Clinical Study Protocol	
Drug Substance	Durvalumab (MEDI4736) + Tremelimumab
Study Code	D419BC00001
Version	9
Date	03 December 2019

A Phase III, Randomized, Open-Label, Controlled, Multi-Center, Global Study of First-Line MEDI4736 Monotherapy and MEDI4736 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer

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VERSION HISTORY

Version 9, 03 December 2019
Section 1.3.2.1 (MEDI4736) was revised to reflect the most recent version of the IB and to provide the most current safety information to the Investigators.
Section 1.3.2.2 (Tremelimumab) was revised to reflect the most recent version of the IB and to provide the most current safety information to the Investigators.
Section 1.3.2.3 (MEDI4736 + tremelimumab combination therapy) was revised to reflect the most recent version of the IB and to provide the most current safety information to the Investigators.

Section 6.7.1 (MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy adverse events of special interest) This section has been updated with the following language, consistent with the IB: AESI/imAEs observed with anti PD-L/PD-1 agents such as durvalumab and durvalumab in combination with tremlimumab 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-Barre syndrome.
Section 6.7.1 (Specific toxicity management and dose modification information – MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy) This section has been updated to clarify that the Toxicity Management Guidelines (TMGs) for durvalumab and tremelimumab will be provided to investigative sites as an Annex to the protocol document.
Appendix G-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), 1 November 2017 Version: Removed from the list of appendices and the document.
Version 8, 26 April 2019
Section 7.8 (Post-study access to study treatment): Revised this section to specify data collection and follow-up for patients who remain on treatment at the final data cutoff and database lock, and permit enrollment in a roll-over study at the final data cutoff and database lock.
Synopsis, Section 8.2 (Sample size estimate), Section 8.5 (Methods for statistical analyses), Section 8.5.15 (Interim analyses), and Section 8.5.15.2 (Interim analysis of overall survival endpoints): Revised these sections as follows: 1. Removed the Interim 3 analysis (ie, second interim analysis for OS) and specified that only the final analysis will be conducted. The rationale for this change is based on the limited increase in maturity of the study between the Interim 2 and Interim 3 analyses (10%) and between the Interim 3 and final analyses (10%).

2. Revised the timing of the final analysis to occur when the target number of events is reached in the durvalumab monotherapy versus standard of care arm only. The rationale for prioritizing durvalumab monotherapy is based on results from AstraZeneca-sponsored studies in second-line urothelial carcinoma (Study CD-ON-MEDI4736-1108 [NCT01693562] and Study D4190C00010 [NCT02261220]) and first-line non-small cell lung cancer (Study D419AC00001 [MYSTIC]).
Section 9.3 (Study timetable and end of study): Cross-referenced Section 7.8 for details regarding study treatment access, data collection, and patient follow-up at the end of study.
Version 7, 24 November 2017
Section 6.7 general guidance of management of IP-related toxicity was updated since the toxicity management guidance of immunotherapy was moved to section 6.7.1
Section 6.7.1 A new section number was given. Previous "MEDI4736 and MEDI4736 + tremelimumab" was now modified to "6.7.1 Specific toxicity management and dose modification information –MEDI4736 and MEDI4736 + tremelimumab". The content was updated to match the latest version of Dosing Modification and Toxicity Management Guidelines (TMG, dated 01 Nov 2017). AESI was updated to match the updated durvalumab and tremelimumab Investigator's Brochures and TMG.
Section number 6.7.2 was added as a result of addition of section number 6.7.1
Appendix G Dosing Modification and Toxicity Management Guidelines was updated to the latest version, 01 Nov 2017 Version
Version 6, 20 September 2017
Synopsis was modified to reflect the changes in Section 2 (Study objectives) and Section 8 (Statistical analyses by Astrazeneca).
Protocol Synopsis and note for Table 3 was modified to reflect that Hepatitis B, C and HIV assessments are not required to be collected a second time during retreatment.

Protocol Synopsis, Section 1.4 (Study design), note for Figure 1 (Overall study design) and Section 8.2 (Sample size estimate): Number of patients in China cohort was changed from approximately 96 to approximately 180, which was based on the change in co-primary endpoints.
Section 1.2.3 (Rationale for cisplatin-ineligible Interim Analysis): Rationale for Cisplatin-ineligible Interim Analysis was added.
Section 1.4 (study design) -Table 1: Additional note was added to Table 1 definition of PD-L1 high vs Low/negative to clarify the detail on scoring instructions for use in circumstances where tumor sample contains low immune cell content, which was used to stratify patients.
Section 2 (study objectives) was revised to include the following major changes: 1. **Changes to primary objectives**: Removal of PFS from co-primary endpoint, and make it a secondary endpoint. This change is based on external data from competitor IO bladder cancer studies and data from AstraZeneca study 1108 (NCT01693562) and study 10 (NCT02261220) in 2nd line bladder cancer patients treated with IO. **2. Changes to secondary objectives:** a. Adding an interim analysis for the following purpose: • To evaluate the efficacy profile in MEDI4736 treated patients who are not eligible for cisplatin-based treatment. • For this interim analysis, BICR review will be carried out only on patients who are not eligible for cisplatin-based treatment. • Adding safety objective to assess the safety and tolerability profile of MEDI4736 monotherapy and SoC in patients who are not cisplatin-eligible. b. Removing the efficacy comparison between monotherapy (or combination therapy) and SoC in cisplatin ineligible patients, as that is replaced by the above new interim analysis. c. Except cisplatin ineligible interim analysis, PFS, APF2, ORR, DoR and DCR will be based on investigator data according to RECIST 1.1 instead of BICR data.

d. Adding specific PRO endpoints to evaluate fatigue and pain as important symptoms of metastatic UC. e. Outcome measure of PK was updated to reflect the nature of the PK sampling scheme that is sparse and would not allow determination of meaningful PK parameters by non-compartmental PK analysis.
Section 4 (Study plan and timing of procedures): Table 3 footnote l, Table 4 footnote k, Table 5 footnote i, Table 6 footnote i, Table 7 footnote g was modified to add confirmation of response (PR/CR) in collecting of confirmatory scans. Table 6 footnote g. ADA samples collection was cancelled from month 6 follow up visit based on safety input. Table 6 footnote e. Table 7 footnote d was added to clairify that PFS2 should be collected after the patient progression endpoint used for the first PFS.
Section 5.1 (Efficacy assessments) was revised to reflect the change in Appendix E to clearly define confirmation of progression.
Section 5.1.1 (Central reading of scans) was revised to reflect that BICR will be performed for cisplatin ineligible patients.
Section 5.2.1 (Laboratory safety assessments), Table 3, Table 4 and Table 5 have been amended to remove Urinalysis testing as it does not contribute to safety analysis. Original Table 10 for urinalysis is removed so that 'Summary of outcome variables and analysis populations' was changed from Table 11 to 10, 'Preplanned statistical and sensitivity analyses to be conducted' was changed from Table 12 to 11.
Section 5.4.2 (Collection of samples to measure the presence of ADAs) was added to clarify that ADA samples will be tested in AstraZeneca designated laboratory. The samples may need to be exported to USA for testing.
Section 6.3.1 (Time period for collection of adverse events) was added with clarity in the duration for SAE/AE collection and follow up.

Section 7.2.1 (Treatment regimens), Table 4-footnote n, Table 5-footnote l: The section was updated to reflect that for patients receiving SoC treatment beyond 6 cycles, the exposure information will be reported in Exposure form and the schedule of assessment will be the same as the one for treatment within 6 cycles.
Section 8.1 (Statistical considerations) was updated to be consistent with Section 2 (study objectives).
Section 8.2 (Sample size estimate)- Changes in this section includes the following: 1. Change in sample size calculation. Based on external data from competitors (IMvigor 211 and Keynote 045) and data from AstraZeneca study 1108 (NCT01693562) and study 10 (NCT02261220) in 2nd line bladder cancer trial, PFS has been dropped from co-primary endpoints. The alpha previously assigned to PFS has been reassigned to OS (MEDI4736 monotherapy vs SoC in PD-L1-High). 2. Statisitical assumptions were revised: Based on the same data sources as mentioned above, the previously assumed 2-month delay in separation of the OS curves should be revised to 6-month. Moreover, study D419BC00001 actually enrolled 40% cisplatin-ineligible patients,compared to 20% as originally planned. As a result, the sample size calculation of OS endpoints has been updated to accommodate these changes, and interim analysis timepoints has also been revised. 3. Wording updated to be consistent with Section 2 (study objectives) and Section 8.5 (MTP), i.e., removing wording regarding PFS (MEDI4736 monotherapy vs SoC) in PD-L1-High population, and adding content for OS (MEDI4736 monotherapy vs SoC) in all comers population.

Section 8.3 (Definitions of analysis sets)- Changes include the following:

1. Section 8.3- Table 10 (Summary of outcome variables and analysis populations) was updated to be consistent with Section 2 (study objectives).
2. Section 8.3.5 (MEDI4736 cisplatin ineligible population) and Section 8.3.6 (Safety analysis set) was updated to add analysis sets definition to support interim analysis in patients who are not cisplatin-eligible.
3. Section 8.3.6 (Safety analysis set): Safety analysis set definition has been revised to be consistent with new Therapeutic Area standard.
4. Section 8.3.7 (PK analysis set): Definition of PK analysis set was updated to reflect the nature of the study design with a comparator arm.

Section 8.4 (Outcome measures for analyses)- Major changes include the following:

1. This section was updated to reflect the changes made in Section 2 (study objectives).
2. Removal of the 3 month timepoint for DCR.
3. Further clarifications have been made around secondary endpoint, time from randomization to second progression.
4. Further clarification has been added around PK variables.
5. Section 8.4.3.1 FACT-BL: text has been added to characterize fatigue and pain as important symptoms of metastatic UC.

Section 8.4.4.1 (Population pharmacokinetics and exposure-response/safety analysis): text was revised to state that the population PK analysis and the relationship between PK and the effect on safety and efficacy endpoints “may” be evaluated instead of “will”; these modeling activities will be performed only if further evaluation of the data from this trial is required.

Section 8.4.4.2 (Pharmacokinetic analysis): text was revised to reflect that PK parameters will be derived from raw data and not from non-compartmental PK analysis due to the sparse PK sampling scheme that would not allow determination of meaningful PK parameters by non-compartmental PK analysis.

Section 8.5 (Methods for statistical analyses)- Major changes include the following:

1. Table 11 was updated to reflect the changes in Section 2 (study objectives) and Section 8.4 (Outcome measures for analyses).

2. MTP was revised to reflect the change in co-primary and secondary endpoints.

    a. PFS (MEDI4736 monotherapy vs SoC) in PD-L1 High population was removed from MTP based on the same data souce as stated in Section 2 (study objective).

    b. OS (Combination therapy vs SoC) in PD-L1 low/neg population was added into MTP as this population may benefit more from combination therapy.

3. Analysis methods was updated to match changes to primary and secondary study objectives.

4. Subsection 8.5.15 (Interim analyses) revised to include a new section. Section 8.5.15.1 (Interim analysis focusing on ORR and DoR) was created to outline additional details regarding new interim analysis in patients who are not cisplatin-eligible. Section 8.5.15.2 (Interim analysis of overall survival endpoints) was also updated to reflect the changes of OS interim analyses timing.

Appendix E (Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria [Response Evaluation Criteria in Solid Tumors])- Changes in this section includes the following:

1. Add clarification for Target lesion to clarify that a bilateral, segmented or multi-lobular organ is considered as a single organ.

