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- **Document title: An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies (STRONG)**
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AstraZeneca

Statistical Analysis Plan

Study Code	D4191C00068
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Study Statistician

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
BoR	Best Objective Response
CI	Confidence interval
CR	Complete Response
CRF	Case Report Form
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse events
DBL	Database lock
DCO	Data cut off
DCR	Disease control rate
DMC	Data monitoring committee
DSUR	Development safety update report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
HL	Hy's Law
ILD	Interstitial lung disease
imAE	Immune-mediated AE
IPD	Important protocol deviation

Abbreviation or special term	**Explanation**
IV	Intravenous
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NIH	National Institute of Health
OAE	Other significant adverse events
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-L1	Programmed death ligand 1
PR	Partial response
PSUR	Periodic safety update report
PT	Preferred term
Q4w	Every 4 weeks
RECIST1.1	Response Evaluation Criteria In Solid Tumors, Version 1.1
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	International system (of units)
SMS	Signal management system
SOC	System organ class
SS	Safety analysis set
T3	Tri-iodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
TTE	Time to event
TTR	Time to resolution
ULN	Upper limit of normal
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
25May2017	Initial version 1.0
12Jun2020	Amendment v2.0 includes updates consistent with protocol amendment v5.0 regarding DCO and final analysis; clarifications regarding important protocol deviations; additional subgroup analyses for selected endpoints (OS, ORR, DCR, and AEs); and other minor changes to ensure consistency.
Date of last signature	Added the possibility that descriptive data from the study may be utilized as supporting evidence for health authority considerations; update of imAE characterization charter version (Appendix 1).

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary Objective

The primary objective is to assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality, including immune-relatedness, of adverse events of special interest (AESIs) in patients who are treated with fixed doses of durvalumab and tremelimumab combination therapy or durvalumab monotherapy.

An AESI is one of scientific and medical interest specific to understanding of the Investigational Product. AESIs for durvalumab ± tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. 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 aetiology.

AESIs observed with durvalumab or tremelimumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and type I diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis, and rare/less frequent imAEs including neuromuscular toxicities such myasthenia gravis and Guillain-Barré syndrome. Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs. In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

1.1.2 Secondary Objectives

The secondary objectives are:

1. To assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality of treatment-emergent adverse events (AEs) (including serious adverse events [SAEs]).

2. To assess the incidence and frequency of durvalumab ± tremelimumab) interruption and discontinuation due to treatment-emergent AEs (including SAEs).

3. To assess overall survival (OS). Patients will be followed for survival until the final data cut-off (DCO).

1.1.3 Exploratory objective

The exploratory objective is to assess overall response rate (ORR) and disease control rate (DCR) based on investigator assessed response to treatment.

1.2 Study design

This is an open-label, multi-center, study to determine the safety of fixed doses of durvalumab 1500 mg and tremelimumab 75mg combination therapy or durvalumab 1500 mg monotherapy in patients with advanced solid malignancies.

The study consists of separate modules. The study design is common to all the modules and is described in the core protocol. The specificity of each module is described in the tumor specific modules. The specificity of each module might include type of tumor, whether the treatment is combination or monotherapy and whether the study population is on second line or first line of treatment.

The core protocol (and each tumor specific module) consists of a screening period, a treatment period, a safety follow-up period (90 days post treatment discontinuation), and a survival follow-up period.

Patients will attend a safety follow up visit 90 days after study treatment discontinuation.

Thereafter, patients will be contacted by phone or electronic communication every 3 months for survival status until the final DCO.

Investigational product, dosage and mode of administration

Durvalumab + tremelimumab combination therapy

- Durvalumab 1,500 mg plus tremelimumab 75mg via intravenous (IV) infusion once every 4 weeks (Q4w), starting on Week 0, for up to a maximum of 4 doses (or cycles) followed by:
- Durvalumab monotherapy 1,500 mg via IV infusion Q4w, starting 4 weeks after the last infusion of the combination or discontinuation of tremelimumab.

OR

Durvalumab monotherapy

- Durvalumab 1,500 mg via IV infusion Q4w, starting on Week 0.

Each tumor specific module will specify combination therapy or monotherapy, and will provide details of infusion duration.

Duration of treatment

Patients may continue receiving therapy as long as they are continuing to demonstrate clinical benefit, as judged by the Investigator, and in the absence of initiation of alternative cancer treatment, unacceptable toxicity, withdrawal of consent, or other reason for treatment discontinuation.

Unless specific treatment discontinuation criteria are met, patients will continue therapy until disease progression.

Progression during treatment

Patients may continue receiving therapy in the setting of unconfirmed progressive disease (PD), at the Investigator's discretion, until PD is confirmed*. Patients with PD by RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of PD may continue to receive treatment for as long as they are gaining clinical benefit.

However, patients will not be permitted to continue immunotherapy if progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) to immunotherapy treatment in target lesions (regardless of the appearance of new lesions) i.e., the response and progression events both occurred in the target lesions while receiving immunotherapy during the same treatment period.

