed publications with regards to the following: 1) any proposed publications will be drafted in agreement with international recommendations, such as those from the

International Committee of Medical Journal Editors (ICMJE) and all elements of the Consort Statement (2010), to maintain integrity of the trial results in all communications; 2) any proposed publications will state the Clinical Research Ethics Committees which approved the trial and the funding sources of the trial; 3) any proposed publications will occur before disclosure of results to lay people; 4) any proposed publications will not report premature or partial data prior to completion of the analysis of the overall results of the trial.

13. STUDY MANAGEMENT

13.1. Training of study site personnel

The principal investigator will maintain a record of all centre staff involved in the clinical trial (doctors, nurses and other staff involved) ensuring that they receive appropriate training to perform the study, and that any new information of relevance to the study will be transmitted to them.
Researchers will be instructed about the procedures of the trial in the investigator meeting and/or initiation visits made by monitors at each participating centre prior to the study start.

13.2. Monitoring of the study

The sponsor's or representative (e.g., CRO's CRA) will maintain contact with the investigator and designated staff by telephone, and/or letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (if regionally required, the heads of the medical institutions) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with Good Clinical Practices and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to the study protocol and data accuracy in accordance with federal regulations. All records at the investigational site are subject to inspection by the local regulatory agency.

13.2.1. Source data

In accordance with ICH E6, Section 6.10, source documents include but are not limited to the following:

- Clinic, office, hospital charts;
- Copies or transcribed healthcare provider notes which have been certified for accuracy after production;
- Recorded data from automated instruments such as x-rays, and other imaging reports: e.g., sonograms, CT scans, MRIs, nuclear medicine scans, ECGs, rhythm strips, electroencephalograms (EEGs), polysomnographs, and pulmonary function tests (regardless of how these images are stored, including microfiche and photographic negatives);
- Records of telephone contacts;
- Drug distribution and accountability logs maintained in pharmacies or by research personnel;
- Laboratory results and other laboratory test outputs: e.g., urine pregnancy test result documentation;

Correspondence regarding a study subject's treatment between physicians or memoranda sent to the EC;

13.3. Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (if regionally required, the heads of the medical institutions) has the responsibility to retain all study documents, including but not limited to the protocol, the Investigator's Brochure, regulatory agency registration documents, ICFs, and EC correspondence. The investigational site should retain study documents until at least 25 years after the finalization of the study.

It is requested that at the completion of the required retention period or, should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

13.4. Quality assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating practices (SOPs), working practice documents, and applicable regulations and guidelines. Site visit audits will be made periodically by the sponsor's or CRO's qualified compliance auditing team, which is an independent function from the study conduct team.

13.5. Study timetable and end of study

End of study is defined as Last Subject Last Visit.

- Expected Recruitment period will be:
    - Stage I 18 months
    - Stage II 12 months
- Research Agreement executed: 2Q 2018
- Projected IRB/IEC approval: 4Q 2018 (Actual: 01/Feb/2019)
- First Subject In: 4Q 2018 (Actual: 10/Apr/2019)
- 50% Enrollment: 3Q 2020
- Last Subject In (100% enrollment): 3Q 2021
- Last Subject Last Visit: 3Q 2022
- Publication: 4Q 2022

14. DATA MANAGEMENT

All software applications used in the collection and validation of data must be properly validated following standard computer system validation and must be compliant to all regulatory requirements.

The Data Management Plan (DMP) defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure data are properly entered, validated, coded, integrated, reconciled and reviewed.

Data required by the protocol are collected on an electronic Case Report Form (eCRF) and entered into a validated data management system which is compliant to all regulatory requirements. As defined by ICH Guidelines, 'the Case Report Form (CRF) is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject'. In this study, CRF should refer to electronic data collection form. Data collected on the CRF must follow the instructions described in the CRF Completion Guidelines. The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRF.

Any corrections to entries made on the CRF must be documented in a valid audit trail where the corrections must be dated, initialled, the reason for change stated, and original data not obscured. Only data required by the protocol for the purposes of the study should be collected.

14.1. Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

15.1. Identity of investigational product(s)

Table 7. List of investigational products for this study

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

16. LIST OF REFERENCES

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APPENDICES

Appendix 1.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy. 28 October2022.

Note: Annex is to be used in any clinical trial protocol within which patients are treated with Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab

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., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (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 imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. 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.

