- **Protocol number: D4191C00068**
- **Document title: An Open-Label, Multi-Centre, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies (STRONG)**
- **NCT number: NCT03084471**
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AstraZeneca

Clinical Study Protocol	
Drug Substance	Durvalumab (MEDI4736) and Tremelimumab
Study Code	D4191C00068
Version	5.0
Date	13 December 2019
EudraCT Number	2016-005068-33

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

Sponsor: *AstraZeneca AB, 151 85 Södertälje, Sweden*

VERSION HISTORY

Version 1, 20 December 2016
Initial creation
Version 2, 01 March 2017 Changes to the protocol are summarized below.
Section 3.9 Discontinuation of investigational product In bullet 3, the following additional details were added regarding adverse events (AEs) that meet criteria for discontinuation as defined in the Toxicity Management Guidelines (Appendix E) Permanent discontinuation of study drug/study regimen should occur for any Grade ≥3 immune-mediated AE, that does not downgrade to Grade ≤1 or baseline status (for patients who entered the study with an existing laboratory abnormality) within 14 days despite maximum supportive care (ie, use of steroids or potent immunosuppressive medication). Certain exceptions are enumerated below for specific immune-mediated AEs: • Pneumonitis / interstitial lung disease (ILD) – For any Grade ≥3 event promptly discontinue study drug/study regimen. • Diarrhea/Enterocolitis - For any Grade ≥3 event promptly discontinue study drug/study regimen. • Nephritis (Serum Creatinine > 3.0 X baseline; >3.0 to 6.0 X ULN) - For any Grade ≥3 event promptly discontinue study drug/study regimen. • Hypothyroidism – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption. • Other toxicities may have slightly different time to resolution for any Grade ≥3 event (ie skin rash, peripheral neuropathy), please refer to Appendix E, Table 7. Immune-mediated Reactions, in core protocol for details. For full guidance on these and other toxicities, please reference Appendix E, Table 7 Immune–mediated Reactions, in core protocol.

Version 3, 19 April 2017

Changes to the protocol are summarized below.

Section 3.1 Inclusion criteria

- Criterion 7 changed from "adequate organ and marrow function independent of transfusion for at least 7 days prior to screening and independent of growth factor support for at least 14 days prior to screening" to "adequate organ and marrow function"

Section 4 STUDY PLAN AND TIMING OF PROCEDURES and Section 5 STUDY ASSESSMENTS

- Collection of tobacco and alcohol use at screening was added.
- Clarifications on the collection of vital signs and physical examination information (including body weight, and height) were added: vital signs should be measured and recorded at all visits from screening to the last treatment visit; physical examination information should only be reported in the case report form (CRF) if abnormalities are reported as AEs.
- In Table 2, urinalysis during treatment visits was changed from "as clinically indicated" to mandatory for consistency with other sections and urinalysis at the safety follow up visit should be done "per institutional care".
- Collection of fresh tumor tissues was described, in case an archival tissue sample was not available.
- Inconsistencies regarding thyroid stimulating hormone (TSH) evaluations were corrected (TSH should be measured at all visits).
- Information was added that autoimmune antibody testing (in case of AEs of possible autoimmune nature) should be performed by a local laboratory.

Section 6.9.1 Data Monitoring Committee

- Independent Data Monitoring Committee (IDMC) comprised of independent experts changed to Data Monitoring Committee (DMC) comprised of internal experts independent from the study team.

Section 7 Investigational product and other treatments

- Provision of Standard-of-Care treatment centrally by AstraZeneca under

certain circumstances when local sourcing is not feasible was removed.

Appendix E Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-related, and Non Immune-mediated Reactions

- Definition of Grade 1 hepatitis according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 4.03 was corrected to aspartate transaminase (AST) or alanine transaminase (ALT) > upper limit of normal (ULN) to 3 × ULN and/or total bilirubin (TB) >ULN to 1.5 × ULN)

Appendix H Tumor Specific Modules

Appendix H was created to include tumor specific modules into the protocol and Module A was revised as follows:

Section 1 Introduction: Minor updates in the introduction.

Section 3.11 Discontinuation of the study:

- Number of patients to be enrolled changed from "1200" to "up to 1200" (also in **Sections 8** and **9.3**).
- Regions where the sub-study will be initially open updated to North America, Europe and Asia.

- **Section 6.8.1 Data Monitoring Committee**: "Independent Data Monitoring Committee (IDMC) comprised of independent experts" was changed to "Data Monitoring Committee (DMC) comprised of internal experts independent from the study team".

Minor editing

Spelling and format errors were corrected.

Version 4.0, 08 February 2018

Changes to the protocol are summarized below.

SYNOPSIS

- Duration of the enrolment period was clarified as "2 to 3 years".
- Title of Module A was updated to indicate that durvalumab monotherapy is at a fixed dose.
- A new appendix, Appendix I, was introduced to describe ancillary studies

and the ancillary study in France was listed.

- Primary study objective was updated to remove 'to collect additional data'.
- Primary study objective on adverse events of special interest was updated to include other inflammatory responses.
- Secondary study objective of overall survival (OS) text was updated.
- Procedures for follow up of patients were clarified.
- Frequency of Data Monitoring Committee meetings was updated to "every 6 months".

Section 1.1 Background and rationale for conducting this study

- Sections were updated to be consistent with the current Investigator Brochure (IB), Edition 12 dated 03 November 2017.

Section 1.2 Rationale for study design, doses and control groups

- Study 1108 study number was corrected.
- Text on dose and treatment regimen justification was added.

Section 1.3 Benefit/risk and ethical assessment

- Section 1.3.1 Potential benefits: Text was added.
- Section 1.3.2 Overall risks: Information on risks of treatment with durvalumab and tremelimumab monotherapies and combined therapy was updated per the current IB, Edition 12 dated 03 November 2017.

Section 1.4 Study design

- Requirement of a confirmatory scan for patients with progressive disease was added.
- Procedures for follow up of patients were clarified to inform that there will be additional tumor assessment, if clinically possible, and a follow–up for AEs for 90 days and for survival thereafter.

Section 2 STUDY OBJECTIVES

- Primary study objective was updated to remove 'to collect additional

data'

- Primary study objective on adverse events of special interest was updated to include other inflammatory responses
- Secondary study objective of overall survival (OS) text was updated.

Section 3.1 Inclusion Criteria

- Inclusion criteria were updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 3.2 Exclusion criteria

- Exclusion criteria were updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 3.8 Restrictions

- Text was updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 3.9 Discontinuation of investigational product

- Procedure for a confirmatory scan for patients who discontinue due to progressive disease was clarified.
- Text was updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 3.10 Criteria for withdrawal

- The text "patients will not be withdrawal of consent to the use of their study generated data" was removed.

Section 3.11 Discontinuation of the study

- The sentence "The study may also be terminated early at the Sponsor's discretion for reasons other than patient safety" was added.

Section 4 STUDY PLAN AND TIMING OF PROCEDURES

- **Table 2** (footnote b), **Section 4.1**, and **Section 4.2.1**: Correction was made to inform that height is collected at screening only.
- **Table 2** (footnote i), **Section 5.3.1**: Procedure for urinalysis of bilirubin

and urobilinogen was clarified.

- **Table 2** (footnote j), **Section 4.1**, and **Section 5.7**: Procedure for collection of tumor biopsies was clarified.

- **Section 4.2.1**: Clarification was added that if the blood and urine samples were taken at screening within 72 hours prior to first dose, they do not need to be repeated on Day 1 (with the exception of urine pregnancy test).

Section 5.2.4 Prior and concomitant medication and cancer treatment history

- Text was added to clarify procedure for collecting data on prior medication.

Section 5.3 Safety assessments

- **Table 3** was presented in an alternative format to align with Sponsor template.

Section 5.7 Biomarker analysis

- Text was updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 6.3 Recording of adverse events

- Text was updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 6.4 Reporting of serious adverse events

- Reference to the Safety Handling Plan was added.

Section 6.5 Adverse events of special interest

- Additional inflammatory responses were included.

Section 6.7 Pregnancy

- Text was updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 6.8 Medication Error

- This section was added to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 6.9 Study governance and oversight

- **Section 6.9.1**: Specific toxicity management and dose modification information: Text was updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 7.1 Identity of investigational product(s)

- Text was updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 7.2 Dose and treatment regimens

- Text was updated to align with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.

Section 7.7 Concomitant medications and other treatments

- **Table 4**: Prohibited concomitant medications: Rows "For all treatment arms" were deleted as this is a single arm study.

Section 10.2 Patient data protection

- Text was added to clarify disclosure of genotype results.

Section 11 LIST OF REFERENCES

- List was updated.

Appendix E: Dose Modification and Toxicity Management Guidelines for Immune–mediated, Infusion-related, and Non Immune-mediated Reactions

Toxicology management guidelines were replaced with guidelines dated 01 November 2017.

Appendix G: Categories of Adverse Events of Special Interest - List of Preferred Terms

This appendix was deleted. Consequently, numbering of the subsequent appendices was updated.

Appendix G: Signature Page

The signature page that was previously given as Appendix H is now Appendix G. The name and contact details of the signatory were updated.

Appendix H: Tumor Specific Modules – Module A

Title of Module A was updated to indicate that durvalumab monotherapy is at a fixed dose

Appendix I: Country-Specific Ancillary Studies

This appendix was added and the ancillary study in France was listed: Predictive Markers of Immune-Mediated Adverse Events and of Treatment Response in Patients Treated with Durvalumab Monotherapy or in Combination with Tremelimumab.

All sections

- The document was updated to be consistent with the current Durvalumab plus Tremelimumab Protocol template Edition 2.1, dated 15 November 2017.
- Minor language and format corrections were made throughout the document.

Version 5.0, 13 December 2019

Changes to the protocol are summarized below.

Synopsis

- The synopsis was aligned to revisions made in Section 1.4 (Study design), Section 2.1 (Primary objective), Section 4.3 (Follow up period), Section 9.3 (Study timetable and end of study) and Section 9.3 (Study timetable and end of study).
- Study dates and duration were updated.

Previous text (revised/deleted text in bold):

It is anticipated that the total enrollment period for the overall study will be approximately 2 to 3 years, with an overall duration of **approximately 5 years**.

Study design

Study Duration		Phase of Development
Estimated date of first patient enrolled (United States)	Q1 2017	Phase IIIb
Estimated date of last patient follow up (Global)	**Q1 2022**	

Revised text (revised/added text in bold):

It is anticipated that the total enrollment period for the overall study will be approximately

2 to 3 years, with an overall duration of 4 to 5 years.

Study design

Study Duration		Phase of Development
Estimated date of first patient enrolled (United States)	Q1 2017	Phase IIIb
Estimated date of final data cut-off (Global)	**Q2 2020**	
Estimated date of last patient follow up (Global)	**Q2 2021**	

Section 1.3.2 Overall risks

The overall risk section was updated to reflect the safety information available in the latest version of the IBs of durvalumab and tremelimumab (data cut-off [DCO] 12 July 2019).

Section 1.3.2.1 Durvalumab

Previous text (revised/deleted text in bold):

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

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 (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.**

Revised text (revised/added text in bold):

Risks with durvalumab include, but are not limited to diarrhea/colitis, pneumonitis/ILD, endocrinopathies **(ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus and diabetes insipidus),** hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, **infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, 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, cough, decreased appetite, dyspnea and nausea. Approximately 10% of patients 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, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program.**

Section 1.3.2.2 Tremelimumab

Previous text (revised/deleted text in bold):

Risks with tremelimumab monotherapy include, but are not limited to GI effects (colitis, diarrhea, enterocolitis and 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 GI events eg, ulcerative colitis, dehydration, nausea and vomiting**; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; **nervous system events** including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré **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, dyspnea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

Revised text (revised/added text in bold):

Risks with tremelimumab monotherapy include, but are not limited to GI effects (colitis, diarrhea, enterocolitis and 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, hepatic events (including **immune-mediated** hepatitis and liver enzyme elevations); pneumonitis and ILD;

neurotoxicity (including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré **syndrome**); thrombocytopenia, anemia and neutropenia; infusion-related reactions **and hypersensitivity/anaphylactic reactions**; renal events (including **nephritis/autoimmune nephritis and acute kidney injury,** autoimmune arthritis, Sjogren's syndrome, giant cell temporal arteritis **and ulcerative colitis**); hyperglycemia and diabetes mellitus.

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

In monotherapy clinical studies, AEs reported at an incidence of ≥20% include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting and dyspnea. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE. **Please see the current version of the IB for a detailed summary of monotherapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the tremelimumab program.**

Section 1.3.2.3 Durvalumab + Tremelimumab

Previous text (revised/deleted text in bold):

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 fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, decreased weight, peripheral edema, hyponatremia, and rash.**

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**.

Revised text (revised/added text in bold):

In durvalumab + tremelimumab combination studies at the dose of durvalumab 20 mg/kg and tremelimumab 1 mg/kg, **AEs reported at an incidence of ≥20% included events such as fatigue, diarrhea, nausea, decreased appetite, pruritus, dyspnea, constipation and anemia. Please see the current version of the durvalumab IB for a detailed summary of combination therapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program, including durvalumab in combination with tremelimumab.**

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately **16%** of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study **Investigator**.