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

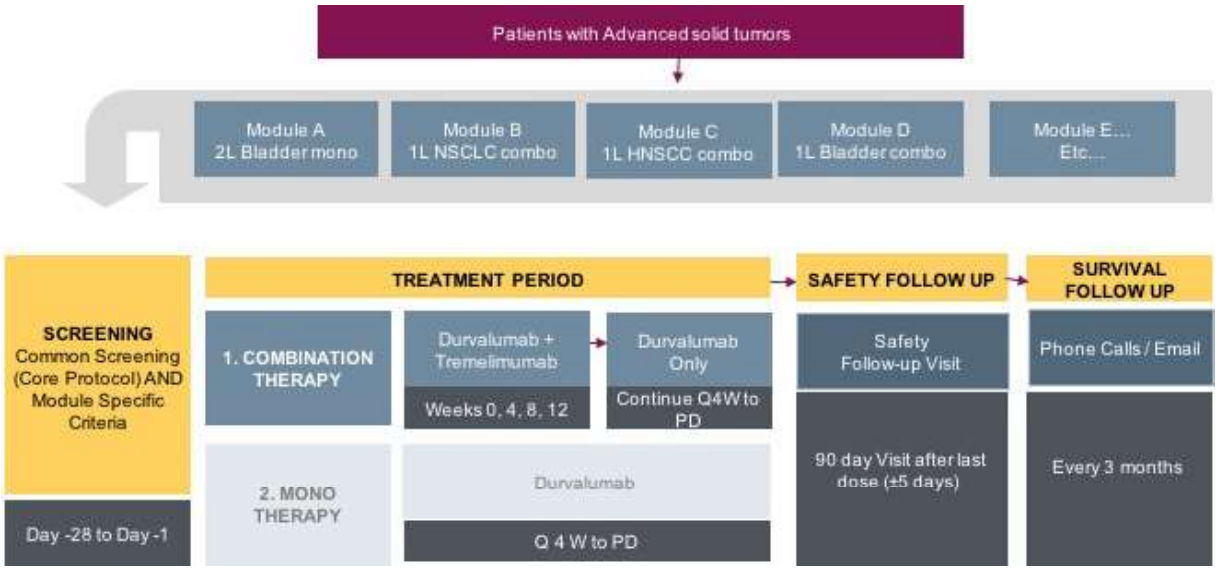
*Where treatment is discontinued due to progressive disease, it is recommended that a confirmatory scan be performed prior to discontinuation to verify progression. According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) modified for confirmation of progression, a confirmatory scan is required following an overall time point assessment of PD, no earlier than 4 weeks after the previous assessment of PD.

Follow up of patients post discontinuation of study drug

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

Follow up for safety and survival

Patients will attend a safety follow-up visit 90 days after study treatment discontinuation. Thereafter, patients will be contacted by phone or email every 3 months for survival status until the final DCO



Tumor specific modules detail which treatment regimen, combination therapy or monotherapy, will be used.

Patients will continue to receive study treatment as long as they are receiving clinical benefit in the opinion of the Investigator unless any of the criteria for treatment discontinuation are met first.

Survival follow-up will continue until the final DCO.

Data Monitoring Committee (DMC)

Interim safety monitoring will be conducted by a DMC.

1.3 Number of subjects

The primary aim of the study is to further characterise the safety profile of fixed doses of durvalumab and tremelimumab combination therapy or durvalumab monotherapy in patients with advanced solid malignancies. The precise sample size and number of AESI that will be included in this single arm study is not known a priori.

However, the following sample sizes have been planned for individual modules:

Module A - Post-Chemotherapy Urothelial and NonUrothelial Carcinoma of the Urinary Tract

A sample size of between 600-1200 patients is planned for module A – durvalumab monotherapy in patients with post-chemotherapy urothelial and non-urothelial carcinoma of the urinary tract. A sample size of up to 1200 patients would have over 75% probability (based on exact binomial probability) of observing at least ten events for an AESI with a true incidence of 1%.

Illustrations of the precision around categorical endpoints (e.g. proportion of patients with a specific AE, proportion of patients with a specific intervention for an AE or outcome for an AE) of varying incidence that could be calculated in the total population from this study are given in Table 1. The precision is based on an exact binomial CI and is illustrated using a range of sample sizes.

Table 1 95% confidence interval per sample size and event incidence

Sample size (number of patients)	Incidence							
	0.1%	1%	2%	5%	10%	15%	20%	50%
600	0.00-0.6	0.4-2.2	1.0-3.5	3.4-7.1	7.7-12.7	12.2-18.1	16.9-23.4	45.9-54.1
800	0.00--0.5	0.4-2.0	1.1-3.2	3.6-6.8	8.0-12.3	12.6-17.7	17.3-23.0	46.5-53.5
1000	0.00-0.6	0.5-1.8	1.2-3.1	3.7-6.5	8.2-12.0	12.8-17.4	17.6-22.6	46.8-53.2
1200	0.02-0.05	0.5-1.7	1.3-3.0	3.8-6.4	8.4-11.8	13.0-17.2	17.8-22.4	47.1-52.9

This sample size may also allow the investigation of safety and efficacy outcomes within sub-groups of patients.

2. ANALYSIS SETS

2.1 Definition of analysis sets

While some listings and tables may be produced based on all subjects screened, the following analysis population will be used for all analyses:

Safety Analysis Set (SAF): all enrolled patients who received at least 1 dose of durvalumab or tremelimumab.

2.2 Protocol Deviations

2.2.1 Important Protocol Deviations

According to ICH E3 guidelines version dated 1995 (ICH 1995),

> "Protocol deviations consist of any change, divergence or departure from the study design or procedures defined in the protocol. Important protocol deviations (IPDs) are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety or well-being."

For the interim analysis, all major deviations were classified as important deviations. For the final analysis, 4 general categories will be considered IPDs and will be listed and summarised.