2. Table E1 (Summary of methods of assessment)- Add clarification in note for Clinical examination as one of the lesion assessment methods which refers to manually palpable tumor lesions.

3. Add Chest X-ray guidance as method of assessment to be used to assess NTL and to identify the presence of new lesions.

4. Revised to clearly define confirmation of progression for SoC vs. Immunotherapy arm patients.
Version 5, 02 Feb 2017
Version history for Japan CSP is added as per local requirement.
An expansion cohort will continue in China once global enrollment has ended. The following sections have been amended to reflect this change: Protocol synopsis; Section 1.4 Study design; Section 8.2 Sample size estimate.
To further assess the efficacy of MEDI4736 +tremelimumab combination therapy compared to SoC and efficacy of MEDI4736 monotherapy compared to SoC in patients who are not cisplatin eligible is added in secondary objectives. The following sections have been amended to reflect this change: Protocol synopsis; Section 2 study objectives.
The information “In Japan, this study will be started after the confirmation of tolerability of MEDI4736 (1.5 g q4W) + Tremelimumab (75 mg q4W) combination therapy in study D4880C00010 which is currently conducted in Japan.” is added in protocol synopsis as this is per PMDA requirement to ensure the safety of Japanese subjects.
Emphasize that a further objective to evaluate consistency in efficacy and safety among Chinese subjects, as required by China FDA. The following sections have been amended to reflect this change: Protocol synopsis; Section 2 study objectives.
Protocol synopsis: “statistical methods” is updated to reflect the change in the split of alpha across the three proposed primary end-points and its impact.
Protocol synopsis: The paragraph “safety data” is about safety analyses, so remove the sentence not relevant with this, which is related with efficacy parameter PFS in subgroup analyses.
Statistical analysis is updated for China cohort. The following sections have been amended to reflect this change: Protocol synopsis; Section 8 Statistical considerations; Section 8.3.1 Full analysis set; Section 8.3.5 Safety analysis set; 8.6 China cohort.

Clarify that written informed consent for retreatment and/or treatment through progression in the setting of PD will specify that treatment beyond evidence of initial PD is not the SoC and that alternative treatment options, including either locally licensed treatments or other clinical trials, are available for this patient population. The following sections have been amended to reflect this change: Protocol synopsis; Section 7.2.2 Duration of treatment, criteria for retreatment, and treatment through progression.
Table of contents: Section 8.3.4 Cisplatin ineligible analysis set and Section 8.6 China cohort are added in the table of contents.
The special term “PMDA” is added in the list of abbreviations and definition of terms.
Section 1.4 Study design: make clarification that the definition of PD-L1 high versus low/negative expression will be used for stratification. Different cutoff of PD-L1 expression may be utilized for analysis based on emerging data.
Section 1.4 Study design: clarify that approximately 96 Chinese patients will be randomized in the same criteria (stratification factors and 1:1:1 fashion) as globally.
Section 3.1 Inclusion criteria: clarify the New York Heart Association ≥Class III heart failure as one criteria for the Cisplatin ineligibility.
The optional genetic research is removed from informed consent. The following sections have been amended to reflect this change: Section 3.3 Patient enrollment and randomization; Footnote a in Section 4 Table 3, Table 4 and Table 5.
Section 3.10.2 withdrawal of the informed consent: give the clarification on the vital status follow up for all patients.
Section 4 Table 3, Table 4 and Table 5: correct that the archival tumor sample should be ≤3 years instend of < 3 years.
Give clarification that after the initial assessment of PD, the confirmatory scan should be performed regardless if removed from drug. The following sections have been amended to reflect this change: Section 4 Table 3, Table 4, Table 5, Table 6 and Table 7; Section 5.1 Efficacy assessments; Section 8.4.1.2 Co-primary endpoints.

Give clarification that the scan in retreatment should occur relative to the date of first dose in retreatment. The following sections have been amended to reflect this change: Section 5.1 Efficacy assessments; Section 7.2.2 Duration of treatment, criteria for retreatment, and treatment through progression.
The appendix number is corrected in below sections: Section 5.2.1 Laboratory safety assessments; Section 5.5.4 Labeling and shipment of biological samples; Section 8.4.6 Calculation or derivation of pharmacogenetics variables; Section 9.4 Data management by AstraZeneca; Section 10.2 Patient data protection.
Section 5.4 Pharmacokinetics: the blood volume collection of PK and ADA listed under the section has been removed and clarify that the samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.
Section 5.5.1.1 Exploratory biomarker data: the content is updated as the exploratory biomarker analyses is only applicable for the blood samples have already been obtained and tumor samples will be used for exploratory biomarker analyses in select countries only.
Section 7.1 Identity of investigational products: the SoC drug supply strategy is added for Japan to clarify the procedure in Japan.
Section 7.2.2 Duration of treatment, criteria for retreatment, and treatment through progression: give clarification that Hepatitis B and C assessments, and HIV assessments don’t need to be collected again during retreatment.
Section 7.7 Concomitant and other treatments: give clarification that the concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment, immunosuppressive medications, herbal and natural remedies are prohibited while the patient is on study treatment.
Section 8.2 Sample size estimate: the statistical method in this part is updated to reflect the impact of the change in the split of alpha across the three proposed primary end-points.
Section 8.3 Definitions of analysis sets: the cisplatin ineligible analysis set is added in the section.

Section 8.3.4 Cisplatin ineligible analysis set:clarify that "Cisplatin ineligible analysis set will include the subset of patients in the FAS whose are not eligible for Cisplatin treatment."
Section 8.5 Methods for statistical analyses: the MEDI4736+tremelimumab combination therapy versus SoC and MEDI4736 monotherapy versus SoC in Cisplatin ineligible population are added under the stratified log-rank test for PFS and OS; The multiple testing strategy is updated to provide the investigators with the most current information; The figure 5 is updated for clarification; Give clarification that the effect of MEDI4736+tremelimumab combination therapy versus SoC treatment will be estimated by the HR together with its corresponding 99.5% CI and p-value for progression-free survival; The interim analyses is updated to provide the investigators with the most current information.
As the blood sample for pharmacogenetics research is only applicable for the samples already obtained, the following sections have been amended to reflect this change: Section 8.4.6 Calculation or derivation of pharmacogenetic variables; Appendix C Pharmacogenetics Research.
Version 4, 12 September 2016
Version 4 (Amendment 3) changes to Amendment 2 (Version 3, 19 August 2016) include all Amendment 2 (Version 3) changes and are summarized below.
Version number, amendment number, and date were updated throughout the document and cross-reference links to appendices were added.
The ordering of study objectives in Section 2 was corrected so that Primary objectives was changed from Section 2.3 to 2.1, Secondary objectives from Section 2.1 to 2.2, and Safety objectives from Section 2.2 to 2.3.
In the final published version of the amendment, the portable document formats (PDFs) of the patient-reported outcomes (PROs) were inserted and the pagination and List of Appendices were updated.
Version 3, 19 August 2016 (not implemented)

Version 3 (Amendment 2) changes to the original protocol (Version 1, 07 August 2015) are summarized below.
The AstraZeneca logo on the title page was updated, and the title page was revised to reflect the current AstraZeneca template, including deleting multiple title pages by country and rows for Administrative Amendment details. The study title was revised to delete "bladder" from "urothelial bladder cancer," and the abbreviation was changed from "UBC" to "UC." "(Japan) AstraZeneca K.K., 3-1, Ofuka cho, Kita-ku Osaka 530-0011, Japan" was added to the title page per local requirement.
Header information was revised to reflect current information, and the footer was revised in accordance with the current AstraZeneca template.
Version history was added to reflect the current AstraZeneca template.
The Synopsis was updated to reflect changes in the body of the amendment. These changes and the rationale for them are detailed in the discussion of the specific sections. The list of abbreviations was updated to include all abbreviations used in Amendment 2. Minor typographical errors, footnotes, and formatting were updated. Editorial and formatting changes were also made for compliance with AstraZeneca's new Clinical Study Protocol template. Urothelial bladder cancer was revised to urothelial cancer, and the corresponding abbreviation was revised from UBC to UC throughout. The designation of programmed cell death ligand 1 (PD-L1) status was changed from "positive" to "High" and from "negative" to "Low/Neg" throughout the document for clarity. "Study Physician" was changed to "AstraZeneca" throughout to allow for responses from other Clinical and Operational Team Members as appropriate. "/Medimmune" was deleted from "Ventana/Medimmune" for clarity. Revisions were made throughout the protocol to use IVRS/IWRS for Interactive Voice Response System and for Interactive Web Response System, respectively, consistently and delete the word "system" afterward because it is redundant.

Subsection 1.2.1.1 (MEDI4736 + tremelimumab combination therapy dose rationale): "Clinical data" was updated to provide the Investigators with the most current information regarding the number of patients dosed and the doses they have received. Revisions were made here and throughout the protocol to designate PD-L1 status as "High" or "Low/Neg" instead of positive or negative.
Subsection 1.3.2.1 (Potential risks: MEDI4736) was revised to reflect the most recent version of the Investigator's Brochure (IB) and to provide the most current safety information to the Investigators. Subsection 1.3.2.2 (Potential risks: Tremelimumab) was revised to reflect the most recent version of the IB and to provide the most current safety information to the Investigators. Subsection 1.3.2.3 (Potential risks: MEDI4736 + tremelimumab combination therapy) was revised to reflect the most recent version of the IB and to provide the most current safety information to the Investigators.
Section 1.4 (Study design): The duration of treatment was removed to allow ongoing treatment. This is based on emerging data that support the use of MEDI4736 beyond 12 months. A statement was added that crossover from Standard of Care (SoC) to either of the immunotherapy treatment arms will not be permitted. The sample size was updated to 1005 patients globally as a result of the addition of co-primary endpoints. Table 1 was revised to include the footnote "Definition of PD-L1 of high versus low/negative expression will be used for stratification and primary analysis. Subset analyses on different definitions of PD-L1 expression may be performed based on emerging data." This change was made to be consistent with the statistical analysis plan. Visceral metastasis was more specifically defined as "presence or absence of lung and/or liver metastasis." Section 1.4 (Study design): Figure 1 (Overall study design) was revised to reflect the increased sample size (1005 patients, 335 per treatment arm) and to add definitions in the footnote. Section 1.4 (Study design): Figure 2 (Study flow chart) was revised to reflect the change to the duration of treatment and add definitions to the footnote.

Section 2 (Study objectives) was revised to include overall survival (OS) as a primary objective with progression-free survival (PFS) based on the emerging immunotherapy data. Section 2.1 (Primary objectives) was revised to include OS in the primary objectives and outcome measures. An explanatory footnote and definitions of abbreviations were also added.
Section 2.2 (Secondary objectives) was revised to reflect the change in primary objectives, add new secondary objectives/outcome measures, and reorder them in order of priority. Redundant objectives were deleted. The previous footnotes for ongoing data analysis and sensitivity analyses for objective response rate (ORR) and duration of response were removed because they are no longer applicable. The Physical Well-Being (PWB) domain of the Functional Assessment of Cancer Therapy - Bladder Cancer (FACT-BL) was replaced with FACT-BL Trial Outcome Index (FACT-BL TOI) as one of the outcome measures because it is a broader concept than PWB, incorporating the Functional Well-Being (FWB) and Bladder Cancer Subscale (BlCS) in addition to PWB. Abbreviations in the table footnote were updated. Section 2.3 (Safety objective): The definitions of abbreviations were added. Section 2.4 (Exploratory objectives) was updated to clarify BICR assessments, to include PWB domain of the FACT-BL, BlCS, and Functional Assessment of Cancer Therapy - General (FACT-G) Total score outcome measures and remove serum PD-L1 and circulating soluble factors as outcome measures. The number of PRO-CTCAE (Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events) symptoms was specified. Additional definitions of abbreviations were added.
Section 3.1 (Inclusion criteria): • Inclusion criterion 3 was revised to include a reference to the National Comprehensive Cancer Network Bladder Cancer Guidelines, revise and clarify the language regarding treatment for locally advanced disease, and clarify that progression is “to Stage IV disease.” • Inclusion criterion 7 was revised to provide a more detailed description of the creatinine clearance level that would render a patient eligible or ineligible for

cisplatin-based therapy and to change the sub-bullet of CTCAE Grade >2 peripheral neuropathy to ≥2. These changes were made for safety and clarity.