Section 1.4 Study Design

Specific instructions for imAE follow-up were deleted and estimated study duration was updated.

Previous text (revised/deleted text in bold):

The protocol (and each tumor specific module in **APPENDIX H**) consists of a screening period, a treatment period, a safety follow up period (90 days post treatment discontinuation **for non-imAEs; 12 months post onset for imAEs)***, and a survival follow up period.

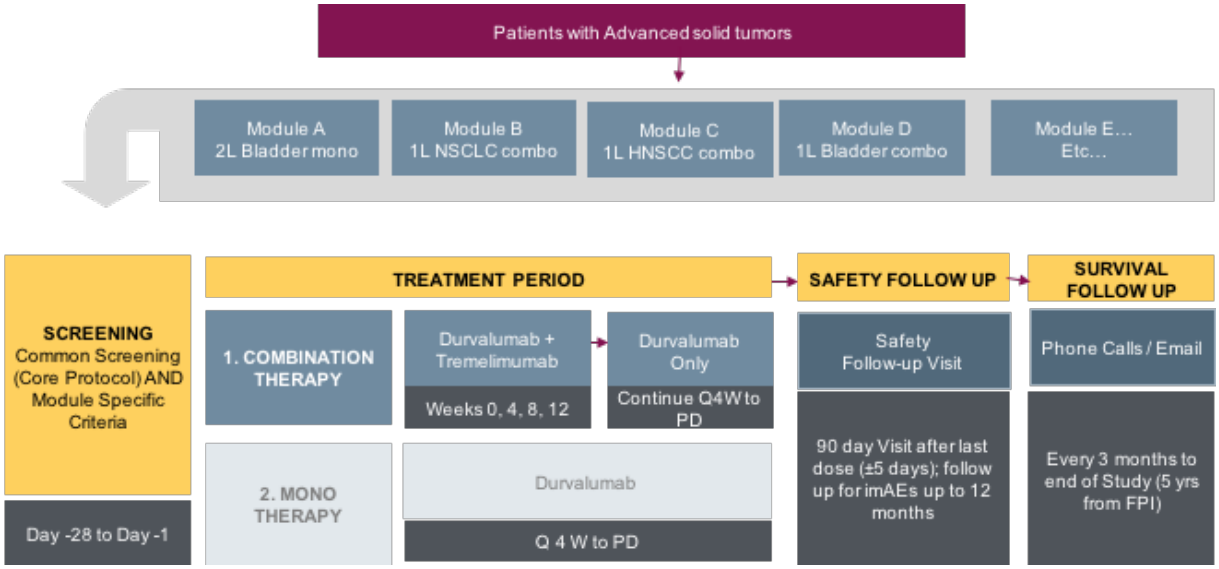
***Any imAEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated and up to 12 months post onset. Non-imAEs are followed up 90 day visit post treatment discontinuation.**

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**. Patients will be followed for up to 5 years from date of first patient treatment initiation. Patients will be followed for survival for a minimum of 6 months following enrollment of last patient.**

[…]

Figure 1 Study flow chart



Tumor specific modules (**APPENDIX H**) 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.
Any imAEs that are unresolved at the patient's last visit in the study are followed up by the Investigator

for as long as medically indicated and up to 12 months post onset. Non-imAEs are followed up 90 days post treatment discontinuation.
Study is expected to run for approximately 5 years from first patient treatment initiation. Follow up will continue for study duration and for minimum follow up to 6 months after last patient enrolled.

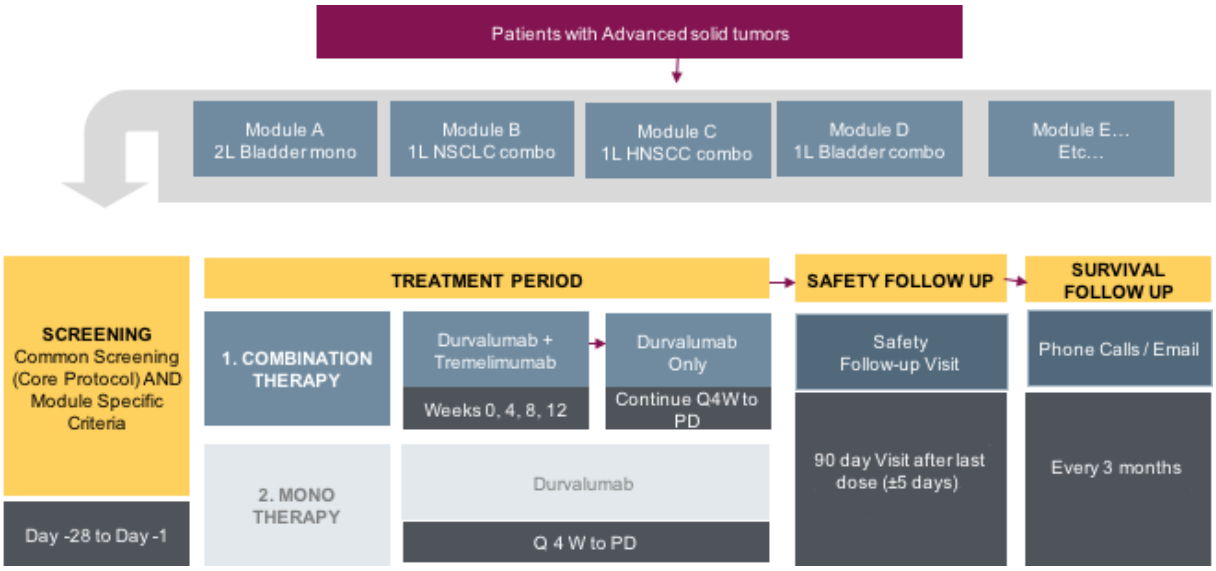
Revised text (revised/added text in bold):

The protocol (and each tumor specific module in **APPENDIX F)** 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 data cut-off (DCO).**

[…]

Figure 1 Study flow chart



Tumor specific modules (**APPENDIX F**) 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.

Section 2.1 Primary objective

The description of adverse events of special interest (AESIs) was revised in alignment with Section 6.5 (Adverse events of special interest) to reflect the safety information available in the latest version of the IBs of durvalumab and tremelimumab.

Previous text (revised/deleted text in bold):

AESIs observed with durvalumab or tremelimumab **to date** include**: diarrhea / colitis and intestinal perforation, pneumonitis / ILD, hepatitis / transaminase increases,), endocrinopathies (ie, events of hypophysitis/ hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus), rash / dermatitis, nephritis / blood creatinine increases, pancreatitis / serum lipase and amylase increases, myocarditis, polymyositis, and neuropathy / neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis).** Other inflammatory responses that are rare / less frequent with a potential immune-mediated etiology include, but are not limited to pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events. In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Revised text (revised/added text in bold):

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.

Section 3.2 Exclusion criteria (applicable to all modules)

An error in the exclusion criteria related to prior treatment with investigational products or investigational anticancer therapy was corrected.

Previous text (revised/deleted text in bold):

Exclusion criterion 4:

Participation in another clinical study with an investigational product during the last 28 days or 5 half-lives, whichever is **shorter**, prior to the first dose of study treatment.

Exclusion criterion 7:

Receipt of any investigational anticancer therapy within 28 days or 5 half-lives, whichever is **shorter**, prior to the first dose of study treatment.

Revised text (revised/added text in bold):

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 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.

Section 3.9 Discontinuation of investigational product

Duration of survival follow-up was updated.

Previous text (revised/deleted text in bold):

Unless they withdraw consent for further follow up, patients who discontinue study therapy will continue on study for acquisition of safety information through 90 days after the last dose of study treatment, and for further collection of information regarding survival **up to 5 years following date of first patient treatment initiation. All patients will be followed for a minimum of 6 months following enrollment of the last patient to the study.**

Revised text (revised/added text in bold):

Unless they withdraw consent for further follow up, patients who discontinue study therapy will continue on study for acquisition of safety information through 90 days after the last dose of study treatment, and for further collection of information regarding survival **until the final DCO.**

Section 3.9.1 Procedures for discontinuation of a patient from investigational product

Duration of survival follow-up was updated.

Previous text (revised/deleted text in bold):

All patients will be followed for survival **up to 5 years following date of first patient treatment initiation. All patients will be followed for a minimum of 6 months following enrollment of the last patient to the study.**

Revised text (revised/added text in bold):

All patients will be followed for survival **until the final DCO.**

Section 3.10.2 Withdrawal of the informed consent

Duration of survival follow-up was updated.

Previous text (revised/deleted text in bold):

Patients who withdraw consent for further participation in the study will not receive any further durvalumab + tremelimumab or further study observation, with the exception of follow up for survival, which will continue until the **end of 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.

[…]

Providing consent allows, survival status will be followed up by phone or electronic communication every 3 months **up to 5 years following date of first patient treatment initiation. All patients should be followed for a minimum of 6 months following enrollment of the last patient to the study** (see Section 4.3).

Revised text (revised/added text in bold):

Patients who withdraw consent for further participation in the study will not receive any further durvalumab + tremelimumab or further study observation, with the exception of follow up for survival, which will continue until the **final DCO** 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.

[…]

Providing consent allows, survival status will be followed up by phone or electronic communication every 3 months **until the final DCO** (see Section 4.3).

Section 3.11 Discontinuation of the study

Time when the study will be closed to accrual was deleted. Further details were provided regarding the reasons (other than patient safety) why the Sponsor may terminate the study.

Deleted text:

It is expected that the overall study will close to accrual in third quarter 2021.

[…]

The study may also be terminated early at the Sponsor's discretion for reasons other than patient safety.

Added text:

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies

have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow up.

4.3 Follow up period

Specific instructions for imAE follow-up were deleted, duration of survival follow up was updated, and clarification was added regarding patients who do not discontinue treatment before the final DCO is reached.

Previous text (revised/deleted text in bold):

After this safety follow up visit, patients will be contacted by phone or email every 3 months **up to 5 years from date of first patient treatment initiation to check survival status** until death, whichever occurs first.

Any imAEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated and up to 12 months post onset. Non-imAEs are followed up until the 90-day post-treatment discontinuation visit.

Revised text (revised/added text in bold):

After this safety follow up visit, patients will be contacted by phone or email every 3 months to check survival status until death **or final DCO**, whichever occurs first.

Patients who do not discontinue treatment before the final data cut-off (DCO) is reached will continue to be followed as indicated in Section 6.3.12.

Section 5.1 Survival assessments

Duration of survival follow-up was updated

Previous text (revised/deleted text in bold):

The survival status of the patient will be collected during the study. After their safety follow up visit (90 days), patients will continue to be followed for survival via phone calls or email every 3 months **up to 5 years following date of first patient treatment initiation. All patients will be followed for a minimum of 6 months following enrollment of the last patient to the study**.

Revised text (revised/added text in bold):

The survival status of the patient will be collected during the study. After their safety follow up visit (90 days), patients will continue to be followed for survival via phone calls or email every 3 months **until the final DCO, with a final check that should generally occur within 7 days of the final DCO.**

Section 5.3.1 Laboratory safety assessments

The requirement to collect local reference ranges in the CRF was removed.

Previous text (revised/deleted text in bold):

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 CRF.

Revised text (revised/added text in bold):

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

Table 3 Laboratory safety variables

The row for additional laboratory tests was updated.

Previous text (revised/deleted text in bold):

Additional laboratory tests (where clinically indicated only) [a]	Free tri-iodothyronine (T3) and free thyroxine (T4)[c], **creatinine [d]**, alkaline phosphatase (ALP), autoimmune antibody test [e]

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

(e) If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the Investigator should collect a blood sample for appropriate autoimmune antibody testing by a local laboratory.

Revised text (revised/added text in bold):

Additional laboratory tests (where clinically indicated only)	Free tri-iodothyronine (T3) and free thyroxine (T4)[c], **creatinine clearance,** alkaline phosphatase (ALP), autoimmune antibody test [d]

(d) If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the Investigator should collect a blood sample for appropriate autoimmune antibody testing by a local laboratory.

Section 6.2 Definitions of serious adverse event

New malignant tumors were added as a category of SAEs.

Added text:

- AEs for new malignant tumors (ie, not the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study) reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used.
  In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a non-serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.
  Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

Section 6.3.12 Safety data to be collected following the final DCO of the study

This section was added to clarify how safety data will be collected for patients who continue receiving treatment of the final DCO is reached.

Added text:

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 6.9.1). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 6.4.

6.4 Reporting of serious adverse events

Clarification was added regarding the reporting of SAEs occurring after the final DCO is reached.

Previous text (revised/deleted text in bold):

All SAEs have to be reported, whether or not considered causally related to durvalumab ± tremelimumab, or to the study procedure(s). All SAEs will be recorded in the CRF.