- Deviation 1: Patients who deviate from key entry criteria per the Clinical Study Protocol v5.0 (CSP).
  - Inclusion Criterion 7: No prior exposure to anti-PD-1 or anti-PD-L1, including on another AstraZeneca study. Exposure to other investigational agents may be permitted after discussion with the Sponsor.
  - Inclusion Criterion 8: Adequate organ and marrow function as defined below:
    - Hemoglobin ≥9.0 g/dL
    - Absolute neutrophil count ≥1.0 × 109 /L
    - Platelet count ≥75 × 109/L

  - Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.
  - ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST≤5 × ULN
  - Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance (CL) >40 mL/min as determined by Cockcroft-Gault (using actual body weight)
- Inclusion Criterion A1: Histologically or cytologically confirmed locally advanced or metastatic urothelial ornon-urothelial carcinoma of the urinary tract (including the urinary bladder, ureter, urethra and renal pelvis)
- Inclusion Criterion A2: Disease that has progressed during or after at least one previous platinum or non-platinum-based chemotherapy, either for PD less than 12 months after adjuvant or neoadjuvant chemotherapy, or metastatic disease
- Inclusion Criterion A3: ECOG performance status 0-2
- Exclusion Criterion 3: Concurrent enrollment in another clinical study, or another sub-study of this protocol, unless it is an observational (non-interventional) clinical study or during the follow up period of an interventional study
- Exclusion Criterion 4: Participation in another clinical study with an investigational product during the last 28 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment.
- Exclusion Criterion 5: Any concurrent chemotherapy, investigational agent, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.
- Exclusion Criterion 7: Receipt of any investigational anticancer therapy within 28 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment.
- Exclusion Criterion 8: Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable.
- Exclusion Criterion 9: Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
- Exclusion Criterion 10: History of allogenic organ transplantation.
- Exclusion Criterion 11: Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, serious chronic GI 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.
- Exclusion Criterion 12: 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 investigational product (durvalumab + tremelimumab) 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
- Exclusion Criterion 13: History of leptomeningeal carcinomatosis
- Exclusion Criterion 14: Has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on baseline brain imaging (please refer to RECIST for details on the imaging modality) obtained during the screening period or identified prior to signing the ICF. Patients whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least 4 weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have resolved or be stable either, without the use of steroids, or are stable on a steroid dose of ?10 mg/day of prednisone or its equivalent and anti-convulsants for at least 14 days prior to the start of treatment. Brain metastases will not be recorded as RECIST Target Lesions at baseline.
- Exclusion Criterion 15: History of active primary immunodeficiency.
- Exclusion Criterion 16: Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive hepatitis B virus [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 virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Exclusion Criterion 17: Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
  - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra articular injection)
  - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Exclusion Criterion 18: Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
  - Patients with vitiligo or alopecia

  - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
  - Any chronic skin condition that does not require systemic therapy
  - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
  - Patients with celiac disease controlled by diet alone.
- Exclusion Criterion 20: Known allergy or hypersensitivity to study drug(s) or compounds of similar biologic composition to the study drug(s), or any of the study drug excipients.
- Exclusion Criterion 21: Any unresolved NCI CTCAE Grade ≥2 toxicities from prior anti-cancer therapy with the exception of vitiligo, alopecia, and the laboratory values defined in the inclusion criteria.
  - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
  - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician
- Exclusion Criterion 24: Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.
- Exclusion Criterion A1: Any other malignancy within 5 years before first dose of IP, except for the following:
  - Patients with a history of prostate cancer (tumor/node/metastasis stage) of stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention
  - Patients who have been adequately treated for a malignancy with a low potential risk for recurrence, eg, cervical carcinoma in situ, non-melanomatous carcinoma of the skin, or ductal carcinoma in situ of the breast that has been surgically cured

- Deviation 2: Patients who met discontinuation criteria (per CSP Section 3.9) but did not discontinue durvulumab.

- Deviation 3: Received prohibited concomitant medications (including other anti-cancer agents). Please refer to the CSP section 7.7 for those medications that are detailed as being ‘excluded’ from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock to identify those likely have an impact on efficacy.

- Deviation 4: A pattern of two or more missed treatments, safety and/or efficacy assessments observed in an individual patient or group of patients that, in the opinion of the principal investigator,

  - were due to the 2020 COVID-19 global pandemic and,
  - had a significant effect on either the completeness, accuracy, and/or reliability of the patient’s data, or the patient’s rights, safety or well-being.

2.2.2 Monitoring of Important Protocol Deviations

The categorisation of IPDs is not automatic and will depend on duration and the perceived effect on study endpoints.

In addition to the programmatic determination of IPDs, monitoring notes or summaries will be reviewed to determine any important post entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified. The final classification of deviations will be made prior to database lock or data freeze. Decisions made will be documented and approved by AstraZeneca prior to analysis.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Safety

The primary outcome measure for the study is the number and proportion of patients with AESI. Pre-defined Medical Dictionary for Regulatory Activities (MedDRA) preferred terms groupings will be used to identify AESI.

'On treatment' will be defined as assessments between date of first dose and 90 days following last dose inclusive.

3.1.1 Adverse Events (AEs)

AEs and SAEs will be collected throughout the study, from time of signature of informed consent and up to 90 days after the last dose of immunotherapy agents (ie, the last dose of durvalumab or tremelimumab). MedDRA (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE Version 4.03).

A treatment emergent adverse event (TEAE) is an AE with an onset date or a pre-existing AE worsening following the first dose of study treatment through to 90 days after the last dose of immunotherapy agents. For the durvalumab + tremelimumab modules, in the event of the components being administered separately, then date of first dose/last dose will be considered as the earliest/latest dosing date of either component. Any AE occurring before study treatment (i.e. before the administration of the first dose on Study Day 1) will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'. However, any AE occurring before the administration of the first dose on Study Day 1 that increases in severity after the first dose will be regarded as treatment emergent and thus will be included in the majority of summary tables.