- Inclusion criterion 8 was revised to correct that available tumor samples could be taken ≤3 years instead of <3 years prior to screening. A correction was made to the final sentence in this criterion: "eligibility" was corrected to "PD-L1 status."

- Inclusion criterion 9 was revised to provide a more detailed description of the creatinine clearance level that constitutes adequate organ function, and to clarify IVRS data entry requirements This change was made for safety and clarity.

- Inclusion criterion 10 was revised for more detail regarding the definition of women as postmenopausal. Having undergone surgical sterilization, bilateral oophorectomy, bilateral salpingectomy, and hysterectomy was added.

Section 3.2 (Exclusion criteria): The section was generally revised to include abbreviations and terminology per AstraZeneca formatting and standards.

- Exclusion criterion 4 was revised to add the following statement for clarity: "Prior local intervesical chemotherapy or immunotherapy is allowed if completed at least 28 days prior to the initiation of study treatment."

- Exclusion criterion 5 was revised to add the National Cancer Institute (NCI) CTCAE Version (4.03), and the first sub-bullet was corrected from Grade <2 neuropathy to Grade ≥2 neuropathy.

- Exclusion criterion 10 was revised for clarity; "but not limited to" was added, and the phrase "celiac disease, irritable bowel disease, or other serious GI chronic conditions associated with diarrhea" was deleted from the main criterion as well as the qualifier of "within the past 3 years prior to the start of treatment." The following sub-bullets were deleted, edited, or added: "psoriasis requiring systemic treatment" was deleted and replaced with "Any chronic skin condition that does not require systemic therapy." "Patients without active disease in the last 3 years may be included but only after consultation with AstraZeneca" was added. "Patients with celiac disease controlled by diet alone may be included but only after consultation with AstraZeneca" was added. These changes were made

to permit appropriate patients to enter the study while maintaining rigorous safety standards.

- Exclusion criterion 11 was revised for clarity to add "uncontrolled diabetes" and "serious chronic GI conditions associated with diarrhea."

- Exclusion criterion 12 was revised to specify "Other malignancy within 5 years before first dose of IP, except for the following pending a discussion with AstraZeneca:
  -Patients with a history of prostate cancer (tumor/node/metastasis stage) of stage ≤T2cN0M0 without biochemical recurrence or progression and that in the opinion of the Investigator are not deemed to require active intervention"
  -Patients who have been adequately treated for malignancy with a low potential risk for recurrence (eg, cervical carcinoma in situ, non-melanomatous carcinoma of the skin, or ductal carcinoma in situ of the breast that has been surgically cured)."

- Exclusion criterion 14 was revised to provide more specificity regarding brain metastases or spinal cord compression that would exclude a patient and that magnetic resonance imaging (MRI) is the preferred test for patients with suspected brain metastases, preferably with intravenous (IV) contrast. These changes were made for clarity, safety, and consistency.

- Exclusion criterion 15 was revised to specify that a clinically significant electrocardiogram (ECG) abnormality at screening requires triplicate ECG results and a mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs obtained over a brief period (eg, 30 minutes). This change was made as a safety measure.

- Exclusion criterion 17, which had been active tuberculosis, was combined with the following criterion and now reads: "Active infection, including tuberculosis (clinical evaluation **that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice**), hepatitis B, hepatitis C, or human immunodeficiency virus (HIV, positive HIV 1 or 2 antibodies). Active hepatitis B virus (HBV) infection is defined by a positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core IgG antibody and the

absence of HBsAg, deoxyribonucleic acid [DNA] negative) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA)." • Exclusion criterion 18 was revised from MEDI4736 or tremelimumab to "IP" since verifying eligibility occurs before randomization.
Section 3.3 (Patient enrollment and randomization) was revised in Item 1 under randomization to define the SoC "based on cisplatin eligibility." Item 2 was revised to read "Ensure PD-L1 status results are received by the IVRS/IWRS from the central laboratory prior to randomization." Item 3 was revised to define visceral metastases as "metastatic disease in lung and/or liver." PD-L1 status results was deleted from Item 4 since it is now part of Item 2. The next to last paragraph now reads: "**It is strongly recommended that patients commence study drug on the same day as randomization by IVRS/IWRS. If same-day treatment is not possible, then the study treatment must occur within 3 working days of randomization.** Patients must not be randomized unless all eligibility criteria have been met.". Clarifying language was added to ensure that creatinine clearance values obtained closest to Cycle 1 Day 1 be used for the purposes of IVRS data entry and randomization.
Section 3.5 (Methods for assigning treatment arms) was revised to allow study treatment to begin within 3 working days of randomization if same-day treatment is not possible, as specified in Section 3.3. This change was made for flexibility while maintaining temporal proximity to screening findings.
Section 3.8 (Restrictions) was revised and reordered for logic and clarity. Bullet 1 now applies to all patients (in all treatment arms) and specifies restrictions on donating blood or blood components. Bullet 2 is now designated for the immunotherapy treatment arms and specifies that 1 highly effective method of contraception is acceptable and to delete the requirement that female patients use a hormonal method in addition to a barrier method. Table 2 was updated to reflect highly effective methods of contraception. A cross-reference to concomitant medication restrictions was added. Section 3.9 (Discontinuation of investigational product) was revised: Criterion 7 was changed to state that "Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with IP." This change was made to clarify this criterion for discontinuation of IP.

Section 3.9.1 (Procedures for discontinuation of a patient from investigational product) was revised to correct the reason(s) for discontinuation, not withdrawal, and to strongly recommend the Investigator to discuss a patient's case with AstraZeneca prior to discontinuing the patient from the investigational product. This change was made to ensure appropriate action was being taken regarding the patient's care and treatment. The statement "All study drugs should be returned by the patient" was deleted as all study drugs are administered at the investigational site.
Section 3.11 (Discontinuation of the study) was revised to add a cross-reference to Section 6.7.2, the new section heading for the IDMC.
Section 4 (Study plan and timing of procedures), introductory paragraph: The following text was added for clarification: "Patients who continue beyond C13 continue with all C13 assessments until termination of treatment (Table 3)." In addition, in this section and throughout the protocol, clarification was made that PRO and RECIST assessments are based on the randomization date.
Section 4 (Study plan and timing of procedures): Descriptions of assessment timing for all treatment arms and for immunotherapy and SoC treatment arms were added before all the tables of Schedules of Assessments to clarify dosing delays and subsequent assessments. A statement was added to all Schedules of Assessments to clarify timing of assessments relative to dosing cycle and date of randomization. The window of ±3 days and for tumor assessment ±7 days was deleted from within the tables since that is now specified above each table. Bolded subheadings were added for clarification.
For clarity, a footnote was added to Schedule of Assessment Tables 3 through 7 that states "PRO assessment dates remain as originally scheduled, as they are based on the date of randomization (not the date of therapy) and are not affected by dose delays."

Table 3 title was updated to reflect the possibility of extension of treatment beyond Cycle 13. A statement was added above Table 3 to clarify IVRS data entry requirements. Table 3: a row was added for Patient follow-up contact on Day 14 of Cycles 1, 2, and 3. This was added for safety. Vital sign checks at every cycle were added for clarity. Timing of quality-of-life assessments was revised to provide the frequency of these assessments beyond Cycle 13. The liver enzyme panel row was deleted because it is redundant with the complete chemistry panel row immediately above. Other rows deleted for patients enrolled after implementation of this version of the protocol were as follows: serum PD-L1 concentration, circulating soluble factors, PBMCs, and miRNA/mRNA, urine for exploratory biomarkers, SNP genotyping, MDSCs, and PGx sample (optional [DNA] element). A window of ±7 days was added to the row for tumor assessment (computed tomography [CT] or MRI). Specifications in the footnotes regarding "pre-dose" were revised from "within 60 minutes prior to start of infusion" to "may not exceed 6 hours prior to start of infusion" to allow flexibility yet maintain standards of safety and for consistency with changes to Section 5.2 (Safety assessments). Sampling was also revised to specify within "1 hour" of the end of infusion for clarity. Footnotes were re-designated in accordance with deletions of rows and items in the table. Footnote "i" was revised to add "NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***." These changes were made to reinforce the use of validated PRO tools in the study and to ensure that they are administered before any medication infusion. The "retreatment" note was revised to eliminate the limitation of 12 months and to specify that retreatment is only applicable to patients in the MEDI4736 + tremelimumab combination arm. Additional definitions of abbreviations were also added.

Section 4 (Study plan and timing of procedures), Table 4. A statement was added above Table 3 to clarify IVRS data entry requirements. Serum or plasma chemistry checks were revised with Day 2 assessments being deleted because it is no longer necessary. The liver enzyme panel row was deleted because it is redundant with the complete chemistry panel row immediately above. Other rows deleted for patients enrolled after implementation of this version of the protocol were as follows: serum PD-L1 concentration, circulating soluble factors, PBMCs, and miRNA/mRNA, urine for exploratory biomarkers, SNP genotyping, MDSCs, and PGx sample (optional [DNA] element). The tumor assessment row was revised to add a window of ±7 days and to change from "until progression" to "until confirmed disease progression." Footnote "i" was revised to add "NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***." These changes were made to reinforce the use of validated PRO tools in the study and to ensure they are administered before any medication infusion. Other footnotes were renumbered as appropriate. Additional definitions of abbreviations were added.
Section 4 (Study plan and timing of procedures), Table 5. A statement was added above Table 3 to clarify IVRS data entry requirements. The liver enzyme panel row was deleted because it is redundant with the clinical chemistry panel row immediately above. Other rows deleted for patients enrolled after implementation of this version of the protocol were as follows: serum PD-L1 concentration, circulating soluble factors, PBMCs, and miRNA/mRNA, urine for exploratory biomarkers, SNP genotyping, MDSCs, and PGx sample (optional [DNA] element). The second tumor biopsy row was revised for consistency to add" is required." The row for tumor assessment (CT or MRI) was revised from "until progression" to "until confirmed disease progression." Table footnotes were updated for clarity and consistency. Footnote "h" was revised to add "NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***." These changes were made to clarify to the site the use of validated PRO tools in the study to properly record this information.