Revised text (revised/added text in bold):

All SAEs have to be reported, whether or not considered causally related to durvalumab ± tremelimumab, or to the study procedure(s). All SAEs will be recorded in the CRF**, except SAEs occurring after the DCO and database closure. After the DCO, SAEs will be reported via paper SAE forms and recorded in AstraZeneca database.**

Section 6.5 Adverse events of special interest

The description of AESIs was revised to reflect the safety information available in the latest version of the IBs of durvalumab and tremelimumab.

Previous text (revised/deleted text in bold):

AESIs observed with durvalumab ± tremelimumab include**:**

- **Diarrhea / colitis and intestinal perforation**
- **Pneumonitis / ILD**
- **Hepatitis / transaminase increases**
- **Endocrinopathies (ie, events of hypophysitis, hypopituitarism adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)**
- **Rash / dermatitis**

- **Nephritis / blood creatinine increases**
- **Pancreatitis / serum lipase and amylase increases**
- **Myocarditis**
- **Myositis / polymyositis**
- **Neuropathy / neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis)**

Other inflammatory responses that are rare / less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, **sarcoidosisuveitis**, and other events involving the eye, skin, hematological **and** rheumatological events.

Revised text (revised/added text in bold):

AESIs**/imAEs** observed with durvalumab ± tremelimumab include **pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as 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**,** 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.**

Section 6.9.1 Specific toxicity management and dose modification information-Durvalumab and durvalumab + tremelimumab

The Dosing Modification and Toxicity Management Guidelines (TMGs) were explained in further details, as the TMGs were removed from the protocol appendices and are provided as a separate document.

Deleted text:

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy and durvalumab + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines (TMGs). The most current version of the TMGs is also available through the following link: https://tmg.azirae.com/. In addition, a version of current TMGs is maintained within the Site Master File. Please contact your clinical trial associate for information on how to gain access to this website.

Added text:

Comprehensive toxicity management guidelines (TMG) have been developed to assist Investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitors durvalumab [Medi4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these 2 compounds, these guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (ie, antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment. The most current version of the TMGs entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy" is provided to the investigative site as an Annex document and is maintained within the Site Master File. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com/. Please contact your clinical trial associate for information on how to gain access to this website.

Section 7.1.1 Durvalumab

Previous text (revised/deleted text in bold):

Drug product should be kept in **secondary** packaging until use to prevent **excessive** light exposure.

[…]

A dose of 1500 mg (only patients >30 kg in weight are eligible) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to **20** 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 (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 **20** mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If weight falls to ≤30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to **20** mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm **in-line** filter. See the study specific drug handling plan for an example of a

weight–based dose calculation.

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**.

Revised text (revised/added text in bold):

Drug product should be kept in **original** packaging until use to prevent **prolonged** light exposure.

[…]

A dose of 1500 mg (only patients >30 kg in weight are eligible) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to **15** mg/mL, and delivered through an IV administration set with a 0.2- or 0.22 µm filter. Add 30.0 mL of durvalumab (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.

If **patient** weight falls to ≤30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to **15** mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. See the study specific drug handling plan for an example of a weight–based dose calculation.

Standard infusion time is 1 hour**; however, if** 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.

Section 7.1.2 Tremelimumab

Previous text (revised/deleted text in bold):

Drug product should be kept in **secondary** container until use to prevent **excessive** light exposure.

[…]

A dose of 75 mg (for patients >30 kg in weight; patients ≤30 kg are not eligible for entry to the study) 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 1 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 (ie, 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 1 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If weight falls to ≤30 kg weight-based dosing at 1 mg/kg 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 1 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-μm **in-line** filter. See the study specific drug handling plan for an example of a weight–based dose calculation.

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**.

Revised text (revised/added text in bold):

Drug product should be kept in **original** container until use to prevent **prolonged** light exposure.

[…]

A dose of 75 mg (for patients >30 kg in weight; patients ≤30 kg are not eligible for entry to the study) 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 filter. Add 3.8 mL (ie, 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.

If **patient** weight falls to ≤30 kg, weight-based dosing at 1 mg/kg will be a 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 filter. See the study specific drug handling plan for an example of a weight-based dose calculation.

Standard infusion time is 1 hour; **however, if** 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.

Section 7.2 Dose and treatment regimens – Durvalumab monotherapy

Deleted text:

Standard infusion time is 1 hour. Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

Section 7.2.1 Duration of treatment and criteria for treatment through progression and for retreatment

Previous text (revised/deleted text in bold):

All treatment will be administered beginning on Day 1 for durvalumab monotherapy or durvalumab + tremelimumab combination therapy until progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

[…]

Patients receiving durvalumab + tremelimumab combination therapy may undergo retreatment as described below:

- Patients who complete the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgement), but subsequently have evidence of PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

[…]

Patients who AstraZeneca 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.

Revised text (revised/added text in bold):

All treatment will be administered beginning on Day 1 for durvalumab monotherapy or durvalumab + tremelimumab combination therapy until **RECIST 1.1-defined radiological** progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

During the treatment period, patients may continue receiving therapy in the setting of unconfirmed radiologic progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), at the Investigator's discretion, until progression is confirmed[*]. A confirmatory scan is required following a RECIST 1.1 overall time point assessment of progression (PD), preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

footnote: [*]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 RECIST 1.1 modified for confirmation of progression, a confirmatory scan is required following an overall time point assessment of progression

(PD), no earlier than 4 weeks after the previous assessment of PD.

[…]

Patients receiving durvalumab + tremelimumab combination therapy may undergo retreatment as described below:

- Patients who complete the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgement), but subsequently have evidence of **RECIST 1.1 (or other tumor assessment method)-defined** PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

[…]

Patients who AstraZeneca and the Investigator determine may not continue treatment after **RECIST 1.1-defined** PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed **RECIST 1.1-defined PD** and for survival.

Post final data cut off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician considers they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 6.9.1).

In the event that a roll-over or safety extension study is available at the time of, or subsequent to, the final DCO and database closure, patients receiving treatment with durvalumab may be transitioned to such a study, and the study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

Section 7.8 Post study access to study treatment

Reference to modules for additional information regarding the possible transition to a long-term extension or an early access program was deleted, as further information was

included in Section 7.2.1 and Section 9.3.

Deleted text:

If applicable, timelines for transition will be agreed with local bodies, which may include regulatory agencies, ECs, and participating institutions. Details will be provided for each tumor-specific cohort and country in individual modules, as applicable.

Section 9.3 Study timetable and end of study

The definition and estimated date of study end was updated.

Previous text (revised/deleted text in bold):

The end of the study is defined as the last visit of the last patient undergoing the study.

The overall study is expected to start in Q1 2017 and end by **Q1 2022**.

See individual modules for end of study information.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with durvalumab or tremelimumab.

Revised text (revised/added text in bold):

The end of the study is defined as the last visit of the last patient undergoing the study.

The overall study is expected to start in Q1 2017 and end by **Q2 2021**.

See individual modules for **the definition of final DCO**.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with durvalumab or tremelimumab.

In the event that a roll-over or safety extension study is available at the time of or subsequent to the final DCO and database closure, patients receiving treatment with durvalumab may be transitioned to such a study, and the study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

10.2 Patient data protection

Further information regarding patient data protection was included.

Added text:

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Appendix D: Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Appendix D was updated to include current AstraZeneca processes for the reporting of potential Hy's law (PHL) and Hy's law cases (HL).

1. Introduction

Added text:

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

4. Follow up

4.1. Potential Hy's Law criteria not met

Added text:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2. Potential Hy's Law criteria met

Previous text (revised/deleted text in bold):

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See section **below on** Actions required when potential Hy's Law criteria are met before and after starting study treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow up and the continuous review of data. Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
  - Complete the **three** Liver CRF Modules as information becomes available
  - **If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures**

Revised text (revised/added text in bold):

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See section **6.** Actions required when potential Hy's Law criteria are met before and after starting study treatment)
- Notify the AstraZeneca representative who will then inform the central Study Team
- **Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important**

medical event' and causality assessment 'yes/related' according to protocol process for SAE reporting.

- **For patients that met PHL criteria prior to starting IMP, the Investigator is not required to submit a PHL SAE unless there is a significant change [#] in the patient's condition**
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow up **(including any further laboratory testing)** and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
  - **Complete follow up SAE Form as required.**
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
  - Complete the 3 Liver CRF Modules as information becomes available.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

5. Review and assessment of potential Hy's Law cases

Previous text (revised/deleted text in bold):

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the

instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, **record the AE /SAE in the CRF accordingly and follow** the AZ standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- **Report an** SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over **3 weeks**, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- **Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.**
- Continue follow up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. **Update the SAE report according to the outcome of the review.**

Revised text (revised/added text in bold):

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, **to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met.** The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter

experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, **update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following** the AZ standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- **Send updated** SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over **15 calendar days** in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- **Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to protocol process for SAE reporting.**
- Continue follow up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. **Update the previously submitted PHL SAE report following protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver**

biochemistry elevations is determined.

References

Previous text (revised/deleted text in bold):

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'**:**

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Revised text (revised/added text in bold):

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation' **Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation**

Appendix E: Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune-Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy

The appendix was deleted from the protocol. The guidelines will be provided separately from the protocol as a standalone document.

Appendix E (previously Appendix F): Eastern Cooperative Oncology Group Performance Scale

The appendix was renumbered due to the deletion of Appendix E. No changes were made to the content of the appendix.

Appendix G: Signature Page

The appendix was deleted, as it is no longer needed. The protocol is signed electronically, and the electronic signature page is added at the end of the protocol.

Appendix F (previously Appendix H): Tumor Specific Modules – Module A

The appendix was renumbered due to the deletion of Appendix E and Appendix G.

Module A was updated to version 4.0, including revisions in the synopsis, Section 2.1 (primary objectives), Section 3.2 (Exclusion Criteria) and Section 9.3 (Study timetable and end of study).

Refer to the version history of Module A for further information.

Appendix G (previously Appendix I): Country-Specific Ancillary Studies The appendix was renumbered due to the deletion of Appendix E and Appendix G. The IOPREDI ancillary study was updated to version 2.0, including revisions of the synopsis, Section 1.2 (Rationale for study design), Section 2.1 (Primary objectives), Section 2.2 (Secondary objectives), Section 3.1 (Inclusion criteria), Section 4 (Study plan and timing of procedures), Section 4.1 (Screening/Enrolment Period), Section 4.2 (Treatment Period), Section 5 (Study assessments), Section 5.1 (Genetics), Section 5.2 (Biomarker analysis), Section 6 (Safety reporting and medical management), Section 8.3 (Definitions of analysis sets), Section 10.4 (Informed consent) and Section 11 (List of references). Refer to the version history of IOPREDI ancillary study for further information.
Minor editorial changes were made to correct typos, style, or formatting, and to update cross-references to protocol sections and appendices (and in particular to the Dosing Modification and Toxicity Management Guidelines, which are no longer appended to the protocol).

This Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

CLINICAL STUDY PROTOCOL SYNOPSIS

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

Study site(s) and number of patients planned

Patients will be enrolled in different tumor specific cohorts (Modules; APPENDIX F) and country-specific ancillary studies (APPENDIX G). Additional tumor specific or exploratory modules may be added in the study.

The following module and country-specific ancillary study were opened:

- Module A: Post-Chemotherapy Urothelial and NonUrothelial Carcinoma of the Urinary Tract With Fixed-dose Durvalumab Monotherapy.
- IOPREDI, French STRONG ancillary study: Predictive Markers of Immune-Mediated Adverse Events and of Treatment Response in Patients Treated with Durvalumab Monotherapy or in Combination with Tremelimumab.

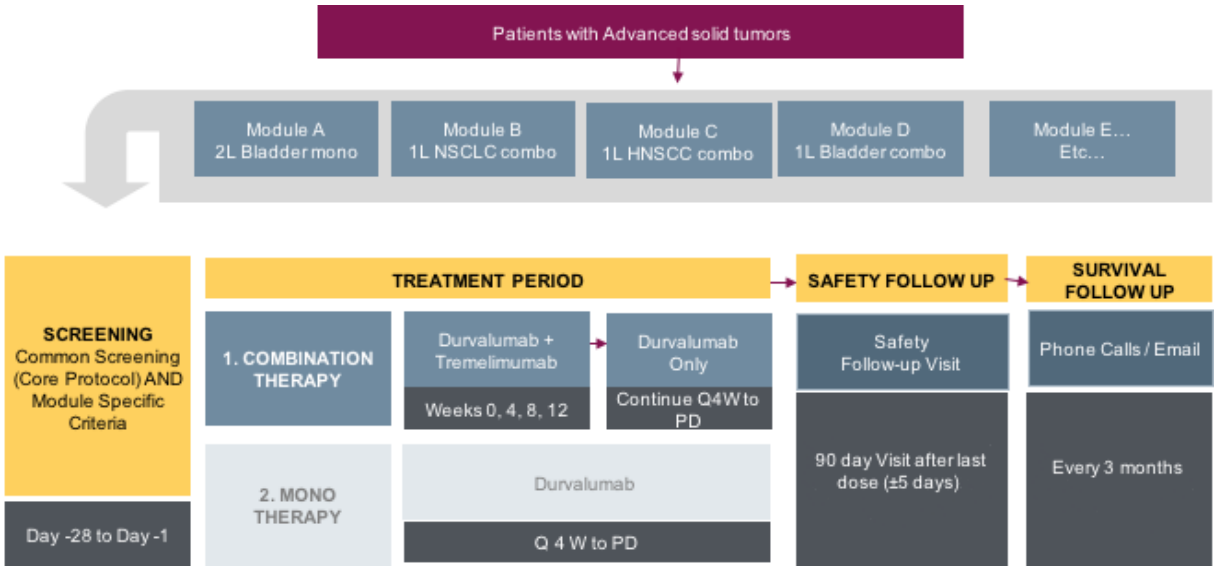
The total number of patients to be enrolled overall and in each module will depend on the types and number of tumor modules added to the main study and country-specific ancillary studies. The number of patients and sites to be involved in individual countries will be dependent on each module or ancillary study.