For patient level summaries, if more than one AE is coded to the same PT for the same patient, the patient will be counted only once in summaries using the most serious grading on causal relationship to study treatment.

3.1.1.1 Primary endpoint - AESI

An AESI is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the

investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs observed with durvalumab or tremelimumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and type I diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis, and rare/less frequent imAEs including neuromuscular toxicities such myasthenia gravis and Guillain-Barré syndrome. Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs. In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Other categories may be added or existing terms may be merged as necessary. An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which preferred terms contribute to each AESI. A further review will take place prior to Database lock (DBL) by a medically qualified expert in collaboration with AstraZeneca to ensure any further terms not already included are captured within the categories.

Immune-mediated AEs

AESIs for durvalumab or tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. An imAE is defined as a subset of AESIs which are associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology.

The identification of imAEs will be made following the AstraZeneca imAE characterization charter (see Appendix 1).

For the DMC safety review, imAEs will be identified through:

- the selection of preferred term

For the interim and final analysis of each module, imAEs will be identified through:

- the selection of preferred term,
- programmatic identification of those potential imAEs requiring medication such as steroids, immunosuppressants and/or hormone replacement therapy

3.1.1.2 Other Significant Adverse Events

During the evaluation of the AE data, a medically qualified expert will review the list of AEs that were not reported as SAEs and ‘Discontinuation of Investigational Product due to Adverse Events’ (DAEs). Based on the expert’s judgment, significant AEs of particular

clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the Clinical Study Report (CSR). A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

3.1.1.3 Designated Medical Events

A pre-defined non product specific list of MedDRA terms used within the business will be provided prior to any database lock, which will be used to summarise specific adverse events for use in PSUR (Periodic Safety Update Report), ePSUR, DSUR (Development Safety Update Report) or SMS (Signal Management System).

3.1.2 Secondary Safety Endpoints

3.1.2.1 Treatment exposure

Exposure will be defined as follows:

Total (or intended) exposure of study treatment

- Total (or intended) exposure = [earliest of (last dose date where dose > 0 mg +28 days, death date, DCO date] – first dose date + 1

Actual exposure of study treatment

- Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above.

Dose reductions are not permitted per section 6.9.1 of the core CSP. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Exposure will also be measured by the number of cycles received. For each immunotherapy agent a cycle corresponds to one dose of treatment. A cycle will be counted if treatment is started even if the full dose is not delivered.

3.1.2.2 Patients who permanently discontinue during a dose interruption

If a decision is made to permanently discontinue study treatment in-between cycles or during a cycle delay then the date of last administration of study medication recorded will be used in the programming.

3.1.2.3 Laboratory data

Laboratory data will be collected throughout the study, from screening to the follow-up visits as described in the CSP. Blood and urine samples for determination of haematology, clinical chemistry, and urinalysis will be collected as described in section 5.3.1 of the CSP. For the definition of baseline and the derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in section 3.1.3 below will be used.

Change from baseline in haematology and clinical chemistry variables will be calculated for each post-dose visit on treatment. CTC grades will be defined at each visit according to the CTC grade criteria using local or project ranges as required, after conversion of lab result to corresponding preferred units. The following parameters have CTC grades defined for both high and low values: Potassium, Sodium, and Glucose so high and low CTC grades will be calculated.

Absolute values will be compared to the project reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). The maximum or minimum on-treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time.

Local reference ranges will be used for the primary interpretation of laboratory data at the local laboratory. Project (AZ standard) reference ranges will be used throughout for reporting purposes. The denominator used in laboratory summaries of CTC grades will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline, to be evaluable the patient need only have 1 post dose-value recorded.

3.1.3 General considerations for safety assessments

Time windows will be defined for any presentations that summarise values by visit using the following conventions:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data should have the potential to be included in the summaries. The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.

For example, the visit windows for vital signs data (with 4 weeks between scheduled assessments) are:

Day 29, visit window 2 – 42
Day 57, visit window 43 – 70
Day 85, visit window 71 – 98
Day 113, visit window 99 – 126
Day 141, visit window 127 – 154
Day 169, visit window 155 – 182
Day 197, visit window 183 – 210
Day 225, visit window 211 – 238

Day 253, visit window 239 – 266
Day 281, visit window 267 – 294
Day 309, visit window 295 – 322
Day 337, visit window 323 – 350

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- For visit based summaries:
  - If there is more than one value per patient within a time window then the closest value to the scheduled visit date should be summarised, or the earlier in the event the values are equidistant from the nominal visit date, or the average if it is not possible to ascertain the earliest. The listings should highlight the value for that patient that went into the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
  - To prevent very large tables or plots being produced that contain many cells with sparse data that is difficult to interpret, for each treatment group visit data should only be summarised if the number of observations is greater than the minimum of 20 and > 1/3 of patients dosed.
- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum.
- Baseline will be defined as the last non-missing measurement prior to dosing with study treatment (excluding unscheduled visit). For the re-treatment period for immunotherapy agents then baseline is similarly defined as the last non-missing measurement prior to the first dose on the re-treatment period. For laboratory data, any assessments made on day 1 will be considered pre-dose. Alternatively, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose with no washout or other intervention in the screening period), the average can be taken as a baseline value. For non-numeric laboratory tests (ie some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on day 1, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarised over time, study day will be calculated in relation to date of first treatment.
- Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e., below the lower limit of quantification) or > x (i.e., above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.
- For missing diagnostic dates, if day and/or month are missing use 01 and/or Jan. If year is missing, put the complete date to missing.
- For missing concomitant medication and AE start dates:
  - If year is missing (or completely missing), do not impute.