Footnote "c" was revised to include "LFT results should be available and reviewed by the treating physician or Investigator prior to the start of each chemotherapy cycle, per local routine practice," and to ensure that patients are adequately monitored. Footnote "i" (previously j) was revised to add "Baseline assessments, ideally, should be performed as close as possible prior to the start of study treatment. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of randomization) and no less than 4 weeks after the initial assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database."
Section 4 (Study plan and timing of procedures), Table 6: Serum PD-L1 concentration, circulating soluble factors, PBMCs, and miRNA/mRNA, urine for exploratory biomarkers, SNP genotyping, MDSCs, and PGx sample (optional [DNA] element). Footnote "a" was revised to state "for women of childbearing potential" with the remainder of the text deleted because this is not applicable to this table. Footnote "b" was revised to be 2-monthly calls instead of 3-monthly calls. Footnote "d" was revised to state "Will be collected until the end of the clinical phase of the study (final study visit)." Footnote "h" was revised to add "NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***." These changes were made to reinforce the use of validated PRO tools in the study.
Section 4 (Study plan and timing of procedures), Table 7: Footnote "a" was revised to state "for women of childbearing potential" with the remainder of the text deleted because this is not applicable to this table. Footnote "b" was revised to be 2-monthly calls instead of 3-monthly calls. Footnote "e" was revised to add "NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***." These changes were made to reinforce the use of validated PRO tools in the study and to ensure that they are administered before any medication infusion.

Section 4.1 (Enrollment/screening period): The second sentence of paragraph 2 was revised to specify that all screening/baseline procedures must be performed within 28 days before randomization, with the exception of the patient's tumoral PD-L1 status (must be performed within -56 days before randomization)." This change was made because 28 days of randomization is more appropriate as the first dose may occur up to 3 days after randomization so this was added for clarity and to ensure consistency of the screening activities in relation to the randomization date. Clarifying language was added to ensure that creatinine clearance values obtained closest to Cycle 1 Day 1 be used for the purposes of IVRS data entry and randomization.
Section 4.2 (Treatment period): The section was revised to extend treatment duration beyond Cycle 13 for patients randomized to the MEDI4736 ± tremelimumab or MEDI4736 monotherapy treatment arms and also to add retreatment information "Note that patients randomized to the MEDI4736 ± tremelimumab or MEDI4736 monotherapy treatment arms may continue to be treated beyond Cycle 13. Patients in the MEDI4736 + tremelimumab arm who complete 4 dosing cycles and subsequently have PD during treatment with MEDI4736 alone may restart combination treatment if they meet eligibility criteria for retreatment (see Section 7.2.2) and are deemed to have clinical benefit per Investigator judgment." This revision is based on emerging data that support the use of MEDI4736 ± tremelimumab past 12 months.
Section 4.3 (Follow-up period): The following statement was added: "For patients who require IP treatment to be held for toxicity and subsequently discontinue therapy without restarting IP, all follow-up assessments will be based on the date of the last dose of IP." This change was made for clarification of follow-up assessment timing.

Section 5.1 (Efficacy assessments) was revised for clarity, to specify that PFS2 is defined by local standard clinical practice and to include that all on-study assessments should utilize the same mode of scanning (CT or MRI) as baseline scans for accurate comparisons. The statement "Schedule of required RECIST assessments is based on the date of randomization, not on the date of C1D1" was added for clarity. A window of ±7 days was added for objective tumor assessments every 8 weeks, and that every 8 weeks is relative to the date of randomization and regardless of dosing delays until confirmed disease progression. Criteria for confirmed progression were added for clarity. Retreatment information was also added. Specific criteria for disease progression were added, and clarification was made regarding patients who discontinue treatment. A paragraph was added to allow patients in the combination arm who subsequently have progressive disease during treatment with monotherapy to restart treatment if they meet the eligibility criteria for retreatment specified in Section 7.2.2. Text in the paragraph on patients who achieve and maintain disease control being allowed to restart treatment was deleted, and the rest of the text was moved to the previous paragraph. Minor edits for consistency and clarity were also made in this section.
Section 5.1.1 (Central reading of scans) was revised for clarity to include "and scans from subsequent non-protocol therapy (if required per protocol)," and regarding the collection of scans for analysis, the term "a random sample of patients" was deleted since central reading will apply to all scans. In addition, the basis of the independent reviews was changed from "results of the RECIST assessment" to "local assessments."
Section 5.2.1 (Laboratory safety assessments): Table 8 was revised to allow optional testing of bicarbonate, gamma glutamyltransferase, and total protein in certain countries. Footnote "b" was revised to change from "baseline" to "Screening, Cycle 1 Day 1" for clarity. Table 9 was revised to remove the following hematology tests: Basophils, eosinophils, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, and red blood cell count because these are unnecessary for safety and to reduce the amount of blood drawn from the patients. Laboratory assessments that are not necessary to monitor safety based on the toxicity profile of the IP or SoC arms were removed to reduce patient burden. Clarifying language was added to ensure that creatinine clearance values obtained closest to Cycle 1 Day 1 be used for the purposes of IVRS data entry and randomization.

Section 5.2.4 (Vital signs) was revised for clarity that vital signs, including body weight, will be recorded for all treatment arms at all visits and blood pressure will be performed with the patient supine or semi-supine. These changes were made for safety purposes and clarity. Additional clarification was made for patients in the immunotherapy treatment arms for the first infusions, and redundant text was deleted. A paragraph specifying collection and measurement of blood pressure and pulse measurements was added for completeness and clarity, and a paragraph specifying monitoring of MEDI4736 combination and monotherapy patients at subsequent infusions was added for completeness and clarity.
A new paragraph providing the same level of detail for vital sign collection was added for patients in the SoC treatment arm for completeness and clarity.
Section 5.2.5 (Other safety assessments): A paragraph was added for additional safety monitoring: "If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix G) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes, such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines (Appendix G) should be followed."
Another paragraph was added (including emphasis) for patients to be contacted 2 weeks after receipt of the first 3 cycles of study drug: "**It is strongly recommended that patients are contacted 2 weeks after receiving the first 3 cycles (Cycle 1 Day 14, Cycle 2 Day 14, and Cycle 3 Day 14) of study drug(s) to ensure early identification and management of toxicities**." This was done to ensure early identification of toxicities.
Section 5.3.1 (Patient-reported outcomes): All subsections were updated to reference "Appendix F" and for clarity a statement was added that PRO assessment dates are based on the randomization date.
Section 5.3.1.3 (PGIC) was revised to add that PGIC was added "for assessing the overall impact of treatment."

Section 5.3.2 (Administration of the patient-reported outcome questionnaires): The first bullet was revised to add "including medication infusion(s)" for clarification. The fifth bullet had the following text added for clarification and consistency: "All questionnaires must be completed using the ePRO device; paper questionnaires are not allowed in this study." These changes were made to clarify that PROs must be administered electronically and before medication infusion.
Section 5.4.2 (Collection of samples to measure the presence of ADAs) was revised to specify blood draw volume.
Section 5.4.3 (Storage and destruction of pharmacokinetic/ADA samples): The first paragraph was revised to allow retention for 15 years from the last patient's last visit date for research purposes.
Section 5.5 (Biomarker analysis) and Table 11: The following sentence was added "Based on availability of tissue, additional exploratory biomarkers may also be evaluated as described in Section 5.5.1.1." Paragraph 3 regarding additional exploratory biomarkers was deleted as these are no longer being collected. The table of timepoints and blood and urine volumes was deleted for the same reason. These exploratory biomarkers were removed to lessen patient burden. The statement of how sPD-L1 concentration will be measured was deleted because that is no longer being performed. Bullet 2 paragraphs 3 and 4 were revised to replace "eligibility" with "PD-L1 status." These changes were made for clarity.
Section 5.5.1 (Evaluation of candidate, predictive markers - tumor PD-L1), Bullet 3 of paragraph 1 was revised to add the phrase "and acceptable tissue sampling" at the end of the paragraph for completeness regarding the contents of the Laboratory Manual. The wording of when the Investigator consults with AstraZeneca was revised from "must" to "should." Following the bullets, the first paragraph was revised to add that PD-L1 status for stratification will be used "to evaluate potential predictive biomarkers." Paragraph 5 was revised to delete the statement regarding RECIST 1.1 target lesions and added specification regarding use of core needle and the timing before imaging scans are acquired.

Subsection 5.5.1.1 (Exploratory biomarker data): This was revised to specify that only tumor and/or blood samples obtained prior to implementation of this version of the protocol will be used for exploratory biomarker analyses in selected countries only. This was a result of the decision to delete sampling for PD-L1, PK, PGx, and soluble factors. The pharmacodynamic changes in biomarker measures paragraph was revised to delete the note "Samples will be obtained from patients randomized to each treatment arm" since they are no longer being collected. The sentence regarding data comparison was revised to include comparison across times of treatment. The statement regarding "similar comparisons" of baseline measures was deleted as those are no longer planned.
Subsection of 5.5.1.1, Tumor markers (in FFPET) was revised to delete the statement regarding CD8 and CD4/FoxP3 and add the statement that "Markers evaluated may change based on the best available information at the time of the biomarker analysis." The second paragraph of the subsection was revised to add that tissues may be assessed for tumor burden and neo-antigen prediction," to delete "CXCL10," and to add "LAG3 and CD274." The remainder of the sentence was deleted and replaced with "targeted RNAseq and/or other gene expression methodologies" as a refinement of what tumor markers will be analyzed and how. The next paragraph heading was revised from "Whole blood for DNA" to "When available, genomic DNA" in recognition that this will apply only to patients enrolled prior to the implementation of this version of the protocol. This statement was added to the next paragraph.
The paragraph regarding genotype correlation was deleted as was the heading "Whole blood gene expression (PaxGene RNA)" and the first sentence under that heading.
The bolded section "Myeloid-derived suppressor cells" was revised to state that flow cytometry may be completed on available patient samples obtained prior to the implementation of this version of the protocol and delete analysis of MDSC count thresholds.

The bolded subsection "Peripheral blood mononuclear cells" was revised to add "Soluble factors (plasma)" to the heading and reduce the number of potential downstream analyses. The separate bolded subsection heading "Soluble factors (plasma)" was deleted as was the first paragraph, which was replaced with "Plasma will be obtained to explore expression of cytokines and chemokines, including but not limited to IFN-γ, interleukin (IL)-18, CXCL9, and CXCL10." The paragraph on use of plasma for detection/quantification of autoantibodies was deleted, as these tests are no longer being performed.
The bolded subsection "Urine-based markers" was revised to state that the samples will be used to explore gene expression analyses as well as cytokine/chemokine analyses and delete the remainder of the specifications.
Section 5.5.3 (Storage, re-use, and destruction of biological samples) was revised for clarity regarding the length of time the biological samples will be retained.
Section 5.6 (Pharmacogenetics) was deleted as these samples are no longer being collected.
Section 6.1 (Definition of adverse events) was revised for clarity that a pre-existing medical condition does not include the progression of the malignancy under evaluation.
Section 6.3.1 (Time period for collection of adverse events) was revised to include the adverse event (AE) and serious adverse event (SAE) follow-up period for all treatment arms and that AEs and SAEs collected prior to randomization will be reported as pre-randomization AEs and SAEs for clarity.
Section 6.3.4 (Relationship to protocol procedures) was revised to add "and after an informed consent has been signed" into the parenthetical about SAEs that occur prior to the administration of IP to clarify that informed consent must be signed before administration of IP.
Section 6.3.7 (Hy's Law) was revised for clarity and to reference "Appendix D."
Section 6.3.8 (Disease progression) was revised for clarity to include "or SAE" regarding metastasis to the primary cancer under study being considered disease progression and not an AE or SAE.