It is anticipated that the total enrollment period for the overall study will be approximately 2 to 3 years, with an overall duration of 4 to 5 years.

Study design

Study Duration		Phase of Development
Estimated date of first patient enrolled (United States)	Q1 2017	Phase IIIb
Estimated date of final data cut-off (Global)	Q2 2020	
Estimated date of last patient follow up (Global)	Q2 2021	

Study Flow chart



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 data cut-off (DCO).

Study design

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

This study is modular in design, each tumor specific Module allowing evaluation of the safety, tolerability, and antitumor activity of the combination of durvalumab + tremelimumab or durvalumab alone in different solid tumors.

The modules are developed as separate components appended to this protocol. Additional modules may be added as part of this protocol as decisions on additional tumor types and/or exploratory sub-studies are made.

One or more of these modules will be opened in a given country / region based on local patient population prevalence, and results of feasibility studies.

The protocol (and each tumor specific module) consists of a screening period, a treatment period, a 90–day safety follow up period, 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 data cut-off (DCO).

Investigational product, dosage and mode of administration

Durvalumab + tremelimumab combination therapy

- Durvalumab 1,500 mg plus tremelimumab 75 mg 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.

Study Objectives

Primary Objective

The common primary objective of all tumor sub-studies is:

1. To assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality, including immune-relatedness, of adverse events (AEs) of special interest (AESIs) in patients with advanced solid malignancies 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 etiology.

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.

The specific safety objective will be further defined in each tumor specific module.

Secondary Objectives

The common secondary objectives of all tumor sub-studies are:

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

2. To assess the incidence and frequency of durvalumab and tremelimumab (as applicable to each tumor Module) interruption and discontinuation due to treatment–emergent AEs (including SAEs).

3. To assess overall survival (OS).

Additional secondary objectives and exploratory objectives may be added to tumor sub-studies in each country / region. Additional sub-studies / exploratory studies may be added to the protocol, in modular fashion.

Exploratory Objective

1. To assess overall response rate (ORR) and disease control rate (DCR) based on Investigator assessed response to treatment (RECIST 1.1).

Target patient population

The target patient population of the protocol includes patients with advanced solid tumors who meet the overall and tumor specific inclusion and exclusion criteria as outlined in each Module.

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

During the treatment period, patients may continue receiving therapy in the setting of unconfirmed radiologic progressive disease (PD) according to Response Evaluation Criteria in

Solid Tumors version 1.1 (RECIST 1.1), at the Investigator's discretion, until progression is confirmed*. A confirmatory scan is required following a RECIST 1.1 overall time point assessment of progression (PD), preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

Patients with PD by RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continue to receive benefit from their treatment and who meet the criteria for treatment in the setting of PD may continue to receive their 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 (complete response [CR] or partial response [PR] as defined by RECIST 1.1) to immunotherapy treatment in target lesions (regardless of the appearance of new lesions) ie, 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 retreatment.

See Section 7.8 for post-study access to treatment information.

Follow up of patients post discontinuation of study drug

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, withdrawal from treatment, or patients who have started a subsequent anticancer therapy, will be followed up for AEs for 90 days, and thereafter followed up to record disease progression and survival (described in the next section). These patients are not eligible for re-treatment at any time.

Survival

All patients in the study should be followed up for survival until the final DCO.

Data Monitoring Committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with AstraZeneca Patient Safety. Issues identified in this study or in other studies but deemed relevant for this study will be addressed promptly,

*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 RECIST 1.1 modified for confirmation of progression, a confirmatory scan is required following an overall time point assessment of progression (PD), no earlier than 4 weeks after the previous assessment of PD.

which could involve amendments to the study protocol and letters to Investigators, as appropriate.

In addition to the ongoing AstraZeneca overall safety monitoring, a Data Monitoring Committee (DMC) comprised of internal experts independent from the study team will be convened and will meet approximately every 6 months after the study has started 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.

Steering Committee

A Steering Committee (SC) will be assembled by AstraZeneca for the executive oversight and supervision of the study. The committee of oncology experts will serve this role through regular scheduled meetings or teleconferences and, if necessary, additional ad hoc meetings. Details of the SC remit, procedures, processes, and meeting frequency, will be outlined in an SC Charter.

Statistical methods

The primary analysis set is the safety analysis set which will include all enrolled patients who received at least 1 dose of durvalumab or tremelimumab.

The safety analysis set will be used for all analyses.

The primary outcome measure for the study is the number and proportion of patients with AESI. Pre-defined MedDRA preferred terms groupings will be used to identify AESI. For each AESI 'grouped' term, the number (%) of patients experiencing any of the specified terms will be presented overall, by seriousness, by causality and by maximum NCI CTCAE grade. The exact 95% CIs around the incidence estimates will also be reported for each AESI type.

While the precise sample size and number of AESIs that will be included in the study overall and in each module is not known a priori, sample sizes are included that would allow the collection of additional data on the incidence, severity, nature, seriousness, intervention/treatment, and causality, including immune-relatedness, of AESIs. See each Module for details.

A detailed description of statistical methods is found in the tumor specific modules.

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LIST OF 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
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the concentration-time curve
BUN	Blood urea nitrogen
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form (electronic/paper)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event

Abbreviation or special term	Explanation
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4 (also known as CD152)
DCO	Data cut-off
DCR	Disease control rate
DMC	Data Monitoring Committee
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR TKI	Epidermal growth factor receptor tyrosine kinase inhibitors
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hy's Law
HNSCC	Head and neck squamous cell carcinoma
HPF	high power field
IB	Investigator's brochure

Abbreviation or special term	Explanation
IC	Immune cells
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
imAE	immune-mediated adverse event
IL	Interleukin
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
INR	International normalized ratio
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the Investigators and/or activities internationally
IP	Investigational product
IRB	Institutional Review Board
IV	Intravenous
IVRS/IWRS	Interactive Voice/Web Response System
LDH	Lactate dehydrogenase
LFT	Liver function test
mAb	Monoclonal antibody
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MEDI4736	Durvalumab
MOA	Mechanism of action
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PCP	Pneumocystis pneumonia
PD	Progressive disease
PD1	Programmed cell death-1
PD-L1	Programmed death ligand 1
PHL	Potential Hy's Law
PK	Pharmacokinetics
PO	Oral, per os
PR	Partial response
Q12W	Every 12 weeks
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red Blood Cell

Abbreviation or special term	Explanation
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SC	Steering Committee
T3	Tri-iodothyronine
T4	Thyroxine
TB / TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TMG	Toxicity Management Guidelines
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WT	Weight

1. INTRODUCTION

1.1 Background and rationale for conducting this study

See tumor specific modules (APPENDIX F) for tumor specific background and rationales.

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 et al 2004).

Programmed death ligand 1 (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 (ICs). 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 (MOA) 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, eg, 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 CTLA-4 and 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 US FDA 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, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there is data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

1.1.2 Durvalumab

Durvalumab is a human 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 ICs. Durvalumab 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 MOA for durvalumab is interference in the interaction of PD-L1 with PD 1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T-cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety

profile of durvalumab monotherapy are summarized in Section 1.3.2.1. Refer to the current durvalumab Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.3 Tremelimumab

Tremelimumab is a IgG2 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 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 Section 1.3.2.2.

Refer to the current tremelimumab IB 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, pharmacokinetics (PK)/pharmacodynamics, and preliminary antitumor activity of durvalumab + tremelimumab combination therapy in patients with advanced non-small cell lung cancer (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 3000 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 Section 1.3.2.3. 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 Rationale for study design, doses and control groups

This study is designed to further evaluate the safety and overall survival (OS) of durvalumab + tremelimumab combination therapy or durvalumab monotherapy using fixed dosing in advanced solid tumor patients.

This study is designed to complement and expand the safety databases from the ongoing Phase III pivotal combination trials – D419AC00001 (MYSTIC), D419AC00003 (NEPTUNE), D419LC00001 (KESTREL), D4193C00002 (EAGLE) and D419BC00001 (DANUBE), and potentially the durvalumab monotherapy studies – D4191C00001 (PACIFIC) and Study D4190C00001 (Study 1108). As most of these studies were initiated using weight-based dosing (mg/kg), expanding data on the safety profile of the fixed-dose combination is warranted, particularly with rare events.

The study will assess short and long-term safety including evaluation of nature of toxicities (adverse events [AEs], serious adverse events [SAEs], immune-mediated adverse events [imAEs]), interventions / treatment, and outcomes of treatment of these.

The study will also yield in depth understanding of rare events, or new imAEs that may occur through long-term administration of study drug.

1.2.1 Dose and treatment regimen justification

In the original studies with durvalumab, the schedule of 10 mg/kg Q2W has been tested. This was then amended to 20 mg/kg Q4W, which represents the same dose with a different schedule. As for tremelimumab, doses tested included 1 mg/kg Q4W, 3 mg/kg Q4W and 10 mg/kg Q4W. The selection of a combination dose and schedule for the combination of durvalumab and tremelimumab for taking forward into the wider program consisted of optimizing durvalumab at a dose that would allow for maximum target suppression, optimize synergy, and balance safety following combination with tremelimumab.

Based on PK/pharmacodynamic (monotherapy and combination) and preliminary efficacy data from the combination in Study D4190C000061, durvalumab doses of 3 and 10 mg/kg Q4W combination cohorts were excluded from further development. The 10 mg/kg Q2W and 20 mg/kg Q4W regimens are expected to have similar AUC at steady state based on PK simulations. Cohorts were therefore narrowed to 15 mg/kg Q4W and 20 mg/kg Q4W of durvalumab. Monotonic increases in pharmacodynamic activity with the combination (increased activation/proliferation markers on CD4 and CD8 T-cells in periphery) were observed with increasing doses of tremelimumab (1, 3, 10 mg/kg) in comparison to durvalumab monotherapy. Safety data from the 15 and 20 mg/kg durvalumab Q4W cohorts demonstrated numerical increases in the frequency of treatment-related AEs and AEs leading to discontinuation of investigational product with increasing doses (>1 mg/kg) of tremelimumab. In addition, clinical activity of the durvalumab and tremelimumab combination did not appear to provide qualitative changes of deeper or more rapid responses with increasing doses of tremelimumab. As a result, the selected dose and schedule of the combination based on data from Study D4190C00006 was 20 mg/kg durvalumab and 1 mg/kg tremelimumab Q4W for 4 doses, followed by 20 mg/kg durvalumab monotherapy Q4W.

1.2.2 Rationale for fixed dosing

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

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

A fixed dosing approach is preferred by the prescribing community because of the 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.

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with durvalumab monotherapy, tremelimumab monotherapy, and durvalumab + tremelimumab combination therapy, respectively, prior to the overall benefit/risk assessment.

1.3.1 Potential benefits

There remains a significant unmet medical need for additional treatment options for advanced solid tumors, including bladder, lung, and head and neck.

Treatment with agents targeting PD-1/PD-L1 (such as durvalumab) or CTLA-4 (such as tremelimumab) has shown activity in several tumor types in a subset of patients deriving meaningful and durable benefit. Efficacy data for patients treated with durvalumab monotherapy in the bladder cancer, lung cancer, and head and neck squamous cell carcinoma (HNSCC) cohorts have shown some clinical activity. Preliminary data generated from patients with NSCLC treated with durvalumab + tremelimumab combination therapy have shown early signs of clinical activity, and data from competitors indicate that the combination may act synergistically (Wolchok et al 2013). Thus, these agents may potentially offer benefit to this patient population. The study design aims to minimize potential risks and intensive monitoring, including early safety assessment, is in place for those risks deemed to be most likely based on prior experience with the investigational products (IPs; including durvalumab and tremelimumab).

See tumor specific modules (APPENDIX F) for description of potential benefits.

1.3.2 Overall risks

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

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

1.3.2.1 Durvalumab

Risks with durvalumab include, but are not limited to diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis, myocarditis, myositis/polymyositis, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, 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, cough, decreased appetite, dyspnea and nausea. Approximately 10% of patients 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, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program.

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 (Section 6.9.1).