  - If year is present and months and day are missing; or year and day are present and month is missing, impute as January 1st.
  - If year and month are present and day is missing, impute day as first day of the month.
- For missing concomitant medications and AE end dates, the following will be applied:
  - If year is missing (or completely missing), do not impute.
  - If year is present and month and day are missing; or year and day are present and month is missing, impute as December 31st.
  - If year and month are present and day is missing, impute day as last day of the month.
  - When the patient has died in the same month/year of partial stop date, use date of death.
- For medications, a conservative approach will be followed and events will be assumed to be concomitant unless the end date is before the first dose of IP. If the start and end dates are both missing it is considered concomitant.
- In addition for AEs if, for a partial start date, the AE start date could (when also considering the AE end date) potentially be on the first study treatment date, the AE start date will be imputed with the first study treatment date to assume a "worst case" scenario; e.g. AE from UNK-Jun-2017 to 23-Jul-2017 with the first study treatment date 21-Jun-2017, then the AE start date will be imputed to 21-Jun-2017.

3.2 Biomarker Variables

PD-L1 expression status (high, low) will be defined for the analysis of Module A according to following criteria:

- High: ≥ 25% tumour cell or immune cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.
- Low: < 25% tumour cell and immune cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control.

3.3 Efficacy

3.3.1 Secondary endpoint

3.3.1.1 Overall survival (OS)

OS is defined as the time from the date of first dose until death due to any cause (ie, date of death or censoring – treatment start date + 1). Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (SUR_DAT, recorded within the SURVIVE module of the electronic case report form [eCRF]).

Note: Survival calls will be made in the week following the date of Data Cut Off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital

status of the patient can be obtained by site personnel from publicly-available resources where it is possible to do so under applicable local laws.

Note that for any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant CRF fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since the SURVIVE module is only completed for patients off treatment).

3.3.2 Exploratory endpoints

RECIST 1.1 response will be assessed by the investigator and not derived programmatically since tumor evaluation will be carried out by the sites per institution standards and detailed tumor measurements are not databased.

3.3.2.1 Objective response

Objective response (using Investigator assessments) is defined as at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of objective response. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be considered responders.

3.3.2.2 Disease control rate

Disease control at 6 or 12 months is defined as a best objective response (BoR) of CR or PR or stable disease (SD) as assessed by the investigator, in the first 6 or 12 months, respectively, following the start of study treatment.

Disease control will be determined based on the Investigator assessments and all data up until the first confirmed progression event. This will use all data up until the progression event that is used for the analysis (ie, unconfirmed progressions are not considered progression events, which means that the BoR that contributes to the assessment of disease control may be after an unconfirmed progression for some patients). Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be considered responders.

3.4 Baseline

3.4.1 Prior and concomitant medications

The WHO Drug B3 dictionary will be used for concomitant medication coding.

Any medications taken by the patient prior to the first dose date of study treatment will be considered prior medication.

Any medication taken by the patient at any time after the date of the first dose (including the date of the first dose) of study treatment up to 90 days after last dose will be considered concomitant medication. Any medication that started prior to the first dose of study treatment and ended after the first dose or is ongoing will be considered as both prior and concomitant medication.

For the purpose of inclusion in prior or concomitant mediation summaries, incomplete medication start and stop dates will be imputed as detailed in Section 3.1.3.

4. ANALYSIS METHODS

4.1 General principles

No hypothesis testing is planned for this single arm study. Each module will be summarised separately.

The general principles as mentioned below will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate, and will be presented separately for each module. Descriptive safety and efficacy data from the STRONG study may be utilized as supporting evidence for health authority considerations.
- Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. For log transformed data it is more appropriate to present geometric mean, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total.
- Exact CIs for proportions will be calculated using the Clopper-Pearson method.
- For percentiles of survival times based on the Kaplan-Meier method (eg, median survival), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, the Klein and Moeschberger extension of the Brookmeyer-Crowley method).
- For point-estimates of survival based on the Kaplan-Meier method (eg, for OS at 12 months), CIs will be calculated using the default method available in the SAS LIFETEST procedure (ie, using Greenwood's estimate of standard error and a log-log transformation).
- For continuous data the mean and median will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- SAS® version 9.3 or higher will be used for all analyses.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of study treatment.

All data collected will be listed.

4.2 Analysis methods

As this is a single arm study, no endpoints are to be subjected to formal statistical analysis.

4.2.1 Safety data

Data from all cycles of treatment will be combined in the presentation of safety data. The following sections describe the planned safety summaries. However, additional safety tables may be required to aid interpretation.

Adverse Events

All AEs will be summarised descriptively, in terms of number of patients (n) and percentage of patients (%) reporting the event by MedDRA system organ class (SOC) and preferred term (PT). The majority of the AE summaries, unless stated otherwise, will be based on TEAEs.

Any adverse events that occur prior to dosing or starting more than 90 days after discontinuing treatment will be presented in a separate summary by SOC and PT.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity and relationship to study drug.