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents 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 the need for 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.

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation

Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy

Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .

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

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE 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 initiating 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 intravenous immunoglobulin (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 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 CTCAE grade/severity)**	**General Guidance**	**For Any Grade** **– Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g. infection, progressive disease)).** **– Monitor patients for signs (e.g. tachypnoea)and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients 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 etiologies 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 (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography (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 improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (<10 mg prednisone or equivalent).**	**For Grade 2** **– Monitor symptoms daily and consider hospitalization , as clinically indicated.** **– Consider Pulmonary and Infectious Diseases Consults;** **– Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent).** **– Consider HRCT or chest CT with contrast, Repeat imaging study as clinically indicated** **– If no improvement within 2 to 3 days, additional workup 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 as tumor necrosis factor (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 or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** **- Consider discussing with Clinical Study Lead.**

Grade 3 or 4	**Permanently discontinue study drug/study regimen.**	**For Grade 3 or 4** – **Hospitalize the patient.** – **Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.** – **Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead,, as needed.** – **Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results** – **Supportive care (e.g., oxygen).** – **If no improvement within 2 days, additional workup 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 or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

Diarrhea/Colitis	**Any Grade** **(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**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).** **– Consider further evaluation with imaging study with contrast.** **– Consult a gastrointestinal (GI) specialist for consideration of further workup.** **– WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL 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 events, 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 improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone, or equivalent).**	**For Grade 2** **– Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide.** **– Consider further evaluation with imaging study with contrast.** **– Consider consult of a gastrointestinal (GI) specialist for consideration of further workup.** **– Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.** **– If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV , prednisone equivalent, reconsult GI specialist and, if indicated ,promptly start immunosuppressants 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 or relevant practice guidelines.** **[a] Caution: it is important 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.** **– Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.**

Grade 3 or 4	**Grade 3** **- For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone per day, or equivalent).** **-For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study investigator, in discussion with AstraZeneca Clinical Study Lead.** **<u>-For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy, Permanently</u> discontinue both durvalumab and tremelimumab for 1) Grade 3 diarrhea colitis or 2) Any grade of intestinal perforation** **Grade 4** **Permanently discontinue** **study drug/study regimen.**	**For Grade 3 or 4** **– Urgent GI consult and imaging and/or colonoscopy as appropriate.** **– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.** **– Monitor stool frequency and volume and maintain hydration.** **– If still no improvement within 2 days, continue steroids and 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 or relevant practice guidelines). 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.**

Hepatitis **Infliximab should not be used for management of immune-relatd hepatitis.** **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])**	**Any Grade** **(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance**	**For Any Grade** **– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications).** **– Monitor and evaluate: transaminases (aspartate aminotransferase (AST)) , alanine aminotransferase (ALT), alkaline phosphatase (ALP)) , and total bilirubin .**
	ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	**– No dose modifications.** **– If it worsens, then consider holding therapy.**	**– Continue transaminase and total bilirubin monitoring per protocol.**
	ALT or AST > 3 ≤ 5 x ULN or total bilir bin > 1.5 ≤ 3 x ULN	**- Hold study drug/study regimen dose until ALT or AST ≤3 x ULN or total bilirubin <1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent).** **- Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT >3 × ULN AND bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevatedALP) and in the absence of any alternative cause.[b]**	**– Regular and frequent checking of transaminases and total bilirubin(e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve.** **– If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed.** **– If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV eq uivalent.**

ALT or AST **> 5-≤ 10 x ULN**	**Hold study drug/study regimen:** **· Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN and after completion of steroid taper (<10 mg prednisone, or equivalent).** **If in combination with tremelimumab, do not restart tremelimumab.**	**– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent.** **– Perform Hepatology Consult, abdominal workup, and imaging as appropriate.** **– If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an immunosuppressants (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. Infliximab should NOT be used.**

Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN **ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN**	**Permanently discontinue study drug/study regimen.**	**− Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent.** **− If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. Infliximab should NOT be used.** **− Perform Hepatology Consult, abdominal workup, and imaging as appropriate.**

Hepatitis (elevated transaminases and total bilirubin) **Infliximab should not be used for management o immune-related hepatitis.** **THIS shaded area is guidance only for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])** **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**	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** **– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]).** **– Monitor and evaluate AST, ALT, ALP, and T. Bili.** **– For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBsAg).** **– For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load.** **– 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 Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.**