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

1.3.2.2 Tremelimumab

Risks with tremelimumab monotherapy include, but are not limited to GI effects (colitis, diarrhea, enterocolitis and intestinal perforation), endocrine disorders (hypo- and hyper-thyroidism, hypophysitis and adrenal insufficiency), skin effects (rash and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, hepatic events (including immune-mediated hepatitis and liver enzyme elevations); pneumonitis and ILD; neurotoxicity (including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré syndrome); thrombocytopenia, anemia and neutropenia; infusion-related reactions and hypersensitivity/anaphylactic reactions; renal events (including nephritis/autoimmune nephritis and acute kidney injury, autoimmune arthritis, Sjogren's syndrome, giant cell temporal arteritis and ulcerative colitis); hyperglycemia and diabetes mellitus.

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

In monotherapy clinical studies, AEs reported at an incidence of ≥20% include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting and dyspnea. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE. Please see the current version of the IB for a detailed summary of monotherapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the tremelimumab program.

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

1.3.2.3 Durvalumab + Tremelimumab

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study D4190C00006, 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 + 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 and tremelimumab monotherapy. Emerging data from Study D4190C00006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with the durvalumab + 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 reported at an incidence of ≥20% included events such as fatigue, diarrhea, nausea, decreased appetite, pruritus, dyspnea, constipation and anemia. Please see the current version of the durvalumab IB for a detailed summary of combination therapy data, including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program, including durvalumab in combination with tremelimumab.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 16% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study Investigator.

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

1.3.3 Overall benefit risk

The toxicity profile of the combination of durvalumab and tremelimumab included fatigue, colitis, diarrhea, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increases, amylase and lipase increases, rash and pruritus, and other immune-mediated reactions, which were mostly reversible and manageable by the available protocol treatment guidelines. Increased toxicities have been seen when these agents are used in combination.

In particular, based on the specific MOA of durvalumab and tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing imAEs during the conduct of this study. Potential imAEs may be similar to those seen with the use of ipilimumab, BMS-936558, and BMS-936559 and may include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Brahmer et al 2012, Hodi et al 2010, Topalian et al 2012). Patients should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy. It is recommended that management of imAEs follow the Dosing Modification and Toxicity Management Guidelines outlined in Section 6.9.1.

Based upon the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, the activity seen with durvalumab in this tumor type, and the strength of the scientific hypotheses under evaluation, the durvalumab monotherapy and durvalumab + tremelimumab combination therapy proposed in this study may have the potential to provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable clinical responses, thereby improving quality of life and potentially extending survival. Furthermore, pre-clinical and clinical evidence indicate that the combination of PD 1/PD-L1 and CTLA-4 targeting agents may provide antitumor activity, with additional synergy from the combination (Wolchok et al 2013). Therefore, the investigation of the potential therapeutic efficacy of durvalumab monotherapy and durvalumab + tremelimumab combination therapy in patients with PD-L1-High and PD-L1 Low/Neg tumors is acceptable, and the overall benefit/risk assessment supports the proposed study design.

1.4 Study Design

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

The protocol (and each tumor specific module in APPENDIX F) 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 data cut-off (DCO).

Investigational product, dosage and mode of administration

Durvalumab + tremelimumab combination therapy

- Durvalumab 1,500 mg plus tremelimumab 75 mg via 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 (APPENDIX F) 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

During the treatment period, patients may continue receiving therapy in the setting of unconfirmed progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), at the Investigator's discretion, until progression is confirmed[*]. A confirmatory scan is required following a RECIST 1.1 overall time point assessment of progression (PD), preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

Patients with PD by RECIST 1.1 (unconfirmed and confirmed) who, in the Investigator's opinion, continue to receive benefit from their 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 (complete response [CR] or partial response [PR] as defined by RECIST 1.1) to immunotherapy treatment in target lesions (regardless of the appearance of new lesions), ie, 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 retreatment.

See Section 7.8 for post-study access to treatment information.

[*] 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 RECIST 1.1 modified for confirmation of progression, a confirmatory scan is required following an overall time point assessment of progression (PD), no earlier than 4 weeks after the previous assessment of PD.

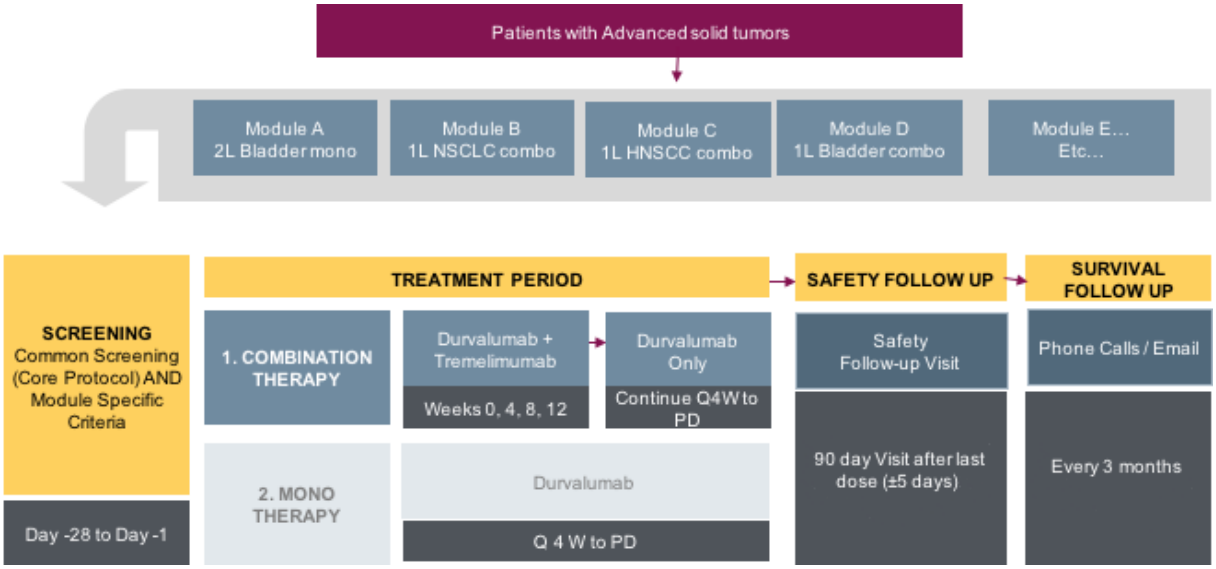
Follow up of patients post discontinuation of study drug

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, or withdrawal from treatment, or patients who have started a subsequent anticancer therapy, will have one additional tumor assessment on a subsequent scan, if clinically feasible, will be followed up for AEs for 90 days, and thereafter followed up for survival (described in the next section). These patients are not eligible for re-treatment at any time.

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.

Figure 1 Study flow chart



Tumor specific modules (APPENDIX F) 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.

2. STUDY OBJECTIVES

2.1 Primary objective

1. 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 durvalumab and tremelimumab combination therapy or durvalumab monotherapy, using fixed dosing.

An AESI is one of scientific and medical interest specific to understanding of the Investigational Product. AESIs for durvalumab and 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 an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA and where there is no clear alternate etiology.

AESIs observed with durvalumab or tremelimumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, 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.

The specific safety objective will be defined in each tumor specific module (APPENDIX F).

2.2 Secondary objectives

The common secondary objectives of all tumor sub-studies are:

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

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

3. To assess OS.

Additional secondary objectives and exploratory objectives may be added to individual modules in each country / region. Additional sub-studies / exploratory studies may be added to the protocol, in modular fashion.

2.3 Exploratory objective

1. To assess overall response rate (ORR) and disease control rate (DCR) based on Investigator assessed response to treatment (RECIST 1.1).

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. Common criteria are included here. For ease of reference, these common criteria have also been incorporated in each of the sub-studies.

Tumor specific additional inclusion and exclusion criteria are included within each module (APPENDIX F).

3.1 Inclusion criteria

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

1. Must have a life expectancy of at least 12 weeks.

2. Age ≥18 years at the time of screening. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative

3. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations. For patients aged <20 years and enrolling in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.

4. Disease not amenable to curative surgery

5. Eastern Cooperative Oncology Group (ECOG) performance status as defined in the specific module.

6. Body weight >30 kg.

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.

8. Adequate organ and marrow function as defined below:

   - Hemoglobin ≥9.0 g/dL
   - Absolute neutrophil count ≥1.0 × 10^9 /L
   - Platelet count ≥75 × 10^9/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)

     Males:

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

     Females:

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

9. Female patients of childbearing potential (ie, not surgically sterile or post-menopausal) who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy (see Section 3.8 and specifically Table 1).

10. Evidence of post-menopausal status or negative urinary or serum pregnancy test (per Section 4) 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).

11. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy (see Section 3.8).

3.2 Exclusion criteria (applicable to all modules)

Please also refer to each specific Module for specific criteria applicable to each module of the study. The exclusion criteria, common to all modules in the study are described in this section.

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

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

2. Previous IP assignment in the present study.

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.

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.

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.

6. Local treatment of isolated lesions for palliative intent is acceptable (eg, local surgery or radiotherapy).

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.

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.

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.

10. History of allogenic organ transplantation.

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

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

13. History of leptomeningeal carcinomatosis

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.

15. History of active primary immunodeficiency.

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.

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

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

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

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.

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

22. For women only, currently pregnant (confirmed with positive pregnancy test) or breast feeding.

23. 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 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy.

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

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

3.3 Patient enrollment and randomization

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed that are not part of routine medical care.

2. Obtain a unique 7-digit enrollment number (E-code), through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). This number is the patient's unique identifier and will be maintained throughout the study.

3. Determine patient eligibility. See Section 3.

4. Obtain signed informed consent for genetic research study (optional and where applicable)

Patients will begin treatment on Day 1. Treatment should start no more than 3 working days after registration.

If a patient does not meet eligibility criteria or withdraws from participation in the study after enrollment, then his/her enrollment number cannot be reused.

Investigator(s) should keep a record / screening log of patients who entered pre-study screening.

3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria (screening failures) must not, under any circumstances, be enrolled or receive study treatment. There can be no exceptions to this rule. Patients who are enrolled (by error), but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician or designee immediately, and a discussion should occur between the AstraZeneca study physician (or designee) and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician or designee must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups (not applicable)

All Modules under this protocol consist of a single treatment regimen. All enrolled patients in a given Module will receive the same treatment.

3.6 Methods for ensuring blinding (not applicable)

The study is not blinded. All modules under this protocol consist of single treatment regimen. All enrolled patients in a given module will receive the same treatment.

3.7 Methods for unblinding (not applicable)

The study is not blinded. All modules under this protocol consist of single treatment regimen. All enrolled patients in a given module will receive the same treatment.

3.8 Restrictions

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

1. Female patient of childbearing 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-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

2. 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).

Note: 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 (ie, 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 (eg, 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 • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants: eg, Implanon® or Norplan® • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices: eg, NuvaRing® • Injection: Medroxyprogesterone injection: eg, Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

3. All patients: Patients should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

4. Restrictions relating to concomitant medications are described in Section 7.7.

3.9 Discontinuation of investigational product

An individual patient will not receive any further IP treatment (durvalumab + tremelimumab combination therapy, durvalumab monotherapy) if any of the following occur in the patient in question:

1. Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 3.10.2)

2. An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing

3. Any AE that meets criteria for discontinuation as defined in the Dose Modification and Toxicity Management Guidelines (see Section 6.9.1)

4. Pregnancy or intent to become pregnant

5. Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)

6. Initiation of alternative anticancer therapy including another investigational agent

7. Clinical progression, ie, Investigator determination that the patient is no longer benefiting from treatment with IP, with or without radiological progression by RECIST 1.1

8. Transition to commercial drug supply. Note: If allowed by local regulations, the study Sponsor may transition patients from study treatment to commercial drug supply when the IP becomes commercially available in the country where the patient is living. See Section 7.8 for post-study access to treatment information.

Unless they withdraw consent for further follow up, patients who discontinue study therapy will continue on study for acquisition of safety information through 90 days after the last dose of study treatment, and for further collection of information regarding survival until the final DCO.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. If possible, they will be seen and assessed by an Investigator. AEs will be followed up (see Section 6). The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow up (see Table 2).

All patients will be followed for survival until the final DCO.

Where treatment is discontinued due to PD, it is recommended that a confirmatory scan be performed prior to discontinuation to verify progression. According to 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.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in Table 2 as an alternative.

Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled. If patients who do not meet eligibility criteria are enrolled in error, these patients should have the reason for study withdrawal recorded as 'Incorrect Enrollment' (ie, patient does not meet the required inclusion/exclusion criteria). Patients may be rescreened.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment. It should be confirmed and documented in source notes if the patient is withdrawing consent to the study treatment or to all study procedures, including survival follow up. Efforts should be made to follow patients until the end of study, but particularly to conduct the 90-day safety follow up.

Patients who withdraw consent for further participation in the study will not receive any further durvalumab + tremelimumab or further study observation, with the exception of follow up for survival, which will continue until the final DCO unless the patient has expressly withdrawn their consent to survival follow up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (See Section 6). The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Providing consent allows, survival status will be followed up by phone or electronic communication every 3 months up until the final DCO (see Section 4.3).