Summary information (the number and percent of patients by SOC and PT) will be tabulated for:

- All TEAEs
- All TEAEs causally related to study medication (as determined by the reporting investigator)
- TEAEs with CTCAE grade 3 or higher
- TEAEs with CTCAE grade 3 or higher, causally related to study medication (as determined by the reporting investigator)
- TEAEs by outcome
- TEAEs with outcome of death
- TEAEs with outcome of death causally related to study medication (as determined by the reporting investigator)
- All treatment-emergent SAEs
- All treatment-emergent SAEs causally related to study medication (as determined by the reporting investigator)
- All treatment-emergent SAEs by maximum NCI CTCAE grade
- TEAEs leading to discontinuation of study medication
- TEAEs leading to discontinuation of study medication, causally related to study medication (as determined by the reporting investigator)
- TEAEs leading to hospitalization
- TEAEs leading to dose interruption of study medication
- Other significant TEAEs
- Other significant TEAEs causally related to study medication (as determined by the reporting investigator)
- Designated medical events
- Infusion reaction TEAEs (as determined by the reporting investigator)

As well as the overall summary of the number and percentage of patients in each SOC/PT category, an overall summary of the number of episodes in each SOC/PT category will be presented. In addition, a truncated AE table of most common AEs and another table showing most common AEs with CTCAE grade 3 or higher, showing all events that occur in at least 5% of patients overall will be summarised by PT, by decreasing frequency. This cut-off may be modified after review of the data. When applying a cut-off (ie, x %), the raw percentage

will be compared to the cut-off, no rounding will be applied first (i.e., an AE with frequency of 4.9% will not appear if a cut-off is 5%).

An overall summary of the number and percentage of patients in each AE category (Any AE, Any AE causally related to treatment, Any AE of CTCAE grade 3 or higher etc…) will be presented.

Each AE event rate (per 100 patient years) will also be summarised by PT within each SOC for the output summarising all AEs. For each preferred term, the event rate is defined as the number of patients with that AE divided by the total drug exposure of patients at risk of AE. The denominator is the total duration of treatment (in years) across all patients calculated as the sum total (of all patients) of days from first dose to the earlier of the date of first onset of the event or the last day of study medication.

As a part of the trial's Disclosure Record to the National Institute of Health (NIH), the following tables will be produced

- TE non-serious AEs
- TE non-serious AEs causally related to study medication (as determined by the reporting investigator)
- TE non-serious AEs occurring in >5% of Patients
- TE non-serious AEs occurring in >5% of patients causally related to study medication (as determined by the reporting investigator)
- Summary of the number of episodes of treatment-emergent SAE in each SOC/PT category
- Number of subjects enrolled per age group as per EU categories.

Fluctuations observed in CTCAE grades during study will be listed for those TEAEs which are CTCAE ≥ 3.

In addition, all AEs will be listed.

Adverse events of special interest (primary outcome)

Summaries of treatment emergent AESI by category and PT will include number (n) and percentage (%) of patients who have:

- At least one treatment-emergent AESI
- At least one treatment-emergent AESI by outcome
- At least one treatment-emergent AESI leading to treatment interruption or discontinuation
- At least one treatment-emergent serious AESI
- At least one treatment-emergent AESI by maximum NCI CTCAE grade
- At least one treatment-emergent AESI causally related to study medication
- At least one treatment-emergent AESI with fatal outcome
- At least one treatment-emergent AESI which required additional treatment with steroids, immunosuppressants and hormone replacement therapy
- Laboratory findings, vital signs and other safety parameters associated with AESI will be summarised as part of the AESI outcome measures.

Length of intervention with steroids, immunosuppressants and/or hormone replacement therapy for AESIs will be calculated based on treatment start and stop dates. Total treatment

times will then be combined for each patient and summarised for patients experiencing at least one treatment-emergent AESI.

The exact 95% CIs around the incidence estimates will also be reported for each AESI type.

A summary of total duration (days) of AESI will be provided. For ongoing AESI, the date of death or data cut-off will be imputed as end date.

Immuno-mediated adverse events

Summaries of treatment-emergent imAEs by AESI category and PT will include number (n) and percentage (%) of patients who have:

- At least one treatment-emergent imAE
- At least one treatment-emergent imAE by outcome
- At least one treatment-emergent imAE leading to treatment interruption or discontinuation
- At least one treatment-emergent serious imAEs
- At least one treatment-emergent imAE by maximum NCI CTCAE grade
- At least one treatment-emergent imAE causally related to study medication
- At least one treatment-emergent imAE with fatal outcome

Subgroup analyses

Subgroup analyses will be conducted for the summary of TEAEs in the following subgroups of the SS:

- Sex (male versus female)
- Age at baseline: <65 vs 65-74 vs ≥75 years of age). This will be determined from the date of birth (BRTHDAT in the DM domain) and baseline visit (VIS_DAT in the VISIT domain) on the eCRF. Patients with a partial date of birth (ie for those countries where year of birth only is given) will have an assumed date of birth of 1st Jan [given year]). Patients with a missing age value will be included using the mean age and categorised accordingly.
- Race: Asian vs non-Asian
- ECOG performance status at baseline: 0-1 vs 2
- Tumor histology: Urothelial (i.e. TCC) vs non-urothelial
- PDL1: high >=25% vs low <25%. If data is available from the central laboratory, the central laboratory result will be used in the group derivation, otherwise, the local test result will be used.

Subgroup analyses will also be conducted for the summary of OS, ORR and DCR in the following subgroups of the SS:

- Age at baseline: <65 vs 65-74 vs ≥75 years of age
- ECOG performance status at baseline: 0-1 vs 2
- Primary tumor location: Bladder vs Renal pelvis and Ureter vs Urethra vs Other
- Stage: III vs IV
- Tumor histology: Urothelial (i.e. TCC) vs non-urothelial
- Previous platinum chemotherapy: platinum vs non-platinum chemotherapy
- Best response to previous therapy (CR vs PR vs SD vs PD)

- Baseline metastases: liver (+/- other visceral or non-visceral metastases) vs lymph node metastases only
- PDL1: high >=25% vs low <25%

No formal comparisons will be performed between the subgroups.