Isolated AST or ALT	**- No dose modifications.**
>ULN and ≤2.5×BLV	**- 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**

	ALT or AST > 2.5- ≤ 5X BLV and ≤ 20xULN	· **Hold study drug/study regimen dose until resolution to AST or ALT ≤2.5.0 x BLV /** - **If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤2.5 x BLV, resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).**	– **Regular and frequent checking of Transaminases and total bilirrubin (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 Clinical Study Lead** – **If event is persistent (>2 days to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone at 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 or equivalent, consider additional work up. If still no improvement within 2 to 3 days despite 2 mg/kg/day of IV methylprefnisolone, consider additional abdominal workip (including liver biopsy) and imagin (i.e; liver ultrasound) and consider starting additional immunosuppresants (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with t hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available.** **Infliximab should NOT be used.**
	ALT or AST >5-7X BLV 20XULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULNd	**-Withhold durvalumab and permanently discontinue tremelimumab** **-Resume study drug/study regimen if elevations downgrade to AST or ALT ≤2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent).**	– **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 Clinical Study Lead, as needed.** – **If investigator suspects toxicity to be immune-mediated, promptly**

		- Permanently discontinue study drug/study regimen if if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days	**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** **additional immunosuppressant. (e.g.,., mycophenolate mofetil 0.5 –** **1 g every 12 hours then taper in consultation with a hepatologist or** **relevant practice guidelines). Discuss with Study Clinical Lead if** **mycophenolate is not available.** **Infliximab should NOT be used.**
	ALT or AST **> 7 X BLV OR > 20** **ULN whichever occurs** **first OR bilirubin >** **3ULN**	**Permanently discontinue** **study drug/study regimen.**	**Same as above** **(except recommend obtaining liver biopsy early)**

Nephritis and/or renal dysfunction	**Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance**	**For Any Grade** **– Patients should be thoroughly evaluated to rule out any alternative aetiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status).** **– Consider consulting a nephrologist.** **– Consider imaging studies to rule out any alternative etiology** **– 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, decreased urine output, or proteinuria).** **Follow urine protein/creatinine ratio every 3-7 days**
	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, including hydration, electrolyte replacement, and diuretics, as clinically indicated** **– Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated.**

Grade 2	**Hold study drug/study regimen until resolution to Grade ≤1 or baseline.** **· If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).**	**For Grade 2** **– Consider, including hydration, electrolyte replacement, and diuretics, as clinically indicated.** **– Follow urine protein/creatinine ratio every 3-7 days** **– Carefully monitor serum creatinine as clinically warranted.** **– Consult nephrologist and consider renal biopsy if clinically indicated.** **– Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out.** **– If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent.** **– If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup.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 daily.** **– Follow urine protein/creatinine ratio every 3-7 days** **– 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 of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant.**

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 GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)1 IS SUSPECTED.** **– PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPHIGOID 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, o 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 improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).**	**For Grade 2** **– Consider dermatology consult and skin biopsy, as indicated.** **– 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 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, study physician, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.**

	Grade 3	**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 (<10 mg prednisone, or equivalent).**	**For Grade** **– Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible.** **– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.** **– Consider hospitalization.** **– Monitor the extent of rash [Rule of Nines].** **– Consider, as necessary, discussing with Clinical Study Lead**
	Grade 4	**For Grade 4** **Permanently discontinue study drug/study regimen**	**For Grade 4** **– Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible.** **– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.** **– Consider hospitalization.** **– Monitor the extent of rash [Rule of Nines].** **– Consider, as necessary, discussing with Clinical Study Lead.**

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 CTCAE grade/severity)**	**General Guidance**	**For Any Grade** **– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections).** **– Consider consulting an endocrinologist for endocrine events.** **– Consider discussing with Clinical Study Lead, as needed.** **– Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.** **– Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c(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 consulting an endocrinologist to guide assessment of early-morning adrenocorticotropin hormone (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 <u>other than hypothyroidism and type 1 diabetes mellitus (TIDM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve.** · **Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent).** · **Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.**	**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 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement** – **Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** – **Isolated type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.</u>** – **For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (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 CTCAE grade/severity)**	**General Guidance**	**For Any Grade** – **Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse).** – **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 gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.**	
Acute Pancreatitis	**Any Grade** **(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance**	**For Any Grade** – **Patients should be thoroughly evaluated to rule out any alternative etiology.** – **Consider Gastroenterology referral**
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** – **Consider IV hydration** – **Consider Gastroenterology referral**