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

- All further participation in the study including any further follow up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples (see Section 5.7.4)

3.10.2.1 Survival status for withdrawn consent and lost to follow up patients

Patients will be considered lost to follow up only if no contact has been established by the time the study is completed (see Section 9.3), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather

than "lost to follow up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow up and evaluations should resume according to the protocol.

In order to support key end point of OS analysis, all enrolled patients' survival status should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up".

1. Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status.

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

3.11 Discontinuation of the study

Sections 3.9 and 3.10 address individual patient discontinuation from treatment and from study.

The overall study will close to new enrollment once all modules in all countries have completed accrual.

Accrual to any given module in any country will close once accrual targets for that module and country have been met.

The study may be stopped if, in the judgement of AstraZeneca, study patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study treatment
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow up must be recorded in the case report form (CRF). All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study

completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow up.

4. STUDY PLAN AND TIMING OF PROCEDURES

Procedures outlined in the table should be performed as indicated. However not all data will be collected on the CRF. Details regarding reporting of AEs, concomitant medications, and test results in the CRFs are provided in Sections 5 and 6.

Additional efficacy and safety procedures may be added to the tumor specific modules as deemed necessary for the tumor cohort or for the country.

For durvalumab monotherapy or durvalumab + tremelimumab combination arms

Patients may delay dosing under certain circumstances.

- Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-mediated AE (see Section 6.9.1).
- 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 efficacy or other assessments (as applicable by tumor Module). Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives

of durvalumab and tremelimumab (see current IBs for durvalumab and tremelimumab.

Additional procedures not forming part of the primary or secondary objectives may be added as sub-study modules to the protocol.

Table 2 Study Plan detailing the procedures

Visit	**Screening**	**Treatment period**			**Safety follow up visit**	**Survival follow up phone calls/emails**	**For details see Protocol Section**
		Baseline (Day 1)	**Treatment visits**				
Visit window	**Day -28 to Day-1**	**0**	**±3 days**	**±5 days**	**±5 days**	**±14 days**	
Week	**Weeks -4 to Week -1**	**Week 0**	**Weeks 4, 8, 12**	**Q4W from Week 16**	**90 days after last dose**	**Every 3 months**	**Section**
Written informed consent	X						4.1
Inclusion/ exclusion criteria (main criteria and tumor specific criteria for each Module)	X	X					3.1 & 3.2; also refer to each Module
Demographics and tobacco and alcohol use	X						5.2.1
Medical history	X						5.2.2
Disease characteristics	X						5.2.3
Cancer treatment history	X						5.2.4
ECG recording [a]	X		As clinically indicated				5.3.3
ECOG performance status	X	X	X	X			5.2.3; also refer to each Module

Visit	**Screening**	**Treatment period**			**Safety follow up visit**	**Survival follow up phone calls/emails**	**For details see Protocol Section**
		Baseline (Day 1)	**Treatment visits**				
Visit window	**Day -28 to Day-1**	**0**	**±3 days**	**±5 days**	**±5 days**	**±14 days**	
Week	**Weeks -4 to Week -1**	**Week 0**	**Weeks 4, 8, 12**	**Q4W from Week 16**	**90 days after last dose**	**Every 3 months**	**Section**
Physical examination, body weight, height and vital signs [b]	X	X	X	X			5.2.2 and 5.3.4
Laboratory Assessments [c]							
Clinical chemistry [d]	X	X [e]	X	X	Per institutional care		5.3.1
Hematology [d]	X	X [e]	X	X			5.3.1
Coagulation	X	As clinically indicated					5.3.1.2
Hepatitis B, C, HIV virology	X						5.3.1.3
Pregnancy test [f]	X(serum)	X [f]	X	X	Per institutional care		5.3.1
TSH [g], free T3, Free T4 [h]	X	X [e]	X	X			5.3.1.1
Urinalysis [i]	X	X [e]	X	X			5.3.1
Optional Blood sample (translational science/ genomics)	At Screening visit or during first treatment visit (prior to dosing)						5.7
PD-L1 results	X (if available)						4.1, 5.7

Visit	**Screening**	**Treatment period**			**Safety follow up visit**	**Survival follow up phone calls/emails**	**For details see Protocol Section**
		Baseline (Day 1)	**Treatment visits**				
Visit window	**Day -28 to Day-1**	**0**	**±3 days**	**±5 days**	**±5 days**	**±14 days**	
Week	**Weeks -4 to Week -1**	**Week 0**	**Weeks 4, 8, 12**	**Q4W from Week 16**	**90 days after last dose**	**Every 3 months**	**Section**
Archival tumor tissue sample provision [j]	X						5.7
Concomitant medications [k]	X	X	X	X	X		5.2.4
AEs / SAEs [l]	X	X	X	X	X		6.3
Combination Therapy Modules							
Durvalumab [m, n]		X	X	X			7.2
Tremelimumab [m, n]		X	X				7.2
Monotherapy Modules							
Durvalumab [m, n]		X	X	X			7.2
Investigator Reported Tumor / Response Assessment		Per Institution Standard			X		RECIST 1.1
Survival status					X	X	5.1
Reason for withdrawal			If applicable	If applicable			3.10

Note: All assessments listed in the table are to be performed prior to dosing during the treatment period. Inclusion/exclusion criteria are to be verified before the first dose of study drug.

(a) Any clinically significant abnormalities detected require triplicate ECG results.

(b) Vital signs are to be measured and recorded at all visits from screening to last treatment visit. Complete physical examination including body weight is recorded at screening and baseline, and height at screening. Targeted physical examination (including body weight) only after baseline full assessment. Physical examination information will only be reported in the CRF if abnormalities are reported as AEs.

(c) Blood and urine samples are to be collected within 72 hours prior to dosing to ensure that the results are available for review on the day of the visit. On the day of the visit, the results must be reviewed prior to IP administration.

(d) Serum or plasma clinical chemistry (including liver function test [LFT) monitoring) and hematology may be performed more frequently if clinically indicated.

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

(f) For women of childbearing potential, a serum pregnancy test is to be performed at screening. Urine pregnancy test (dip-stick or at the local laboratory) or serum pregnancy test at baseline visit and every treatment visit. 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.

(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 and 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) Urinalysis: Tests for urine bilirubin and urobilinogen will be done (per institutional standard method) at baseline only, and repeated only as clinically indicated.

(j) Archival tumor tissue for PD-L1 central testing and for banking and retrospective exploratory testing: This procedure is optional for the patient and requires consent. An archival, formalin-fixed, paraffin-embedded tumor block should be sent to the central laboratory. If an archival tumor block cannot be shipped to the central laboratory, then unstained slides with newly cut sections should be provided as described in the Laboratory Manual. If an archival sample is not available and if the patient provides consent, a sample should be collected via an image-guided core needle biopsy (at least 18 gauge or larger core diameter) or an excisional tumor biopsy. This procedure should be followed only if a biopsy is technically feasible and not associated with unacceptable clinical risk.

(k) Screening and baseline medications and use of corticosteroid or other immunosuppressive drugs and any other drugs/interventions to manage AESIs and AEs/SAEs (including dose, route, duration).

(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, electrolyte, full blood count, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

4.1 Screening/Enrollment period

Procedures will be performed according to the Study Plan.

All screening procedures must be performed within 28 days before dosing (Day -28 to Day -1). The screening evaluations may be carried out over more than one day. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. However, if evaluations that have been performed within 28 days prior to the date of dosing for other purposes prior to informed consent are otherwise suitable for use as screening evaluations, those evaluations need not be repeated if the patient consents to allow use.

1. Obtain written informed consents and appropriate privacy act document authorization

2. Assign enrollment number

3. Perform complete physical examination including body weight and height

4. Collect vital signs

5. Collect urine for urinalysis

6. Collect blood samples for:

    - Clinical chemistry
    - Hematology
    - Coagulation tests
    - Hepatitis B and C, HIV virology
    - Serum pregnancy test
    - Thyroid stimulating hormone (TSH) and if TSH is abnormal or there is clinical suspicion of an AE related to the endocrine system, free T3 and free T4

7. Collect demographic characteristics, tobacco and alcohol use, medical history and disease characteristics, prior and concomitant medication, and cancer treatment history

8. Assess AEs

9. Assess ECOG performance status

10. Perform electrocardiogram (ECG)

11. Collect PD-L1 status, expression, and details of sample and testing, if available

12. Provision of archival tumor tissue sample for PD-L1 testing and for banking and retrospective testing. This procedure is optional for the patient and requires consent. An archival, formalin-fixed, paraffin-embedded tumor block should be sent to the central laboratory.

    - If a tumor block cannot be shipped to the central laboratory, and if there is sufficient sample to allow PD-L1 testing, then unstained slides with newly cut tumor sections should be provided as described in the Laboratory Manual.

    - If an archival sample is not available and if the patient consents, then a sample should be collected either by an image-guided core needle biopsy (at least 18-gauge or larger core diameter needle) or by an excisional tumor biopsy. This procedure is optional for the patient and should be done only if the biopsy is technically feasible and is not associated with unacceptable clinical risk.

13. Collect blood sample for translational science/ genomics (optional)

4.2 Treatment period

Procedures will be performed according to the Study Plan. For Day 1 of treatment, pre-dose/dosing/post-dose procedures are shown under the baseline visit (Section 4.2.1). After Day 1, pre-dose/dosing/post-dose procedures should be performed as shown below in Section 4.2.1.

4.2.1 Baseline visit (Day 1)

Pre-Dose

The following assessments are to be completed pre-dose:

1. Collect blood and urine sample for laboratory evaluation within 72 hours prior to dosing (see Table 3 for tests, including pregnancy test, as specified in Section 5.3.1). If these samples (with the exception of the urine pregnancy test) were collected at the screening visit within 72 hours prior to dosing on Day 1, then these samples are not required to be repeated for dosing on Day 1. Collect blood sample for TSH, and free T3 and free T4 (if TSH is abnormal or there is clinical suspicion of an AE related to the endocrine system). Urine pregnancy test can be done using dip-stick or at the local laboratory. Coagulation tests only required if clinically indicated.

2. Review of results by treating physician or Investigator prior to dosing for at least the following tests: Blood urea nitrogen (BUN), serum creatinine, electrolytes, hematology, liver function tests, urinalysis (excluding urine microscopy), and pregnancy test (for women of childbearing potential).

3. Perform complete physical examination including body weight.

4. Assess AEs and ongoing relevant medical conditions.

5. Update concomitant medications.

6. Assess ECOG performance status.

7. Take vital signs before administration of study treatment.

8. Assess inclusion/exclusion criteria.

Dosing and post-dose

After the above assessments are completed:

1. Administer study treatment per Module (durvalumab + tremelimumab combination therapy or durvalumab monotherapy).

2. Take vital signs as per institutional care recommendations for the administration of mAbs.

3. Assess AEs during and subsequent to infusion.

4.2.2 Treatment period

Pre-dose

1. Collect blood and urine sample for laboratory evaluation within 72 hours prior to dosing (see Table 3 for tests, including pregnancy test, if required) as specified in Section 5.3.1. Collect blood sample for TSH, and free T3 and free T4 (if TSH is abnormal or there is clinical suspicion of an AE related to the endocrine system). Urine pregnancy test can be done using dip-stick or at the local laboratory per institutional practice.

2. Review of results by treating physician or Investigator prior to dosing for at least the following tests: BUN, serum creatinine, electrolytes, hematology, liver function tests, urinalysis (excluding urine microscopy), and pregnancy test (for women of childbearing potential).

3. Perform targeted physical examination including body weight.

4. Assess AEs and ongoing relevant medical conditions.

5. Update concomitant medications.

6. Assess ECOG performance status.

7. Take vital signs before administration of study treatment (durvalumab + tremelimumab combination therapy or durvalumab monotherapy as per Module).

8. Recording of Investigator assessment of treatment response.

Dosing and post-dose

After the above assessments are completed:

1. Administer study treatment.

2. Take vital signs as per institutional care recommendations for the administration of monoclonal antibodies.

3. Assess AEs during and subsequent to infusion.

4.3 Follow up period

Procedures will be performed according to the Study Plan.

All patients who discontinue study treatment will attend a safety follow up visit 90 days after study treatment discontinuation.

The following procedures will be performed:

1. Assess AEs.

2. Update concomitant medications.

3. Record Investigator assessment of treatment response.

4. Record subsequent therapy.

5. Record survival status.

After this safety follow up visit, patients will be contacted by phone or email every 3 months to check survival status until death or final DCO, whichever occurs first.

Patients who do not discontinue treatment before the final DCO will continue to be followed after the final DCO, as indicated in Section 6.3.12.

5. STUDY ASSESSMENTS

The Investigator will ensure that data are recorded on the electronic CRFs (eCRFs) as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

5.1 Survival assessments

The survival status of the patient will be collected during the study. After their safety follow up visit (90 days), patients will continue to be followed for survival via phone calls or email every 3 months until the final DCO, with a final check that should generally occur within 7 days of the final DCO.