Section 6.3.10 (Deaths) "Safety Physician" was revised to "monitor" throughout this section for clarity of reporting, and the final phrase of Bullet 2 was revised to "and should assign a single main cause as well as any contributory causes of death."
Section 6.4 (Reporting of serious adverse events) was revised to include "including supporting data" to be recorded in the eCRF and also include instructions to enter into the eCRF any follow-up information on a previously reported SAE.
Section 6.5 (Overdose) was revised to add information on overdose treatment for patients randomized to SoC and recording of an overdose for safety and clarity.
Section 6.7 (Management of IP-related toxicities) was revised to add "IP-related," delete the specification regarding continuing "the same dose of the" IP, and add a bolded bullet specifying "**It is important to note that these Guidelines are prepared by the Sponsor to assist the Investigator in the exercise of his or her clinical judgment in treating these types of toxicities.**" A statement was made that all toxicities will be graded according to NCI CTCAE Version 4.03, and a paragraph was added referencing the IB for MEDI4736 and tremelimumab and the Dosing Modification and Toxicity Management Guidelines. An explanatory statement regarding the guidelines was added. Outdated and redundant text was deleted.
The heading "MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy adverse events of special interest" was added, and updated information for adverse events of special interests (AESIs) for MEDI4736 ± tremelimumab was added, including a bulleted list of AESIs observed with MEDI4736 ± tremelimumab. These changes were made for clarity and safety, and outdated and redundant information was deleted. The last paragraph was expanded to provide for postponing dosing.
The heading 6.8 (Study governance and oversight) was deleted, and the heading 6.7.2 "IDMC" was added for clarity. Section 6.7.2 paragraph 2 the timing of the second IDMC meeting was changed to "approximately" 3 months after the first IDMC meeting or when 90 patients are enrolled, whichever occurs first.
Section 7.1 (Identity of investigational products) and subsections were revised to update the investigational product information.

Section 7.2.1 (Treatment regimens): Text and Figure 3 and Figure 4 were revised to reflect that dosing may continue beyond Cycle 13, and a paragraph was added to include more specific information on patients who are deemed by the Investigator as unable to tolerate a cisplatin regimen for clarity and as a safety measure. A new paragraph was added regarding changing from cisplatin to carboplatin: "Patients randomized to the SoC arm with cisplatin and gemcitabine who receive at least 1 cycle of cisplatin and gemcitabine and by physician's determination are unable to tolerate subsequent cisplatin cycles will be allowed to change from cisplatin to carboplatin 1 time. The criteria justifying the change from cisplatin to carboplatin during study treatment must be documented in the eCRF."
Section 7.2.2 (Duration of treatment, criteria for retreatment, and treatment through progression) was edited to revise the Section title and to add in italicized subheadings for clarity. In addition, the limit of 12 cycles of treatment was deleted to allow continued study treatment at the Investigator's discretion and to include retreatment information. These changes were based on emerging data that support the use of MEDI4736 past 12 months. Revisions were made to clarify the criteria for retreatment (an italicized subheading, "Retreatment"). Italicized subheading "Criteria for retreatment and treatment through progression" was added, new text was added, and the existing text under this subheading was revised for clarity and completeness. The statement regarding continued safety monitoring and follow up for patients who discontinue treatment due to toxicity or symptomatic deterioration or who commenced subsequent anticancer therapy was revised for clarity. Outdated and redundant text was deleted.
Section 7.3 (Labeling) was revised to include Japan and other countries.
Section 7.6 (Accountability) was revised to remove the sentence that it is the responsibility of the Investigator to ensure that the patient has returned all unused study drug because this is not applicable since the study drugs are administered intravenously.
Section 7.7 (Concomitant and other treatments) was revised for clarity and to include collection of data for safety purposes regarding herbal and natural remedies and palliative treatment for oncologic emergencies and the reason they were prescribed. The table of prohibited medication/class of drug was revised for completeness.
Section 7.8 (Post-study access to study treatment) was revised to reflect the change in the duration of treatment.

Section 8.2 (Sample size estimate): Changes were made to sample size (approximately 1340 patients enrolled to randomize 1:1:1 approximately 1005 patients over a period of 16 months, with approximately 335 patients being randomized to each treatment arm. Explanation of the sample size was added, and corresponding changes throughout the section were made for consistency. Also revised and/or added were the timing of the final analysis of PFS, the final analysis of OS, and a second interim analysis; specifications for all of these factors are provided.
Section 8.2 (Sample size estimate): Sections on MEDI4736 versus SoC (OS in PD-L1-High UC) and MEDI4736 versus SoC (PFS in PD-L1-High UC) were added. Throughout the statistical section, changes were made to reflect the change in PD-L1 terminology from positive or negative to High or Low/Neg.
Section 8.3 (Definitions of analysis sets): Table 11 was revised to add OS as an outcome variable in addition to PFS.
Section 8.4.1 (Calculation or derivation of efficacy variables) and subsection 8.4.1.2 (Co-primary endpoints: Progression-free survival) were revised for clarity and to change the analysis of PFS by the "Investigator" to by "BICR" as a more rigorous standard. PFS analysis will be based on full Blinded Independent Central Review (BICR) data instead of site Investigator data (with a BICR random sample).
Subsection 8.4.1.1 (RECIST 1.1-based endpoints) was revised to move the new bolded subsection "Blinded Independent Central Review of RECIST 1.1-based assessments." The statement regarding prior radiotherapy reports was deleted, consistent with BICR strategy as outlined in the Imaging Charter.
Subsection 8.4.1.2 (Co-primary endpoints) heading was revised from "primary" to "co-primary" endpoints and to clearly state the co-primary endpoints. The section was also revised to change the analysis of PFS by the "Investigator" to by "BICR" as a more rigorous standard. The rules for the determination of date of progression by the reviewer were revised for clarity. The section was also updated to move subsection "Overall survival" from the secondary endpoints to the co-primary endpoints section. Additional text clarifying how the date of progression will be determined was added.
Section 8.4.1.3 (Secondary endpoints) was revised to delete "Overall survival" since it is now a co-primary endpoint and no longer a secondary endpoint.

Subsection 8.4.1.3 (Secondary endpoints: Proportion of patients alive and progression free at 12 months, Objective response rate, and Duration of response) was revised to change the analysis of PFS by the "Investigator" to by "BICR" as a more rigorous standard.
Subsection 8.4.1.3 (Secondary endpoints: Objective response rate) was revised to remove the description of the algorithm for ORR. Subsection 8.4.1.3 (Duration of response) was revised for assessment by BICR and delete the description of the algorithm regarding DoR.
Subsection 8.4.1.3 (Secondary endpoints: Disease control rate) was revised to change the duration of stable disease from"52 weeks" to "48 weeks," and days were revised accordingly. Analysis of PFS by the "Investigator" was changed to by "BICR" as a more rigorous standard to support the Phase 3 study. Information for unconfirmed disease progressions was removed.
Subsection 8.4.1.3 (Secondary endpoints: Best objective response) was revised for clarity, and the analysis of PFS by the "Investigator" was changed to by "BICR" as a more rigorous standard. The latter part of the paragraph on BoR being determined programmatically was deleted as redundant.
Section 8.4.3 (Calculation or derivation of patient-reported outcome variables) was edited for clarity and to delete the redundant use of "questionnaires." Subsection 8.4.3.1 (FACT-BL): The subsection was revised for clarity and to include the FACT-BL TOI as the sum of PWB, FWB, and BlCS and to detail the use of TOI as an efficient summary index for clinical trials. Subsection 8.4.3.1 (FACT-BL: HRQoL visit responses) was updated to reference "Appendix F."
Section 8.4.3.2 (PGIC) was revised to specify that "Very Much Improved and Much Improved" categories will be grouped and compared with the other response categories grouped.
Section 8.4.6 (Calculation or derivation of pharmacogenetic variables) was revised to include the statement "obtained prior to implementation of this version of the protocol" because no new samples will be taken after this version is implemented.

Section 8.5 (Methods for statistical analyses) was revised to include OS as a co-primary endpoint with PFS. The number of PFS and the number of OS events were updated with the most recent data, and the terminology for PD-L1 status was updated. Section 8.5 (Methods for statistical analyses): Table 12 was revised to change the analysis of PFS by the "Investigator" to by "BICR" as a more rigorous standard to support the Phase 3 study. A secondary analysis using stratified log-rank test was added for OS. OS co-primary analysis using a stratified log-rank test for combination therapy and monotherapy versus SoC (intent-to-treat and PD-L1-High populations, respectively) was added, as was a secondary PFS analysis using BlCR tumor data: "MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1-High population)." The following analyses were added: "MEDI4736 monotherapy versus SoC (ITT population); MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1-Low/Neg population); MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (PD-L1-Low/Neg population) MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (ITT population)." The following other analyses were added: "MEDI4736 monotherapy versus SoC (ITT population); MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1-Low/Neg population); MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (PD-L1-Low/Neg population); MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (ITT population)." Changes were also made for DoR, BoR, and PROs in accordance with changes made elsewhere regarding statistical methodology. Abbreviations were added to the table.
Section 8.5 (Methods for statistical analyses): "Multiple testing strategy" was updated to include additional hypothesis testing and details of the analysis of OS and interim analyses for clarity. Section 8.5 (Methods for statistical analyses): Figure 5 was updated.

Section 8.5.1 (Progression-free survival) was revised to change the heading from "Analysis of the primary variable" to "Progression-free survival." Analysis of PFS by the "Investigator" was changed to by "BICR" as a more rigorous standard. The percent confidence interval was changed from "95%" to "99%," and the secondary PFS analysis was removed. An exploratory analysis of PFS using the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) data obtained from the BICR was added. Secondary analysis of PFS based on the programmatically derived RECIST 1.1 using the Investigator tumor assessments was removed and replaced with a secondary analysis of PFS based on the programmatically derived RECIST 1.1 using the BICR data, and details on the analysis were added. Obsolete and redundant text was deleted. The description of the estimation of the HR and its CI was revised to state it will be estimated form the stratified Cox proportional hazards model and the Cox 1972 reference was added here and in the References section.
Section 8.5.2 (Overall survival) was revised for OS as a co-primary endpoint. Assumption of proportionality, sensitivity analysis, and subgroup analyses were added.
Section 8.5.5 (Objective response rate) was revised to change the analysis of PFS by the "Investigator" to by "BICR" as a more rigorous standard. ORR sensitivity analysis was removed since it is no longer needed.
Section 8.5.6 (Duration of response) was revised, deleting detailed analyses and stating that "Descriptive data will be provided for the DoR in responding patients." This programmatic change resulted in deletion of the Ellis et al 2008 reference.
Subsection 8.5.9.1 (FACT-BL) was revised to include the FACT-BL TOI and the FACT-G Total score, to delete the PWB for the secondary endpoints and put the PWB as an exploratory endpoint, and to delete the TOI from the exploratory endpoints.
Subsection 8.5.10 (Healthcare resource use [HOSPAD]) was revised to specify that "The module is for all non-study protocol-related hospital admissions; any routine hospital visits for study protocol-related requirements do not need to be captured."
Subsection 8.5.15 (Interim analyses) was revised to include an additional interim analysis of OS, and details of the interim analyses were included.

Section 10.3 (Ethic and regulatory review) was revised to include Japan and other countries where applicable, and Institutional Review Board and informed consent form information was added.
Section 10.4 (Informed consent) was revised from "Japan sites only" to "Japan and other countries where this is applicable."
Section 11 (List of references) was updated to include references for "Fleischer et al 2011, Cox 1972, and Investigator Brochures for Tremelimumab and Durvalumab" and delete reference to Ellis et al 2008.
Appendices A, B, C, D, E, F, G, and H were inserted into the document.
In Appendix C (Pharmacogenetics Research) the sentence referring to blood volume specifications in the protocol was deleted as no new samples will be taken upon implementation of this version of the protocol.
In Appendix D, "Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law," a cross reference to Appendix G was added for clarity.