	Grade 3, or 4	**For Grade 3** **Hold study drug/study regimen until resolution of elebated enzymes and no radiologic findings. If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).** **For Grade 4** **Permanently discontinue study drug/study regimen.**	**For Grade, 3, or 4** **– Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent.** **– IV hydration**
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** **(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance** **– Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis.** **– Patients may be febrile.** **– Mental status should be normal**	**For Any Grade** **– Consider neurology consult** **– Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis.** **– Exclude bacterial and viral infections. (ie HSV)** **– Consider IV acyclovir until polymerase chain reactions are available**
	Any Grade	**Permanently discontinue study drug/study regimen**	**For Any Grade** **– Consider neurology consult** **– Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis.** **– Exclude bacterial and viral infections. (ie HSV)**

			– Consider IV acyclovir until polymerase chain reactions are available **– Consider, as necessary, discussing with Clinical Study Lead.(Last bullet)** **– Consider hospitalization.** **– Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.**
Encephalitis	**Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance** **Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality.**	**For Any Grade** **– Consider neurology consult** **– Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders.** **– Exclude bacterial and viral infections. (ie HSV)** **Consider IV acyclovir until polymerase chain reactions are available.**
	Grade 2	**For Grade 2** **Permanently discontinue study drug/study regimen**	**For Grade 2** **– Consider, as necessary, discussing with the Clinical Study Lead.** **– Once infection has been ruled out methylprednisolone 1 2 mg/kg/day.** **– For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3-5 days plus IVIG or plasmapheresis.**

	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 Clinical Study Lead.** **– Consider hospitalization.** **– Once infection is ruled out, start methylprednisolone g IV daily for 3-5 days for progressive symptoms.** **–Consider adding IVIG or plasmapheresis.**
Transverse Myelitis	**Any Grade**	**General Guidance** **– Permanently discontinue immunotherapy** **– Consider MRI of the spine and brain Once imaging is complete, consider lumbar puncture** **– Consider testing to rule out additional aetiologies: B12, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel for anti-Hu and anti-CRMP5/CV2**	**For Any Grade** **– Consider neurology consult** **– Inpatient care** **– Consider prompt initiation of high methylprednisolone pulse dosing** **– Strongly consider IVIG or plasmapheresis**

Peripheral neuropathy	**Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance**	**For Any Grade** – **Patients should be evaluated to rule out any alternative etiology for neuropathy (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 neurological consult.** – **Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.**
	Grade 1	**No dose modifications.**	**For Grade 1** – **Consider discussing with the Clinical Study Lead, as needed.** – **Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction.**

Grade 2	**Hold study drug/study regimen dose until resolution to Grade ≤1.**	**For Grade 2** **– Consider discussing with the Clinical Study Lead, as needed.** **– Consider EMG/NCS** **– Consult a neurologist.** **– Observation for additional symptoms o or consider initiating prednisone 0.5-1 mg/kg orally.** **– If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS.** **– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).**
Grade 3 or 4	**For Grade 3 or 4** **· Permanently discontinue study drug/study regimen.**	**For Grade 3 or 4** **– Consider discussing with Clinical Study Lead, as needed.** **– Recommend hospitalization.** **– Monitor symptoms and consult a neurologist.** **–Treat per Guillain-Barré Syndrome recommendations**

Guillain-Barré Syndrome (GBS)		**General Guidance**	**− Recommend hospitalization** **− Obtain neurology consult** **− Obtain MRI of spine to rule out compression lesion** **− Obtain lumbar puncture** **− Antibody tests for GBS variants** **− Pulmonary function tests** **− Obtain electromyography (EMG) and nerve conduction studies** **− Frequently monitor pulmonary function tests and neurologic evaluations** **− Monitor for concurrent autonomic dysfunction** **− Initiate medication as needed for neuropathic pain**
	Grade 2-4	**Grade 2-4** **Permanently discontinue**	**− Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		**General Guidance**	**− Obtain neurology consult** **− Recommend hospitalization** **− Obtain pulmonary function tests** **− Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies** **− Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis** **− Obtain electromyography (EMG) and nerve conduction studies** **− Consider MRI of brain/spine to rule out CNS involvement by disease** **− Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)**