The survival status (including cause of death) and the date of death or last follow up date will be collected.

No further efficacy assessments will be performed during the study. Evaluation of treatment benefit will be performed by the Investigator according to standard medical practice before each treatment administration.

5.2 Demographics/Medical, medication, surgical history

5.2.1 Demographics

Patient characteristics including age, gender, ethnicity (if available or allowed by local regulations), race (if available or allowed by local regulations), and geographic residence will be collected. Tobacco and alcohol use will also be collected.

5.2.2 Physical examination, vital signs and medical history

At screening and baseline, a complete physical examination (including body weight and height) will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems. After baseline, only targeted physical examination (including body weight) is necessary.

Physical examination information will only be reported in the CRF if abnormalities are reported as AEs. For information on how AEs based on physical examination should be recorded and reported, see Section 6.3.

Findings from medical history and physical examination will 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 at or below the pre-study baseline.

5.2.3 Disease characteristics and ECOG

Tumor histology (based on medical records), stage at diagnosis, current stage, ECOG performance status, as well as co-morbidities and relevant medical history, will be collected.

The standard ECOG performance status scale and criteria (Oken et al 1982) will be used (refer to APPENDIX E).

5.2.4 Prior and concomitant medication and cancer treatment history

For cohorts that allow prior anticancer therapy (see Modules), therapy type (targeted or non-targeted) and agents received, start and end-dates, radiation therapy, and surgery received prior to study enrollment must be documented. Additionally, any medication that the patient has ingested 30 days prior to study entry, including dose, frequency and the medical condition for which it was prescribed, must be documented.

5.3 Safety assessments

5.3.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, coagulation (only if clinically indicated), and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Sections 4.1 through 4.3 and Table 2).

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 and units) will be recorded on the appropriate CRF.

The laboratory variables to be measured are presented in Table 3.

Table 3 Laboratory safety variables

Hematology/ Hemostasis (whole blood)	White blood cell (WBC) count with differential, platelet count, red blood cell (RBC) count, hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC)
Clinical chemistry (serum or plasma)	Serum creatinine, total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), thyroid stimulating hormone (TSH), blood urea nitrogen (BUN), lipase, amylase, electrolytes (potassium, calcium, sodium), lactase dehydrogenase
Urinalysis (local laboratory or dip-stick per institutional care) [a]	Hb, leukocytes, protein, glucose, bilirubin [a], urobilinogen [a], ketones, specific gravity
Urine microscopy	WBC/high power field (HPF), RBC/HPF, epithelial cells, casts, crystals
Pregnancy test for women of child-bearing potential	Serum pregnancy tests performed for all women of childbearing potential at screening. At baseline and each treatment visit, a urine pregnancy test (dip-stick or at a local laboratory) or serum pregnancy test will be performed
Other safety tests (screening only) [b]	Hepatitis B surface antigen, hepatitis C antibody, HIV antibodies (eg, HIV-1 and HIV-2)
Additional laboratory tests (where clinically indicated only)	Free tri-iodothyronine (T3) and free thyroxine (T4)[c], creatinine clearance, alkaline phosphatase (ALP), autoimmune antibody test[d]

(a) Tests for urine bilirubin and urobilinogen will be done (per institutional standard method) at baseline only, and repeated only as clinically indicated.

(b) At screening only, for the evaluation of eligibility criteria.

(c) If TSH is abnormal or there is clinical suspicion of an AE related to the endocrine system then free T3 and free T4 testing will be done.

(d) If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the Investigator should collect a blood sample for appropriate autoimmune antibody testing by a local laboratory.

The hematology and clinical chemistry should be performed at a local laboratory at or near to the Investigator site. Urinalysis should be performed at a local laboratory (at or near to the Investigator site) or by dip-stick per institutional care. Tests for urine bilirubin and urobilinogen will be done (per institutional standard method) at baseline only, and repeated only as clinically indicated.

Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Clinically significant (as assessed by the Investigator) laboratory abnormalities will be recorded in the CRF as AEs. Laboratory results relevant to / associated with AESIs will be recorded in the CRF.

Additional safety samples may be collected during the study if clinically indicated at the discretion of the Investigator and according to standard medical practice. The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated, and retained at center as source data for laboratory variables. For information on how AEs based on laboratory tests

Note: In case a patient shows an AST or ALT ≥3 ULN or total bilirubin ≥2 ULN please refer to APPENDIX D for further instructions (also see Section 6.3.8).

5.3.1.1 Thyroid stimulating hormone

Perform TSH at all visits. Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

5.3.1.2 Coagulation

Activated partial thromboplastin time (APTT) will be performed at screening and if clinically indicated.

International normalized ratio (INR) will be performed at screening and if clinically indicated. Patients taking warfarin may participate in this study; however, it is recommended that INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Each coagulation test result will be recorded in the CRF.

5.3.1.3 Other lab tests

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

5.3.2 ECOG

The standard ECOG performance status scales and criteria (Okazaki and Honjo 2007) will be used (refer to APPENDIX E).

5.3.3 ECG

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

5.3.4 Physical exam, vital signs

At screening and baseline, a complete physical examination (including body weight and height) will be performed and include an assessment of the following: general appearance,

respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities) and neurological systems. After baseline, only targeted physical examination (including body weight) is necessary.

Physical examination information will only be reported in the CRF if abnormalities are reported as AEs. For information on how AEs based on physical examination should be recorded and reported, see Section 6.3.

Vital signs including pulse, blood pressure (systolic and diastolic), and temperature will be monitored at screening and at every visit during the study. During durvalumab and tremelimumab infusions, vital signs should be monitored as per institutional care recommendations for the administration of monoclonal antibodies. Vital signs will be measured and recorded at all visits from screening to the last treatment visit.

5.3.5 Other safety assessments

5.3.5.1 Immune-mediated adverse events

Safety findings supporting the monitoring and evaluation of imAEs, including radiographic or pathologic findings, or pulmonary function tests (in case of pneumonitis or ILD), should be reported in the CRF. Reporting of an imAE will trigger reporting of additional relevant / associated safety findings.

For management of imAEs please refer to the Dosing Modification and Toxicity Management Guidelines as indicated in Section 6.9.1.

5.3.5.2 Autoimmune antibody test

If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the Investigator should collect a blood sample for appropriate autoimmune antibody testing by a local laboratory. For management of imAEs please refer to the Dosing Modification and Toxicity Management Guidelines as indicated in Section 6.9.1.

5.4 Other assessments (not applicable)

5.5 Pharmacokinetics (not applicable)

5.6 Pharmacodynamics (not applicable)

5.7 Biomarker analysis

Pre-treatment tumor PD-L1 expression data, if available, will be collected on the CRF for all patients.

At the screening visit, an archival tumor block (formalin-fixed paraffin-embedded), if available, will be obtained from all patients. The provision of archival tumor tissue block is optional for the patients and requires a patient consent. If an archival tumor block exists and

there is sufficient quantity to allow for PD-L1 analysis, then the tumor tissue block should be shipped to the central laboratory. If a tissue block is unavailable, unstained slides with newly cut sections from the tissue block should be provided. If an archival sample is not available and if the patient provides consent, a sample should be collected via an image-guided core needle biopsy (at least 18-gauge or larger core diameter) or an excisional tumor biopsy sample. This procedure should be done only if the biopsy is technically feasible and is not associated with unacceptable clinical risk.

Instructions and guidelines for collecting archival tumor sample and for the storage, and shipment of biologic samples are given in the Laboratory Manual.

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent or additional research (not described in this protocol) but relevant to evaluating biological and/or clinical response to immunotherapy, either now or in the future on remaining biological samples (eg blood or tumor tissue). The purpose of this additional research is to investigate further the potential side effects of the study drugs and the underlying mechanism of the diseases under study.

The results may be pooled with biomarker data from other durvalumab/tremelimumab studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, clinical study Investigator, general physician, or any other third party, unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

5.7.1 Storage, re-use and destruction of biological samples

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the Clinical Study Report (CSR) in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab or tremelimumab to generate hypotheses to be tested in future research.

5.7.2 Labeling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see APPENDIX B.

Any samples identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

5.7.3 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of, or until further shipment, and will keep documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, and auditing of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca Biobank during the entire life cycle.

5.7.4 Withdrawal of Informed Consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of or destroyed and the action documented
- Ensure that the organization(s) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and the signed document is returned to the study site

- Ensure that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE 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 (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). 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.

6.2 Definitions of serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, and follow up), that fulfills 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/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

- AEs for new malignant tumors (ie, not the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study) reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used.
  In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a non-serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.
  Malignant tumors that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

For further guidance on the definition of a SAE, see Additional Safety Information in APPENDIX A.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse events and SAEs will be collected from time of the patient signing the ICF until the follow up period is completed (90 days after the last study treatment administration). 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.

6.3.2 Follow up of unresolved adverse events

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 CRF. 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.

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- 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
- 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 4.03 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 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2 and the Additional Safety Information in APPENDIX A. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2 and APPENDIX A. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2 and APPENDIX A.

6.3.4 Causality collection

The Investigator will assess causal relationship between durvalumab (monotherapy Modules), or between durvalumab and tremelimumab (combination therapy Modules) 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 durvalumab?' (monotherapy Modules) or and 'Do you consider that there is a reasonable possibility that the event may have been caused by durvalumab or tremelimumab?' (combination therapy Modules)?'

For SAEs, causal relationship will also be assessed for other medication, study procedures and alternative etiologies. 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 A.

6.3.5 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 (ie, 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 (eg, 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.

6.3.6 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 CRF. 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.

6.3.7 Adverse events based on examinations and tests

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

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (eg, 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.

6.3.8 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 D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.3.9 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which durvalumab + tremelimumab combination therapy or durvalumab monotherapy 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, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.3.10 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 durvalumab ± tremelimumab and have been identified after the patient's inclusion in this study.

6.3.11 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 CRF 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 CRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the CRF. 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 occurs as a result of an event that started post 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.

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

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 6.9.1). All data obtained post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 6.4.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to durvalumab ± tremelimumab, or to the study procedure(s). All SAEs will be recorded in the CRF, except SAEs occurring after the DCO and database closure. After the DCO, SAEs will be reported via paper SAE forms and recorded in AstraZeneca database.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca study representatives (or designees) within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca study representative (or designee) works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow up is undertaken immediately. Investigators or other site personnel inform AstraZeneca study representatives of any follow up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The reference documents for definition of expectedness are the IBs for durvalumab and tremelimumab, as applicable to the tumor specific Module.

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such.**

The Safety Handling Plan contains detailed timelines and region-specific instructions for safety reporting.

6.5 Adverse events of special interest

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 for durvalumab ± tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone

replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA 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.

In Japan, in the event of imAE or suspected imAE, the AstraZeneca study team may request relevant clinical information (including images) for those patients who demonstrate the event, and may request the independent review by external experts based on the acquired clinical information.

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

AESIs/imAEs observed with durvalumab ± tremelimumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as 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, 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.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab IBs. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 6.9.1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgement in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

6.6 Overdose

6.6.1 Durvalumab or tremelimumab

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

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

The designated AstraZeneca 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 an SAE, the standard reporting timelines apply; see Section 6.6. For other overdoses, reporting must occur within 30 days.

6.7 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca. except for pregnancy discovered before the study patient has received any study drugs.

6.7.1 Maternal exposure

If a patient becomes pregnant during the course of the study durvalumab and tremelimumab should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that durvalumab ± tremelimumab may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 informs the appropriate AstraZeneca study representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca study representative (or designee) works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.3.12) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.7.2 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.

6.8 Medication Error

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

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

Medication error includes situations where an error.

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

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

- Drug name confusion

- Dispensing error, eg, 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, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, 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), eg, 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 AstraZeneca representatives within 1 day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca 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 6.3.12) and within 30 days for all other medication errors.

6.9 Management Durvalumab ± Tremelimumab related toxicities

For AEs that are considered at least partly due to administration of durvalumab ± tremelimumab the following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab or tremelimumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab and tremelimumab (see Section 6.9.1).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

All toxicities will be graded according to NCI CTCAE, Version 4.03.

6.9.1 Specific toxicity management and dose modification information-Durvalumab and durvalumab + tremelimumab

Comprehensive toxicity management guidelines (TMG) have been developed to assist Investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitors durvalumab [Medi4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanisms of toxicities observed with these 2 compounds, these guidelines are applicable to the management of patients receiving either drug as monotherapy or in combination. Additionally, these guidelines are applicable when either drug is used alone or in combination and is administered concurrently or sequentially with other anti-cancer drugs (ie, antineoplastic chemotherapy, targeted agents), as part of a protocol specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatment. The most current version of the TMGs entitled “Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions (MEDI4736) Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy” is provided to the investigative site as an Annex document and is maintained within the Site Master File. In addition, a version of the current Dosing Modification and Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com/. Please contact your clinical trial associate for information on how to gain access to this website.

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 3.9 of this protocol and the Dosing Modification and Toxicity Management Guidelines).