Appendix E (Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria [Response Evaluation Criteria in Solid Tumors]): In Section 2, the footnote was expanded for clarity; under Target lesions, clarification was provided regarding considering lymph nodes as a single organ. Section 3.1 (CT and MRI) was revised to add "each preferably with IV contrast" for CT and MRI and equivalent changes throughout the appendix. Additional detail was added regarding patients who are sensitive to IV CT contrast as well as recommendations to maintain the same imaging modality across all imaging timepoints; "is not feasible or it is medically contra indicated" was changed to "cannot be performed" for clarity. In Section 3.7, clarifying text regarding cytological confirmation of the neoplastic origin of any effusion was added. In Section 3.9, a paragraph was added regarding a recommendation not to use combined ^{18}F-Fluoro-deoxyglucose positron emission tomography (FDG-PET)/CT. In Section 4.2.1, clarifying language regarding lymph nodes considered as a single organ was added, and the last bullet was revised to include "and the intervention recorded in the RECIST eCRF." In Section 4.5, second paragraph, "regularly scheduled" was added before "tumor assessments" for clarity. In Section 5, italics were added to the bullets for emphasis, and "target lesion" was added before "diameters" for clarity. In Section 5.1, "anatomical" was added before "sites" in paragraph 3 for clarity. In Section 6, the following text was added: "All images will be collected, quality checked, and stored centrally by an Imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. The management of patients will be based solely upon the local assessments conducted by the Investigator.
Further details of the BICR will be documented in the Independent Review Charter (also referred to as 'Imaging Charter')."
Appendix F (Patient-reported outcomes questionnaires) cover page was revised to add the individual patient-reported outcome assessment questionnaires: FACT-BL, PRO-CTCAE, PGIC, and EQ-5D-5L.
Appendix H (Amendment 1 Summary of Changes) was added to include the summary of changes for Amendment 1 as an appendix instead of in the version history section.

Clinical Study Protocol (Japan) version 3, 2 October 2015
Clinical Study Protocol Amendment J2 For changes to the protocol, refer to the above document.
Clinical Study Protocol (Japan) version 2, 14 September 2015
Clinical Study Protocol Amendment J1 For changes to the protocol, refer to the above document.
Clinical Study Protocol (Japan) version 1, 7 August 2015
Revised Clinical Study Protocol 1 (Translation only)

Version 2, 07 August 2015 Amendment 1.
The summary of changes for Amendment 1 is provided in Appendix H.

Version 1, 28 July 2015
Initial creation.

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study 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.

PROTOCOL SYNOPSIS

A Phase III, Randomized, Open-Label, Controlled, Multi-Center, Global Study of First-Line MEDI4736 Monotherapy and MEDI4736 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Cancer

International coordinating investigator

Professor Thomas Powles, Clinical Professor of Genitourinary Oncology, Barts Cancer Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ

Study site(s) and number of patients planned

The study will plan to enroll approximately 1340 patients globally in order to randomize (1:1:1) approximately 1005 patients to MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or Standard of Care (SoC) (cisplatin + gemcitabine or carboplatin + gemcitabine) over a period of 16 months. Therefore, approximately 335 patients will be randomized to each of the treatment arms. Closing of global cohort enrollment will be defined as closing recruitment across all sites except for those located in China. The global ITT population will include all patients randomized into global cohort. Once global enrollment has ended, recruitment into an expansion cohort will continue in China until approximately 180 Chinese patients have been randomized. Identification of China cohort patients will be clearly defined in SAP and by distinct Subject ID

Study period		Phase of development
Estimated date of first patient enrolled	Q3 2015	III
Estimated date of last patient completed	Q3 2019	III

In Japan, this study will be started after the confirmation of tolerability of MEDI4736 (1.5 g q4W) + Tremelimumab (75 mg q4W) combination therapy in study D4880C00010 which is currently conducted in Japan.

Study design

This is a randomized, open-label, controlled, multi-center, global Phase III study to determine the efficacy and safety of MEDI4736 monotherapy (1.5 g intravenous [IV] every 4 weeks [q4w]) and MEDI4736 (1.5 g IV q4w) in combination with tremelimumab (75 mg IV q4w) for up to 4 doses/cycle each followed by MEDI4736 (1.5 g IV q4w) versus SoC

(cisplatin + gemcitabine or carboplatin + gemcitabine doublet) first-line chemotherapy in treatment-naïve patients with histologically or cytologically documented, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3; or M1) transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra) and to allow sufficient flexibility for Investigators and patients to select the agents that reflect their normal clinical practice and national guidelines.

The patients enrolled in the study will be randomized (1:1:1) to treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC (cisplatin + gemcitabine or carboplatin + gemcitabine, based on cisplatin eligibility). Crossover from SoC to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy will not be permitted. Patients will be stratified according to cisplatin eligibility (eligible or ineligible), programmed cell death ligand 1 (PD-L1) status (High or Low/Neg, based on Ventana assay), and visceral metastasis (presence or absence of lung and/or liver metastasis). Tumor assessments will be performed every 8 weeks (q8w; ±7 days) relative to the date of randomization until confirmed disease progression (patients enrolled in the platinum-gemcitabine arm [SoC] will discontinue study drug at the first assessment of disease progression) according to the objective tumor response by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).

Objectives

Primary objectives:	**Outcome measures:**
To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS in patients with unresectable Stage IV UC	OS
To assess the efficacy of MEDI4736 monotherapy versus SoC in terms of OS in patients with unresectable Stage IV PD-L1-High UC	OS

OS Overall survival; PD-L1 Programmed cell death ligand 1; SoC Standard of care; UC Urothelial cancer.

Secondary objectives:	**Outcome measures:**
To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of PFS in patients with PD-L1-High UC	PFS using Investigator assessments according to RECIST 1.1 [a]
To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of PFS in patients with UC	PFS using Investigator assessments according to RECIST 1.1 [a]

Secondary objectives:	**Outcome measures:**
To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of PFS and OS in patients with UC	PFS using Investigator assessments according to RECIST 1.1 [a] OS
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of PFS and OS in patients with PD-L1-Low/Neg UC	PFS using Investigator assessments according to RECIST 1.1 [a] OS
To assess the efficacy profile of MEDI4736 monotherapy in patients who are not cisplatin-eligible	ORR, DoR, DCR, TTR, and PFS, using BICR assessments according to RECIST 1.1[b] OS
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in terms of PFS, OS, OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with PD-L1-Low/Neg UC and all patients with UC	OS OS24 PFS, APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with UC	OS24 APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with PD-L1-High UC	OS24 APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with UC	OS24 APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with PD-L1-Low/Neg UC	OS24 APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in patients with PD-L1-High UC	PFS, APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] OS and OS24 PFS2 as defined by local standard clinical practice

Secondary objectives:	Outcome measures:
To assess disease-related symptoms and HRQoL in UC patients treated with MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared with SoC and each other using the FACT-BL questionnaire	FACT-BL: Fatigue, Pain, Derived NFBlSI-18 score, FACT-BL TOI, and FACT-BL Total score
To assess the PK of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Serum concentration of MEDI4736/tremelimumab PK parameters (such as peak concentration and trough, as data allow; sparse sampling)
To investigate the immunogenicity of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Presence of ADAs for MEDI4736 and tremelimumab (confirmatory results: positive or negative)

a The analysis will be based on programmatically derived investigator assessments according to RECIST 1.1. See Section 8 for further details.
b The analysis will be based on programmatically derived BICR assessments according to RECIST 1.1. See Section 8 for further details.

ADA Antidrug antibody; APF12 Proportion of patients alive and progression free at 12 months from randomization; BICR Blinded Independent Central Review; DCR Disease control rate; DoR Duration of response; FACT-BL Functional Assessment of Cancer Therapy - Bladder Cancer; FACT-BL TOI Functional Assessment of Cancer Therapy - Bladder Cancer Trial Outcome Index; HRQoL Health-related quality of life; NFBlSI-18 National Comprehensive Cancer Network - FACT Bladder Symptoms Index-18; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomization; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PFS2 Time from randomization to second progression; PK Pharmacokinetics; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SoC Standard of care; TTR Time to response; UC Urothelial cancer.

Safety objective:	Outcome measures:
To assess the safety and tolerability profile of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC	AEs, laboratory findings, vital signs, and ECGs
To assess the safety and tolerability profile of MEDI4736 monotherapy and SoC in patients who are not cisplatin-eligible	AEs, laboratory findings, vital signs, and ECGs

AE Adverse event; ECG Electrocardiogram; SoC Standard of care.

A further objective to meet China FDA requirement is to evaluate consistency in efficacy and safety among Chinese subjects for benefit-risk assessment of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC.

Target patient population

Adult patients (age ≥18 years) with histologically or cytologically documented, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3; or M1) transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal

pelvis, ureters, urinary bladder, and urethra), who have not been previously treated with first-line chemotherapy.

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

Duration of treatment

Patients randomized to the MEDI4736 + tremelimumab combination therapy and the MEDI4736 monotherapy arms will begin treatment on Day 1 until progressive disease (PD) is confirmed, unacceptable toxicity occurs, withdrawal of consent, or another discontinuation criterion is met. According to RECIST 1.1 modified for confirmation of progression, a confirmatory scan will be required following an overall timepoint assessment of progression, preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

Patients randomized to treatment in the SoC arm (cisplatin + gemcitabine or carboplatin + gemcitabine) will begin treatment on Day 1 for up to 6 cycles until the first assessment of disease progression or until unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. A confirmatory scan will not be required if PD is identified on the SoC arm in order to discontinue treatment; however, a confirmatory scan is required following an overall timepoint assessment of initial progression, even if a subsequent treatment is started, and no earlier than 4 weeks after the previous assessment of PD.

Retreatment

Patients randomized to the MEDI4736 + tremelimumab combination therapy arm who meet the retreatment criteria (described below) may receive retreatment 1 time at the Investigator's discretion. During retreatment, patients will follow the same schedule of assessments as the original treatment period (with the exception of the pharmacokinetics and anti-drug antibody assessments, Hepatitis B and C assessments, and HIV assessments which do not need to be collected a second time):

- Patients who complete the 4 dosing cycles of the combination of durvalumab (MEDI4736) and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment) but subsequently have evidence of PD during the durvalumab (MEDI4736) monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

- Patients who restart treatment after PD must have a baseline tumor assessment within 28 days of restarting treatment with MEDI4736 + tremelimumab combination therapy; all further scans will occur q8w (±7 days) relative to the date of randomization until disease progression

Criteria for retreatment and treatment through progression

Treatment through progression in either the MEDI4736 monotherapy arm, the MEDI4736 + tremelimumab combination therapy arm, or retreatment in the MEDI4736 + tremelimumab combination therapy arm are at the Investigator's discretion. The Investigator will ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not provide further benefit to patients. Moreover, these patients must meet the following specific criteria for treatment in the setting of PD:

- Written informed consent for retreatment and/or treatment through progression in the setting of PD will specify that treatment beyond evidence of initial PD is not the SoC and that alternative treatment options, including either locally licensed treatments or other clinical trials, are available for this patient population

- Absence of clinical symptoms or signs (including worsening of laboratory values [eg, new or worsening hypercalcemia]) indicating clinically significant disease progression and no decline in Eastern Cooperative Oncology Group performance status that can be attributed to disease progression

- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis or respiratory failure due to tumor compression or spinal cord compression) that cannot be managed by protocol-allowed medical interventions

- However, a patient in the MEDI4736 monotherapy arm with confirmed disease progression will not be permitted to continue therapy with MEDI4736 if disease progression occurred after confirmed response (complete response [CR] or partial response [PR], as defined by RECIST 1.1) in the target lesions. Additionally, a patient in the MEDI4736 + tremelimumab combination treatment arm with confirmed disease progression during the combination portion of therapy that occurred after confirmed response (CR or PR, as defined by RECIST 1.1), will not be permitted to continue immunotherapy if disease progression occurred in the target lesions that previously responded to immunotherapy.