	Grade 2	**Permanently discontinue**	**– Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily)** **– Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)**
	Grade 3-4	**Permanently discontinue**	**– Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement** **– Start plasmapheresis or IVIG** **– Consider rituximab if refractory to plasmapheresis or IVIG** **– Frequent PFT assessments** **– Daily neurologic evaluations**

Myocarditis	**Any Grade** **(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance** **Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.**	**For Any Grade** **– Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (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)** **– The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function.** **– Consider discussing with the Clinical Study Lead, 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, including any other diagnostic procedures as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.**

	Grade 2, 3 or 4	- **If Grade 2-4, permanently discontinue study drug/study regimen.**	**For Grade 2-4** – **Monitor symptoms daily, hospitalize.** – **Consider cardiology consultation and a prompt start of high-dose/pulse corticosteroid therapy** – **Supportive care (e.g., oxygen).** – **If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab , IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant or relevant practice guidelines).** **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** **– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).** **– 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, and 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 Clinical Study Lead** **– Initial work-up should include clinical evaluation, creatine kinase, aldolase,lactate** **dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) 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.
	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 Clinical Study Lead.**

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.** – **Consider Rheumatology or Neurology consult, and initiate evaluation.** – **Consider, as necessary, discussing with the Clinical Study Lead.** – **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 <u>along with receiving input</u> 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 3 days, consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice) guideline.** **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

	Grade 3	**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 3** **– Monitor symptoms closely; recommend hospitalization.** **– Consider Rheumatology and / or Neurology consult** **– Consider discussing with the Clinical Study Lead, 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 a TNF inhibitor (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 or relevant practice guidelines). 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.**

	Grade 4	**For Grade 4**	**Grade 4**
		Permanently discontinue	**− Monitor symptoms closely; recommend hospitalization.**
		study drug/study regimen.	**− Consider Rheumatology and/or Neurology consult**
			− Consider discussing with the Clinical Study Lead, 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 a TNF inhibitor (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 or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.

1 SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE 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 Clinical Study Leadmay 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**	**For Grade 2, 3, or 4** **Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines (see pag 4))**

	with systemic steroids and following full taper
Grade 3	**Hold study drug/study regimen**
Grade 4	**Permanently discontinue study drug/study regimen**

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 Clinical Study Lead."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	**General Guidance**	**For Any Grade** – **Manage per institutional standard at the discretion of 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 standard, appropriate clinical practice guidelines, and society guidelines.**

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 CTCAE 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- 3	**Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.**	**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 Clinical Study Lead."

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

List of Abbreviations

AChE	**Acetylcholinesterase**	**ILD**	**Interstitial lung disease**
ACTH	**Adrenocorticotropic hormone**	**imAE(s)**	**Immune-mediated adverse event(s)**
ALT	**Alanine aminotransferase**	**INR**	**International normalized ratio**
ASCO	**American Society of Clinical Oncology**	**IU**	**International units**
AST	**Aspartate aminotransferase**	**IV**	**Intravenous**
(T) Bili	**(Total) Bilirubin**	**IVIG**	**Intravenous immunoglobulin**
BNP	**B-type natriuretic peptide**	**LDH**	**Lactate dehydrogenase**
BUN	**Blood urea nitrogen**	**LFTs**	**Liver function tests**
CRP	**C-reactive protein**	**LLN**	**Lower limit of normal**
CSP	**Clinical Study Protocol**	**MRCP**	**Magnetic resonance cholangiopancreatography**
CT	**Computed tomography**	**MRI**	**Magnetic resonance imaging**
CTCAE	**Common Terminology Criteria for Adverse**	**NCCN**	**National Comprehensive Cancer Network**
CTLA-4	**Cytotoxic T-lymphocyte antigen-4**	**NCI**	**National Cancer Institute**
DILI	**Drug-induced liver injury**	**PD-L1**	**Programmed cell death ligand-1**
ECG	**Electrocardiogram**	**PJP**	**Pneumocystis jirovecii pneumonia**
ECHO	**Echocardiogram**	**PO**	**By mouth**
ESMO	**European Society of Medical Oncology**	**SCAR**	**Severe cutaneous adverse reaction**
GI	**Gastrointestinal**	**SITC**	**Society for Immunotherapy of Cancer**
HBcAb	**Hepatitis B core antibody**	**SJS**	**Stephen Johnson Syndrome**
HBeAg	**Hepatitis B envelope antigen**	**T1DM**	**Type 1 diabetes mellitus**