Time-to-event analyses

Time-to-event of AESI and imAE:

Time-to-onset of AESI/imAE (by AESI/imAE category) and time-to-intervention with steroids, immunosuppressants and/or hormone replacement therapy to treat an AESI/imAE will be defined as time from first dose of durvalumab +/- tremelimumab to first onset of the event.

Time-to-event (TTE) is defined in months as follows:

TTE (months) = (Date of event or censoring–Date first dose of durvalumab [durvalumab + tremelimumab for the combinations modules]+1)/(365.25/12)

Time-to-resolution (TTR) of an AESI/imAE type is defined as the time from the first onset of an AESI/imAE type to the resolution of the AESI/imAE type. TTR is defined in months as follows:

TTR (months) = (Date of AESI/imAE resolution or censoring–Date of AESI/imAE onset+1)/(365.25/12)

Analysis of TTR will only include patients who have experienced an AESI/imAE.

The distribution of TTE and TTR times will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958) and summarised using the median, twenty-fifth and seventy-fifth percentiles. TTE and TTR of imAE of NCI CTCAE grade >=3 will also be produced.

Deaths

A summary of deaths will present number (n) and percentage (%) of patients for the following categories:

- Total number of deaths (including deaths occurring within 90 days after last dose of study medication and deaths occurring after the 90 days post dosing window)
- Death related to disease under investigation ONLY, as determined by investigator (including deaths occurring within 90 days after last dose of study medication and deaths occurring after the 90 days post dosing window)
- TEAEs with outcome of death ONLY
- AEs with outcome of death ONLY and onset date falling after 90 days follow-up period
- Deaths related to disease under investigation, as determined by the investigator, and with TEAE with outcome of death
- Deaths related to disease under investigation, as determined by the investigator, and with AE with outcome of death and onset date falling after 90 days follow-up period
- Deaths that occurred 90 days after last dose, and unrelated to AE (ie no AE with outcome of death) or disease under investigation

- Patients with unknown reason for death
- Other deaths

Summary of long term tolerability

To assess long term tolerability, provided that there are a sufficient number of patients with events to warrant it (≥ 10 events), prevalence plots and cumulative incidence plots will be presented for each AESI category and for any other events considered important after review of the safety data.

A prevalence plot provides information on the extent to which the events may be an ongoing burden to patients. The prevalence at time t after first dose of study treatment is calculated as the number of patients experiencing the event divided by the number of patients receiving study treatment or in safety follow-up at time t; generally, t is categorised by each day after dosing. The prevalence will be plotted over time. Multiple occurrences of the same event are considered for each patient but a patient is only counted in the numerator whilst they are experiencing one of the occurrences of the event. The raw cumulative incidence is the actual probability that a patient will have experienced their first occurrence of the event by a given time point.

Treatment exposure

The following summaries related to study treatment will be produced for the SS:

- Total exposure, actual exposure, and total number of cycles received will be summarised separately for the initial treatment phase and the re-treatment phase. For the modules with combination therapy, those summaries will be carried out once for each drug separately and once for combination separately from monotherapy.
- Number of, reasons for, and duration of dose delays/interruptions of durvalumab and tremelimumab. Dose interruptions will be based on investigator initiated dosing decisions. In addition, interruptions due to AEs and due to reasons other than AEs will be summarized separately.
- Number of infusions received.
- Exposure over time will be plotted.

For patients on study treatment at the time of the OS analysis, the DCO date will be used to calculate exposure.

Subsequent Therapy

Subsequent therapies received will be summarized.

Laboratory assessments

Laboratory assessments are to be measured 90 days after last dose during the safety follow-up visit, per institutional care guidance only. Data obtained up until the 90 days following discontinuation of immunotherapy agents or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for reporting. This will more accurately depict laboratory toxicities attributable to study treatment only as a number of toxicities up to 90 days following discontinuation of immunotherapy agents are likely to be attributable to subsequent therapy.

A small selection of summaries of laboratory data may also be produced containing data from initiation of the first subsequent therapy following discontinuation of study treatment until 90 days following discontinuation of immunotherapy agents (i.e. summarising the laboratory data collected on patients taking subsequent therapy during the safety collection follow-up window post discontinuation of study treatment). These outputs will only be produced if the number of laboratory toxicities observed warrant the inclusion of such outputs for interpretational purposes. Any data post 90 days last dose will not be summarised.

Data summaries will be provided in International System (SI) of units.

For continuous laboratory assessments absolute value, change from baseline and percentage change from baseline will be summarised using descriptive statistics at each scheduled assessment time.

Shift tables for laboratory values by worst NCI CTCAE grade will be produced The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- Haematology: Haemoglobin, Leukocytes, Lymphocytes (count, absolute), Neutrophils (count, absolute), Platelets.
- Clinical chemistry: ALT, AST, ALP, Total bilirubin, LDH, calcium, lipase, amylase , Sodium – hypo and – hyper, Potassium – hypo and – hyper, Creatinine, Urea nitrogen.

For the parameters with no CTCAE grading that are listed in the CSP, shift tables from baseline to worst value on-treatment will be provided (Haemoglobin, Erythrocytes, LDH, TSH, Urea nitrogen.

Urinalysis

Additional summaries will include a shift table for urinalysis (Hemoglobin, Leucocytes, Glucose, Ketones, Protein) comparing baseline value to maximum on-treatment value.