Retreatment is not permitted for patients in the SoC arm.

Patients whom AstraZeneca and the Investigator determine may not continue treatment after PD will enter follow-up. All 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.

Investigational product, dosage, and mode of administration

MEDI4736 monotherapy

- MEDI4736 1.5 g via IV infusion q4w, starting on Week 0

MEDI4736 + tremelimumab combination therapy

- MEDI4736 (1.5 g via IV infusion q4w) over a 1-hour period in combination with tremelimumab (75 mg IV q4w) over a 1-hour period for up to 4 doses/cycle each, followed by MEDI4736 (1.5 g IV q4w) until confirmed progression or until other discontinuation criteria are met. The first MEDI4736 monotherapy dose (1.5 g IV q4w) will be administered 4 weeks after the final dose of MEDI4736 in combination with tremelimumab.

- Tremelimumab will be administered first; the MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion. If there are no clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of MEDI4736 can be given immediately after the tremelimumab infusion has finished.

SoC

Patients eligible for cisplatin will receive 1 of 2 gemcitabine + cisplatin options:

1. IV infusions of cisplatin 70 mg/m^2 on Day 2 of each 28-day cycle + gemcitabine 1000 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle, for up to 6 cycles or

2. IV infusions of cisplatin 70 mg/m^2 on Day 1 of each 21-day cycle + gemcitabine 1000 to 1250 mg/m^2 on Days 1 and 8 of each 21-day cycle, for up 6 cycles

Patients in the SoC arm who are ineligible for cisplatin will receive IV infusions of carboplatin with an area under the curve (AUC) of 4.5 to 5 (AUC 4 is permitted only if required by local standard clinical practice) on Day 1 of each 21-day cycle + gemcitabine 1000 mg/m2 on Days 1 and 8 of each 21-day cycle, for up to 6 cycles. In a rare scenario, if at the Investigator's discretion, patients in the SoC arm who have not progressed continue the SoC treatment beyond 6 cycles, the exposure information will be reported in exposure eCRF and the schedule of assessments beyond 6 cycles will be the same as the one for the treatments within 6 cycles.

Statistical methods

The primary objectives of this study are to assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of overall survival (OS) in patients with unresectable Stage IV urothelial cancer (UC) and to assess the efficacy of MEDI4736 monotherapy versus SoC in terms of OS in patients with unresectable Stage IV PD-L1-High UC.

OS is defined as the time from the date of randomization until death due to any cause. Thus, the co-primary endpoints of this study are OS in patients with UC and OS in patients with unresectable Stage IV PD-L1-High UC. To control Type I error, the 5% alpha will be split into significance levels of 1.5%, and 3.5% and will be used for the analysis of OS in patients with UC and OS in patients with PD-L1-High UC, respectively. The study will be considered positive (a success) if either of the OS analysis results (in patients with UC or in patients with PD-L1-High UC) is statistically significant.

Secondary efficacy analyses include OS for MEDI4736 monotherapy versus SoC in patients with UC, OS for MEDI4736 + tremelimumab combination therapy versus SoC in patients with PD-L1-Low/Neg UC, the proportion of patients alive at 24 months from randomization (OS24), progression free survival (PFS), proportion of patients alive and progression-free at 12 months from randomization (APF12), objective response rate (ORR), duration of response (DoR), disease control rate (DCR), and time from randomization to second progression (PFS2) in the above populations, as well as ORR, DoR, DCR, time to response (TTR), PFS and OS in the MEDI4736 monotherapy treated UC patients who are not eligible for cisplatin-based treatment at baseline (per eCRF). All tumor assessment-related endpoints will be assessed by Investigator except these defined for the subgroup of MEDI4736 monotherapy treated UC patients who are not eligible for cisplatin-based treatment.

Unless otherwise specified, efficacy data will be summarized and analyzed on an intent-to-treat (ITT) basis, and the treatment arms will be compared on the basis of randomized treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.

Approximately 1005 patients will be randomized globally 1:1:1 to MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC. The randomization will be stratified according to cisplatin eligibility (eligible or ineligible), PD-L1 status (High and/or Low/Neg), and visceral metastases (presence or absence of lung and/or liver metastasis). PD-L1 status stratification will be based on natural prevalence rates. Randomization of cisplatin-eligible patients will be capped at a maximum 85% of the planned total number of patients.

The final analysis of OS will be performed when approximately 327 target OS events (81% maturity) have occurred in PD-L1-High UC patients treated across the MEDI4736 monotherapy and SoC treatment arms.

Two interim analyses will be performed. The first interim (Interim 1) will focus on ORR and DoR in patients who are not cisplatin-eligible and treated with MEDI4736 monotherapy, and the second interim (Interim 2) will focus on co-primary OS endpoints. Interim 1 will be conducted when all patients in the global cohort have at least 6 months follow-up.

For the co-primary OS endpoints in the ITT population (MEDI4736 + tremelimumab combination therapy versus SoC), 1 interim analysis will be undertaken, and the interim analysis for OS endpoint in the PD-L1-High population (MEDI4736 monotherapy versus SoC) will be conducted at the same time:

- The OS interim analysis (Interim 2) will be conducted when approximately 80% of target OS events have occurred in UC patients treated across the MEDI4736 + tremelimumab combination therapy and SoC treatment arms (440 events, 66% maturity); AND in PD-L1-High UC patients treated across the MEDI4736 monotherapy and SoC treatment arms (262 events, 65% maturity).

For the co-primary OS endpoint in the ITT population (MEDI4736 + tremelimumab combination therapy versus SoC), if exactly 80% of the target OS events are available at the time of the interim analysis (ie, 440/550 deaths have occurred), with an overall 2-sided alpha level of 1.5%, the 2-sided alpha to be applied at the OS interim analysis would be 0.56%. The 2-sided alpha to be applied for the final OS analysis would be 1.33%.

For the co-primary OS endpoint in the PD-L1-High population (MEDI4736 monotherapy versus SoC), if exactly 80% of the target OS events are available at the time of the interim analysis (ie, 262/327 deaths have occurred), with an overall 2-sided alpha level of 3.5%, the 2-sided alpha to be applied at the OS interim analysis would be 1.58%. The 2-sided alpha to be applied for the final OS analysis would be 3.03%.

MEDI4736 + tremelimumab versus SoC (OS in all-comers UC)

If OS at 12 months was 55% with MEDI4736 + tremelimumab combination therapy (with 14.8-month median OS) and 48% with SoC (with 11.3-month median OS) and assuming the true average HR is 0.73, then the trial will have at least 87% power to demonstrate statistical significance at a 2-sided alpha level of 1.33% (with overall alpha for OS of 1.5%) for the comparison of MEDI4736 + tremelimumab combination therapy versus SoC, with the smallest treatment difference that could be statistically significant being an average HR of 0.81. With a 16-month recruitment period and a minimum follow-up period of 30 months assumed, it is anticipated that this analysis will be performed approximately 46 months after the first patient has been randomized.

MEDI4736 versus SoC (OS in PD-L1-High UC)

If OS at 12 months was 56% with MEDI4736 monotherapy (with 15.3 month median OS) and 48% with SoC (with 11.3 month median OS) and assuming the true average HR is 0.71, then the trial will have at least 84% power to demonstrate statistical significance at a 2-sided alpha level of 3.03% (with overall alpha for OS of 3.5%) for the comparison of MEDI4736 monotherapy versus SoC, with the smallest treatment difference that could be statistically significant being an average HR of 0.79. With a 16-month recruitment period and a minimum follow-up period of 30 months assumed, it is anticipated that this analysis will be performed approximately 46 months after the first patient has been randomized.

MEDI4736 versus SoC (OS in all-comers UC)

If OS at 12 months was 55% with MEDI4736 monotherapy (with 14.4 month median OS) and 48% with SoC (with 11.3 month median OS) and assuming the true average HR is 0.75, then the trial will have at least 91% power to demonstrate statistical significance at a 2-sided alpha level of 4.29% (with overall alpha for OS of 5%) for the comparison of MEDI4736

monotherapy versus SoC, with the smallest treatment difference that could be statistically significant being an average HR of 0.84. With a 16-month recruitment period and a minimum follow-up period of 30 months assumed, it is anticipated that this analysis will be performed approximately 46 months after the first patient has been randomized.

OS will be analyzed using a stratified log-rank test (stratified for cisplatin eligibility [ie, eligible or ineligible], PD-L1 expression tumor status [High or Low/Neg, for analysis in the ITT population only], and visceral metastasis [presence or absence of lung and/or liver metastasis]). The effect of treatment will be estimated by the HR together with corresponding ([1-adjusted alpha] × 100%) confidence intervals and p-values.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm.

Safety data

Data from all cycles of treatment will be combined in the presentation of safety data. Adverse events (AEs; both in terms of Medical Dictionary for Regulatory Activities preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and electrocardiograms. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the Statistical Analysis Plan.

China data

After the end of global recruitment (i.e. LSI, globally), recruitment into an expansion cohort will continue in China until approximately 180 Chinese patients have been randomized. To evaluate consistency, the efficacy and safety data in China cohort will be analyzed separately as required by China FDA, applying the same statistical methods as for global cohort analysis unless specified (refer to Section 8.6 for further details). Due to patients in the expansion cohort being recruited late, data cutoffs for China cohort analyses may be different from global data cutoff to ensure an appropriate evaluation. The analysis will be performed when the OS data from the China patients is of similar maturity where significant clinical efficacy is established in the global cohort. Safety and tolerability will be summarized for the China-only Safety Analysis Set.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this clinical study protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen-presenting cells
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
B7-H1	B7-homolog 1
β-hCG	beta-Human chorionic gonadotropin
BICR	Blinded Independent Central Review
BlCS	Bladder Cancer Subscale
BoR	Best objective response
BP	Blood pressure
BSC	Best supportive care
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CrC1	Creatinine clearance
CRF	Case report form
CRO	Contract Research Organization
CSA	Clinical Study Agreement
CSP	Clinical study protocol
CSR	Clinical study report

Abbreviation or special term	Explanation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
C_{trough}	Trough plasma concentration
$C_{trough,ss}$	Trough plasma concentration at steady state
DCR	Disease control rate
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EQ-5D-5L	EuroQol 5-dimension, 5-level health state utility index
ESMO	European Society for Medical Oncology
EU	European Union
EWB	Emotional Well-Being
FACT-BL	Functional Assessment of Cancer Therapy - Bladder Cancer
FACT-G	Functional Assessment of Cancer Therapy – General
FAS	Full analysis set
FDA	Food and Drug Administration
FDG-PET	^{18}F-Fluoro-deoxyglucose positron emission tomography
fT_3	Free triiodothyronine
fT_4	Free thyroxine
FWB	Functional Well-Being
GCP	Good Clinical Practice Japan only: Unless otherwise noted, ‘GCP’ shall mean ‘the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practise’ (ICH GCP) and the Japanese ‘Good Clinical Practice for Trials on Drugs (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications’ [GCP Ordinance]).