HBsAg	**Hepatitis B surface antigen**	**T3**	**Triiodothyronine**
HBV	**Hepatitis B virus**	**T4**	**Thyroxine**
HCC	**Hepatocellular cancer**	**TEN**	**Toxic Epidermal Necrolysis**
HCV	**Hepatitis C virus**	**TMG(s)**	**Toxicity management guideline(s)**
HgA1c	**Hemoglobin A1C**	**TSH**	**Thyroid stimulating hormone**
ICI(s)	**Immune checkpoint inhibitor(s)**	**ULN**	**Upper limit of normal**

Appendix 2. Schedule of study procedures: follow-up for patients who have completed durvalumab and tremelimumab treatment and achieved disease control (until confirmed progression of disease) and patients who have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progression of disease

Evaluation	Time Since Last Dose of MEDI4736							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated							
ECOG performance status	X	X	X	X	X (and month 9)	X	X	X
Subsequent anticancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					X
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[b]	X							
Patient questionnaire (patient reported outcomes)[c] and health resource use, if applicable	X		X	For patients who achieve disease control following 12 months/48 weeks of treatment, patient questionnaires and information relating to health resource use should be completed every 12 weeks relative to the date of randomisation until confirmed PD by RECIST 1.1 by investigational site review. For patients who discontinue study drug due to toxicity or a reason other than confirmed PD, patient questionnaires and information relating to health resource use should be completed relative to the date of				

				randomisation as follows: every 8 weeks for the first 48 weeks, then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review.
Tumour assessment (CT or MRI)	For patients who **achieve disease control following 12 months of treatment**, tumour assessments should be performed every 12 weeks relative to the date of **first infusion** thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please see in section 9 for timings of confirmatory scans. For patients who **discontinue MEDI4736 due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the relative to the date of **first infusion** as follows: every 8 weeks for the first 48 weeks (), then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review. Please refer for timings of confirmatory scans. Upon confirmed PD, scans should be conducted according to local standard clinical practice.			

[a] Full physical exam

[b] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[c] For patient questionnaires different approaches based on indication and study design

Appendix 3. Schedule of study procedures: follow-up for patients who have discontinue durvalumab and tremelimumab treatment due to confirmed progression of disease at the investigator discretion

Evaluation	Time Since Last Dose of MEDI4736							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination[a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated ---------->							
ECOG performance status[b]	X	X	X	X	X	X	X	X
Subsequent anticancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[c]	X							
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumor and self-antigens in circulation), if applicable	X							
miRNA/mRNA (to examine immune cell gene expression profiles in circulation), if applicable	X							
PBMCs, if applicable	X							
Patient questionnaire (patient reported outcomes)[d] and health resource use, if applicable	X		X					

Tumour assessment (CT or MRI)	For patients who **continue on MEDI4736 post-confirmed progression** at the investigator's discretion (following consultation with the sponsor), tumour assessments should be performed relative to the date of **first infusion** per until MEDI4736 is stopped. For patients who **discontinue MEDI4736 following confirmed progression**, **scans should be conducted according to local clinical practice**.

[a] Full physical exam

[b] PS to be collected if available at the 2 monthly calls to obtain subsequent anticancer therapy and survival status

[c] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[d] For patient questionnaires different approaches based on indication and study design

Appendix 4. Durvalumab dose volume calculations

For durvalumab flat dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000/50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL).

3. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL)/10.0 (mL/vial)

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

Dose (mL) = 1.5 g ×1000/50 (mg/mL) = 30.0 mL

3. The theoretical number of vials required for dose preparation:

Number of vials = 30.0 (mL)/10.0 (mL/vial) = 3 vials

Appendix 5. Tremelimumab dose volume calculations

For tremelimumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

Dose (mL) = X mg/20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL).

3. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL)/20 (mL/vial)

Or

Number of vials = Dose (mL)/1.25 (mL/vial)

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

Dose (mL) = 75 mg/20 (mg/mL) = 3.8 mL

3. The theoretical number of vials required for dose preparation:

Number of vials = 3.8 (mL)/20 (mL/vial) = 1 vial

Or

Number of vials = 3.8 (mL)/1.25 (mL/vial) = 3 vial

Appendix 6. Contact details

Appendix 7. Sites and Investigators Participants

Appendix 8. Drug shipment form

Document included in the Investigator Site File