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. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgement in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab combination therapy regimen by the reporting Investigator.

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

6.10 Study governance and oversight

6.10.1 Data Monitoring Committee

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified in this study or in other studies but deemed relevant for this study will be addressed promptly, which could involve amendments to the study protocol and letters to Investigators, as appropriate.

In addition to the ongoing AstraZeneca overall safety monitoring, a Data Monitoring Committee (DMC) comprised of internal experts independent from the study team will be convened and will meet approximately every 6 months after the study has started 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.

6.10.2 Steering Committee

A Steering Committee (SC) will be assembled by AstraZeneca for the executive oversight and supervision of the study. The committee of oncology experts will serve this role through regular scheduled meetings or teleconferences and, if necessary, additional ad hoc meetings. Details of the SC remit, procedures, processes, and meeting frequency will be outlined in an SC Charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

AstraZeneca will supply durvalumab or durvalumab and tremelimumab as applicable for each Module.

Investigational product	Dosage form and strength	Manufacturer
Durvalumab (MEDI4736)	50 mg/mL solution for infusion after dilution	Astra Zeneca
Tremelimumab	20 mg/mL solution for infusion after dilution	

7.1.1 Durvalumab

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. 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 original packaging until use to prevent prolonged light exposure.

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration 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 (only patients >30 kg in weight are eligible) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22 μm filter. Add 30.0 mL of durvalumab (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.

If patient weight falls to ≤30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab

concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. See the study specific drug handling plan for an example of a weight–based dose calculation.

Standard infusion time is 1 hour; however, if 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.

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

Preparations are to be in accordance with the study specific drug handling instructions.

7.1.2 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400 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% (w/v) polysorbate 80; it has a pH of 5.5 and a density 1.034 g/mL. The nominal fill volume is 20 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 original container until use to prevent prolonged light exposure.

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 start of administration should not exceed

- 24 hours at 2°C to 8°C (36°F to 46°F) or
- 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 >30 kg in weight; patients ≤30 kg are not eligible for entry to the study) 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 filter. Add 3.8 mL (ie, 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.

If patient weight falls to ≤30 kg, weight-based dosing at 1 mg/kg 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 filter. See the study specific drug handling plan for an example of a weight-based dose calculation.

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

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

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

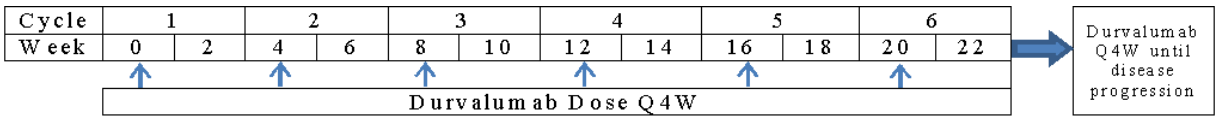
Preparations are to be in accordance with the study specific drug handling instructions.

7.2 Dose and treatment regimens

Durvalumab monotherapy

Patients in the durvalumab monotherapy treatment group will receive 1500 mg durvalumab via IV infusion Q4W until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. (Note: If a patient's weight falls to 30 kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between Investigator and study physician, until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W).

Figure 2 Durvalumab dosing regimen



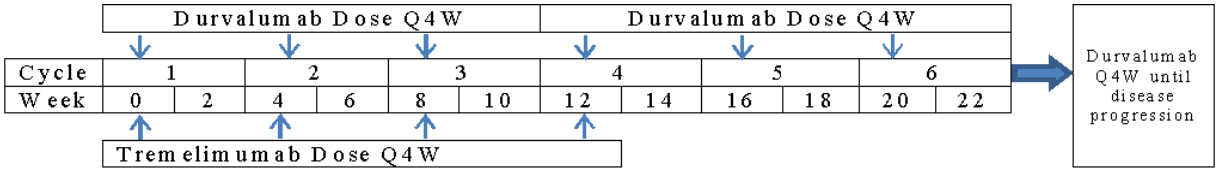
Durvalumab + tremelimumab combination therapy

Patients in the durvalumab + tremelimumab combination therapy Modules will receive durvalumab (1500 mg Q4W) in combination with tremelimumab (75 mg IV Q4W) for up to 4 doses/cycles each, followed by durvalumab 1500 mg Q4W until disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is

met. The first durvalumab monotherapy dose at 1500 mg Q4W will be 4 weeks after the final dose of durvalumab in combination with tremelimumab. (Note: If a patient's weight falls to 30 kg or below [≤30 kg], then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W and 1 mg/kg tremelimumab Q4W after consultation between Investigator and study physician, until the weight improves to above 30 kg [>30 kg], at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg plus tremelimumab 75 mg Q4W).

Tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. Standard infusion time for each is 1 hour; however, if 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 can be given immediately after the tremelimumab infusion has finished.

Figure 3 Durvalumab + tremelimumab dosing regimen



7.2.1 Duration of treatment and criteria for treatment through progression and for retreatment

All treatment will be administered beginning on Day 1 for durvalumab monotherapy or durvalumab + tremelimumab combination therapy until RECIST 1.1-defined radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

During the treatment period, patients may continue receiving therapy in the setting of unconfirmed radiologic progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), at the Investigator's discretion, until progression is confirmed*. A confirmatory scan is required following a RECIST 1.1 overall time point assessment of progression (PD), preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

*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 RECIST 1.1 modified for confirmation of progression, a confirmatory scan is required following an overall time point assessment of progression (PD), no earlier than 4 weeks after the previous assessment of PD.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible for continuing durvalumab±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 meeting the retreatment criteria below will follow the same treatment guidelines followed during the original treatment period, including the same dose and frequency of treatments and the same schedule of assessments.

Patients who meet the criteria for retreatment may only receive retreatment once.

Patients receiving durvalumab + tremelimumab combination therapy may undergo retreatment as described below:

- Patients who complete the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgement), but subsequently have evidence of RECIST 1.1 (or other tumor assessment method)-defined PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

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

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG performance status to >1
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention
- The patient still fulfills the eligibility criteria for this study (see Sections 3.1 and 3.2) with the exception of inclusion criteria 6 and exclusion criteria 2 and 3. Patients must also agree to re-consenting to restart durvalumab + tremelimumab combination therapy

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), ie, the response and progression events both occurred in the target lesions while receiving immunotherapy during the same treatment period.

During the retreatment period, patients in the durvalumab + tremelimumab combination therapy group will resume durvalumab dosing at 1500 mg Q4W with 75 mg of tremelimumab Q4W for 4 doses (or cycles) each. Patients will then continue with durvalumab monotherapy at 1500 mg Q4W, beginning at Week 16, 4 weeks after the last dose of combination therapy, until disease progression.

Patients who AstraZeneca and the Investigator determine may not continue treatment after RECIST 1.1-defined PD will be followed up for survival. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until confirmed RECIST 1.1-defined PD and for survival.

Post final data cut off (DCO)

Patients who continue to receive benefit from their assigned treatment at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician considers they are gaining clinical benefit. For patients continuing to receive durvalumab treatment following the final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patients' safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Section 6.9.1).

In the event that a roll-over or safety extension study is available at the time of, or subsequent to, the final DCO and database closure, patients receiving treatment with durvalumab may be transitioned to such a study, and the study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

7.3 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local language in accordance with local requirements.

In Japan, labels will be prepared in accordance with Good Clinical Practice (GCP) Ordinance. Details are specified in the document explaining the reconstitution procedures and other handling procedures for the IPs.

IP will be provided with either single panel labels or multi-language booklet labels.

Label text prepared for durvalumab will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

7.4 Storage

The Investigator, or an approved representative (eg, pharmacist), will ensure that all IP is stored in a secured area, in refrigerated temperatures (2°C to 8°C) and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

7.5 Compliance

The administration of all study treatments (including IPs) should be recorded in the appropriate sections of the CRF.

Treatment compliance will be assured by reconciliation of site drug accountability logs.

7.6 Accountability

The study treatment provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient.

Drug accountability should be performed until the patient stops durvalumab and tremelimumab completely. Study site personnel will account for all vials of durvalumab and tremelimumab received at the site, for all unused vials, and for appropriate destruction of durvalumab and tremelimumab. Certificates of delivery, destruction, and return should be signed.

In Japan, study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage', which describe the specific requirements. The Investigator(s) is responsible for ensuring that the patient has returned all unused study drug.

7.7 Concomitant medications and other treatments

Screening and baseline medications, use of corticosteroid or other immunosuppressive drugs, and any other drugs to manage AESIs or imAEs (including dose, route, duration) should be recorded in the appropriate sections of the CRF.

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including the 90 day follow up period following the last dose of study drug. Any concomitant medication(s), including herbal preparations, taken during this time will be recorded in the CRF.

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer also to the Dosing Modification and Toxicity Management Guidelines as indicated in Section 6.9.1.

Table 4 Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
For the durvalumab ± tremelimumab treatment arms only	
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 (eg, 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)
Epidermal growth factor receptor tyrosine kinase inhibitors (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.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concurrently unless agreed by the Sponsor

Table 5 Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, 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

7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

7.8 Post-study access to study treatment

The study will close to new enrollment when accrual targets for each module in each country have been met (or for other reasons as outlined in Section 3.11).

In the opinion of the Investigator, if patients are still benefiting from treatment at the time of study closure, the patients will continue to be provided with study drug. This may include, but not be limited to, transition to a long-term extension trial or an early access program as permitted by applicable regulations.

8. STATISTICAL ANALYSES BY ASTRAZENECA

See tumor specific Modules (APPENDIX F) for statistical details.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

The sections below outline general principles. Any additional specific details applicable to tumor specific modules or countries will be described in the Modules.

9.1 Training of study site staff

Before the first patient is entered into the study, an AstraZeneca study representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and eCRF system(s) utilized. Additional recommendations and training requirements regarding the recognition, monitoring, and management of AESIs/imAEs will be provided to study personnel.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca study representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual, and that study treatment accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient’s biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient

Details will be outlined in a Monitoring Plan.

The AstraZeneca study representative will be available between visits if the Investigator(s) or other staff at the center need information and advice about the study conduct.

9.2.1 Source data

Study sites will maintain source data in accordance with GCP or local regulations.

9.2.2 Study agreements

The Principal Investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

9.3 Study timetable and end of study

The end of the study is defined as the last visit of the last patient undergoing the study.

The overall study is expected to start in Q1 2017 and end by Q2 2021.

See individual modules for the definition of final DCO.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with durvalumab or tremelimumab.

In the event that a roll-over or safety extension study is available at the time of or subsequent to the final DCO and database closure, patients receiving treatment with durvalumab may be transitioned to such a study, and the study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any patient who would be proposed to move to such a study would be given a new Informed Consent.

9.4 Data management by AstraZeneca or delegate

Data Management details will be provided separately for each module and country dependent on delivery model and so are not specified in the protocol.

Any data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in data management plans. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Data management plans will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Serious Adverse Event (SAE) Reconciliation

SAE reconciliation reports are produced according to the SAE reconciliation plan and reconciled with the Patient Safety database and/or the investigational site.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 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 International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

If mandatory genetic testing is required on any of the STRONG modules, the following applies. AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician, unless required to do so by law.

Precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.3 Ethics and regulatory review

An EC (ie, IRB and Independent Ethics Committee [IEC]) should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, ECs and Principal Investigators with safety updates/reports according to local requirements.

Each Principal Investigator is responsible for providing the ECs with reports of any serious and unexpected adverse drug reactions from any other study conducted with tremelimumab. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

In Japan:

An IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The head of the study site will ensure the distribution of these documents to the applicable IRB, and the Principal Investigator to the Investigator and study site staff.

The opinion of the IRB should be given in writing. The head of the study site should submit a notification of direction/determination as well as the IRB written approval to AstraZeneca and the Principal Investigator before enrollment of any patient into the study.

The IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

The head of the study site should seek the opinion of the IRB with respect to the appropriateness of continuing the study at the study site at least once a year when the duration of the study exceeds one year. The Principal Investigator should submit progress reports to the IRB via the head of the study site at the time of the protocol re-approval.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority with notification provided, according to local regulations. AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, IRB, the head of the study site and the Principal Investigator with safety updates/reports according to local requirements.

The head of the study site should submit a written report to the IRB providing the details of all safety relative information reported by AstraZeneca.

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that he/she is free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF is given to the patient.

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

10.5 Changes to the clinical study protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International coordinating Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant EC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator(s). For distribution to EC see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's EC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each EC.

In Japan:

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the study protocol to be amended, the amendment should be submitted to the head of the study site and be approved by its IRB. If applicable, AstraZeneca should submit a notification to the regulatory authority before it is implemented. If a protocol amendment requires a change to a particular center's ICF, then AstraZeneca and the center's IRB should be notified by the Principal Investigator. Approval of the revised ICF by AstraZeneca and by the IRB is required before the revised form is used. If an administrative change is required, such a change should be notified to or approved by each IRB according to local requirements.

10.6 Audits and inspections

Authorized study representatives of AstraZeneca, a regulatory authority, or an EC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

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