Liver Enzyme Elevations and Hy's law

The following summaries will include the number (%) of patients who have:

- Elevated ALT, AST, and Total bilirubin during the study
- ALT ≥ 3x –≤ 5x, > 5x – ≤8x, > 8x. >10x and >20x Upper Limit of Normal (ULN) during the study
- AST ≥ 3x- –≤ 5x, > 5x – ≤8x, > 8x. >10x and >20x ULN during the study
- Total bilirubin ≥2x-≤3x, >3x-≤5x, >5x ULN during the study
- ALT or AST ≥3x - ≤5x, >5x - ≤8x, >8x, >10x and >20x ULN during the study
- ALT or AST ≥3x ULN and Total bilirubin ≥2x ULN during the study

(Potential Hy's law): The onset date of ALT or AST elevation should be prior to or on the date of Total Bilirubin elevation

- Narratives will be provided in the CSR for patients who have ALT ≥ 3x ULN plus Total bilirubin ≥ 2x ULN or AST ≥ 3x ULN plus Total bilirubin ≥ 2x ULN at any visit.

Liver biochemistry test results over time for patients with elevated ALT or AST (ie ≥ 3x ULN), and elevated Total bilirubin (ie ≥ 2x ULN) (at any time) will be plotted. Individual

patient data where ALT or AST (ie ≥ 3x ULN) plus Total bilirubin (ie ≥ 2x ULN) are elevated at any time will be listed also.

Plots of ALT and AST vs. Total bilirubin will also be produced with reference lines at 3×ULN for ALT, AST, and 2×ULN for Total bilirubin. In each plot, Total bilirubin will be in the vertical axis.

Assessment of Thyrotoxicity

Thyroid function tests free T3 and free T4 are to be measured 90 days after last dose during the safety follow up visit, per institutional care guidance only. Data obtained up until the 90 days following discontinuation of immunotherapy agents or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for reporting.

For TSH absolute value and change from baseline will be summarised using descriptive statistics at each scheduled assessment time. Shift tables showing the change from baseline to maximum and from baseline to minimum will also be produced. Free T3 and free T4 will be listed only as they are to be tested only if clinically indicated.

ECGs

ECG data will not be summarized nor listed as only high/low values are reported in eCRF

Vital signs

Vital signs will summarised by study visit. Box plot of absolute values will be produced.

Physical examination

Individual physical examination data will not be listed. Physical examination abnormalities will be reported as AEs and included in AE listings.

ECOG performance status

Shift in Eastern Cooperative Oncology Group (ECOG) performance status (see appendix F of the CSP) will be summarised.

Other Safety Data

Data from positive pregnancy tests will be listed only. Safety findings reported in the CRF to support the monitoring and evaluation of imAEs will be listed.

4.2.2 Efficacy data

Overall survival

OS will be summarised using the Kaplan-Meier method with median OS and its associated 95% confidence interval reported as well as the proportion of patients alive at 1, 2, 3, 4 and 5 years.

Objective Response Rate and Disease Control Rate

Objective response rate (ORR) and Disease control rate (DCR) at 6 and 12 months will be calculated for the SAF as the percentage of patients (%) with objective response and

controlled disease, respectively. ORR and DCR will be reported with the associated 95% exact Clopper-Pearson confidence interval.

The denominator used for ORR and DCR rates will be the number of patients with anassessment in the time period. A summary of investigator assessment (responding, stable or progressing) will be provided for those patients with an alternative method of assessment (e.g. WHO).

4.2.3 Demographic and baseline characteristics data

The following will be summarised for all patients in the SS (unless otherwise specified):

- Patient disposition (including screening failures)
- Important protocol deviations
- Inclusion in analysis set
- Demographics (age, age group [<50, >=50-< 65, ≥ 65 years and additionally ≥ 75 years], sex, race and ethnicity)
- Medical History
- Patient characteristics at baseline (weight, weight group [< 40 kg >=40-<75 kg, >=75-<120 and >= 120 kg, body mass index (BMI) and BMI group [underweight <19, ideal 19-25, overweight 25-30, Obese > 30 and Severely obese > 35])
- Patient recruitment by country and centre
- Prior medications (with a start date prior to study treatment start date)
- Previous cancer therapy, radiotherapy and surgery as entered in the corresponding CRF pages.
- Disease characteristics at baseline (time since diagnosis, primary tumour location, histology type, tumour grade and overall disease classification, best response to previous therapy)
- Extent of disease at baseline (ECOG)
- Physical examination at baseline
- Prohibited concomitant medications (see section 2.2.)
- Concomitant medications
- Alcohol consumption
- Tobacco consumption
- PD-L1
- Interstitial lung disease

5. INTERIM ANALYSES

Interim safety monitoring will be conducted by a DMC.

5.1 Data Monitoring Committee

A DMC comprised of internal experts independent from the study will be convened and will meet after the study has started on a regular basis to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. Full details

of the DMC remit, procedures, processes, meeting frequency and interim analyses can be found in the DMC Charter.

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

6. CHANGES OF ANALYSIS FROM PROTOCOL (NOT APPLICABLE)

None.

7. REFERENCES

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association. 1958;53:457–81.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Structure and Content of Clinical Study Reports E3; Version 4; No 1995

8. APPENDIX

8.1 Appendix 1 imAE charter (v6 27Apr2020).

durvalumab_tremelimumab imAE Charter

PAREXEL International Electronic Signature Page

This page is the manifestation of the electronic signature(s) used in compliance with PAREXEL International's electronic signature policies and procedures and in compliance with applicable regulations.

UserName: PPD
Title: Manager, Biostatistics, GDO
Date: Thursday, 23 July 2020, 01:21 PM GMT Standard Time
Meaning: Document contents approved.
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