Abbreviation or special term	Explanation
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HBsAg	HBV surface antigen
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Hazard ratio
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon-gamma
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
IP	Investigational Product
irAE	Immune-related adverse event
IRB	Institutional review board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFT	Liver function test
LIMS	Laboratory Information Management System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor, and Welfare
MIBC	Muscle-invasive bladder cancer
miRNA	Micro-ribonucleic acid
MMRM	Mixed Model Repeated Measurements
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTP	Multiple testing procedure
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NFBlSI-18	National Comprehensive Cancer Network - FACT Bladder Symptoms Index-18
NMIBC	Non-muscle-invasive bladder cancer
NSCLC	Non-small-cell lung cancer
NTL	Non-target lesion
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
OS24	Proportion of patients alive at 24 months from randomization
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
PFS2	Time from randomization to second progression
PGIC	Patient Global Impression of Change
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Meidcal Devices Agency
PR	Partial response

Abbreviation or special term	Explanation
PRO	Patient-reported outcomes
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PS	Performance status
PWB	Physical Well-Being
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q8w	Every 8 weeks
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of care
sPD-L1	Soluble programmed cell death ligand 1
SWB	Social Well-Being
TBL	Total bilirubin
TFST	Time to first subsequent therapy
TKI	Tyrosine kinase inhibitor
TL	Target lesions
TOI	Trial Outcome Index
TSH	Thyroid-stimulating hormone
TSST	Time to second subsequent therapy or death
TTR	Time to response
UC	Urothelial cancer
ULN	Upper limit of normal
WBDC	Web Based Data Capture

Abbreviation or special term	Explanation
WT	Weight
W/V	Weight/volume

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Bladder cancer is the most common tumor of the entire urinary tract and is the ninth most common cancer diagnosis worldwide, with more than 330000 new cases each year and more than 130000 deaths per year, with an estimated male:female ratio of 3.8:1.0. At any point in time, 2.7 million people have a history of urinary bladder cancer (Ploeg et al 2009, Babjuk et al 2014). Almost 90% of carcinomas of the urinary bladder are transitional cell carcinomas, the most common primary malignancy of the urinary tract, and may be found along its entire length.

At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive bladder cancer (MIBC) (Babjuk et al 2014). Nevertheless, approximately 40% of the patients with NMIBC will progress to muscle-invasive disease in 5 years depending on tumor pathological features (Sylvester 2006).

Muscle-invasive tumors are usually treated by radical cystectomy and chemotherapy. Cisplatin-containing combination chemotherapy with gemcitabine/cisplatin or methotrexate, vinblastine, adriamycin, and cisplatin is standard in advanced surgically unresectable and metastatic patients who are fit enough to tolerate cisplatin.

In first-line cisplatin/gemcitabine-based chemotherapy, the reported objective response rate (ORR) is approximately 49% with a limited median duration of response (DoR) of 9.6 months. ORR is represented by partial response (PR) of approximately 37% and complete response (CR) of approximately 12%. Approximately 33% of patients achieved stable disease (SD). The median time to progressive disease (PD) was 7.4 months (95% confidence interval [CI], 6.6 to 8.1 months) with a median survival of 13.8 months (95% CI, 12.3 to 15.8 months) (Von der Maase et al 2000).

Despite the high rate of disease control (above 80%) in the first-line setting (Von der Maase et al 2000), disease progression invariably occurs after discontinuing chemotherapy, even in patients who initially respond to chemotherapy.

Besides response to chemotherapy, other prognostic factors are the Karnofsky performance status (PS) of <80% and presence of visceral metastases, ie, lung or liver. These so-called Bajorin prognostic factors have also been validated for newer combination chemotherapy regimens and carboplatin combinations.

Approximately 40% of patients are unfit for cisplatin-containing chemotherapy due to a poor PS, impaired renal function, or comorbidity (de Wit 2003). Patients unfit for cisplatin-based chemotherapy may be offered with a carboplatin-based regimen or single-agent taxane or gemcitabine (Bellmunt et al 2014).

Carboplatin containing chemotherapy is less effective than cisplatin-based chemotherapy in terms of CR and survival and should not be considered interchangeable or standard. Several randomized Phase II trials of carboplatin versus cisplatin combination chemotherapy have produced lower CR rates and shorter overall survival (OS) for the carboplatin arms. In patients who are not eligible for cisplatin-based chemotherapy, ORR values are approximately 30% to 40%, median progression-free survival (PFS) was 5.8 months, with median OS rarely exceeding 10 months (De Santis et al 2012).

To date, no standard therapy has been established for patients who recur or are refractory to first-line therapy, or in the maintenance setting (National Comprehensive Cancer Network (NCCN Bladder Cancer Guidelines). Second-line vinflunine, by way of superiority over best supportive care (BSC), has shown modest activity and is approved in Europe. Treatment at the time of relapse has been largely unsuccessful, with low response rates and a median time to relapse of approximately 2 to 3 months.

The limited number of treatment options reflects the poor outcome. There is still a significant unmet medical need in urothelial cancer (UC).

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). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors (Peggs et al 2009). This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-homolog 1 (B7-H1) (programmed cell death ligand 1 [PD-L1]).

Several lines of evidence documenting the immune dysfunction associated with bladder cancer support the hypothesis that immunotherapy can alter the process of carcinogenesis (Carneiro et al 2014).

PD-L1 is a protein expressed in a broad range of cancers, including bladder cancer, at a high frequency. In some cancers (eg, lung and renal cell carcinoma), taking into consideration the limitation of published literature, the expression of PD-L1 seems to be associated with reduced survival and an unfavorable prognosis (Mu et al 2011, Topalian et al 2012). Regarding bladder cancer, PD-L1 is expressed by 12% of bladder tumor cells, 27% of tumor-infiltrating immune cells, and up to 50% of malignant urothelial cells in carcinoma in situ (Carneiro et al 2014). However, such estimates are preliminary, based on small sample sizes, and without standardized methods for measuring PD-L1. In addition, 95% of lymphocytes that invade bladder tumors express the PD-1 receptor. Urothelial expression of PD-L1 was also predictive of mortality following cystectomy in patients with organ-limited disease. PD-L1 expression is significantly associated with higher grade and stage in bladder cancer patients (Inman et al 2007). 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 therapeutically to enhance antitumor immune response in patients with bladder cancer (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 PD-L1-High tumors (Powles et al 2014).

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors. In a recent work published by Carthon et al (Carthon et al 2010), all 12 patients with localized urothelial carcinoma of the bladder treated with ipilimumab, administered in a preoperative setting, had measurable immunologic pharmacodynamic effects, consisting of an increased frequency of $CD4^{+}ICOS^{hi}$ T cells, a marker shown to correlate with improved OS, in tumor tissues and the systemic circulation.

Combining immunotherapy agents has been shown to result in improved response rates relative to monotherapy, for example in the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma (Wolchok et al 2013). The rationale for combining MEDI4736 and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity in both PD-L1-High and -Low/Neg populations (Pardoll 2012). In addition, CTLA-4 antagonists have been shown to upregulate PD-1, and PD-1 has been shown to upregulate CTLA-4, further strengthening the rationale for combining tremelimumab and MEDI4736 (Curran et al 2010). Initial data from ongoing studies have demonstrated higher ORRs and disease control rates (DCRs) in non-small-cell lung cancer (NSCLC) patients with PD-L1-Low/Neg tumors receiving MEDI4736 + tremelimumab combination therapy (30% and 70% [7 out of 10 patients], respectively) compared to MEDI4736 monotherapy (10% and 42%, respectively; Antonia et al 2014a, Antonia et al 2014b). In melanoma, the combination of CTLA-4 and PD-1 blockades has been shown to result in higher ORRs and 1-year and 2-year survival compared with either agent alone, regardless of PD-L1 expression status (Sznol et al 2014).

1.1.2 MEDI4736

MEDI4736 is a human mAb of the immunoglobulin G 1 kappa subclass that inhibits the binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action for MEDI4736 is interference of the interaction of PD-L1, expressed on cancer cells and a subset of leukocytes, with the PD-1 (cluster of differentiation [CD] 279) and B7-1 (CD80) molecules on antigen-presenting cells (APCs) and T cells. By binding to PD-L1 on tumor cells, the mechanism of action of MEDI4736 includes stimulation of the patient's antitumor immune response.

MEDI4736 has been given to humans as part of ongoing studies as monotherapy or in combination with other drugs. As of 14 July 2014, 509 patients have been enrolled and treated in 10 ongoing clinical studies of MEDI4736 (5 employing MEDI4736 as monotherapy and 5 as combination therapy). No studies have yet been completed. Currently, AstraZeneca is investigating the efficacy and safety of MEDI4736 both as monotherapy and in combination with other anticancer agents in a range of different tumor types, including 2 ongoing Phase I/II studies with UC patient cohorts where the effect of MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab, respectively, are being investigated. Details on the safety profile of MEDI4736 are summarized in Section 1.3.2.1. Refer to the MEDI4736 Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information; see Section 6.7 for guidance on management of MEDI4736-related toxicities (MEDI4736 IB).

The majority of the safety data currently available for MEDI4736 is based on the first-in-human monotherapy study (Study CD-ON-MEDI4736-1108; referred to hereafter as Study 1108) in patients with advanced solid tumors and is summarized in Section 1.3.2.1. Expansions in different tumor types are ongoing, including a bladder cancer expansion cohort that has a target enrollment of 60 patients. Patient recruitment and data collection in this cohort are ongoing.

MEDI4736 monotherapy exhibits non-linear (dose-dependent) pharmacokinetics (PK) approaching linearity with the ≥3-mg/kg dose, likely due to saturable target-mediated clearance, and has a half-life of approximately 21 days. Of the 220 patients who received MEDI4736 monotherapy from Study 1108 for whom PK/anti-drug antibody (ADA) data were available as of 14 July 2014, 5 patients (1 patient each in the 0.1- and 3-mg/kg cohorts and 3 patients in 10-mg/kg cohort) were ADA positive, with an impact on PK/pharmacodynamics in 1 patient in the 3-mg/kg cohort.

1.1.3 Tremelimumab

Tremelimumab, a CTLA-4 mAb of the immunoglobulin G 2 kappa isotype, is an immunomodulatory therapy that is being developed by AstraZeneca for use in the treatment of cancer. CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T-cells upregulate CTLA-4, which binds to B7 ligands on APCs, sending an inhibitory signal that limits T-cell activation. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to B7, leading to indirect prolongation and enhancement of T-cell activation and expansion. Thus, the mechanism of action of tremelimumab is indirect and is applied through enhancing T-cell-mediated immune response.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cutoff date of 12 November 2014 (for all studies except Study D4190C00006, which has a cutoff date of 4 December 2014), 1010 patients have received tremelimumab monotherapy (excluding 497 patients who have been treated in the blinded Phase IIb study, D4880C00003) and 197 patients have received tremelimumab in combination with other agents. More than

800 of these patients had melanoma and were treated at a dose of 15 mg/kg every 90 days. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.2. Refer to the Tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.7 for guidance on management of tremelimumab-related toxicities.

Tremelimumab exhibited a biphasic PK profile with a long-terminal phase half-life of 22 days. Overall, a low incidence of ADAs (<6%) was observed in treatment with tremelimumab.

1.1.4 MEDI4736 in combination with tremelimumab

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/pharmacodynamics, and preliminary antitumor activity of MEDI4736 + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized was MEDI4736 every 2 weeks (q2w) or every 4 weeks (q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses, then tremelimumab every 12 weeks for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

As of 27 January 2015, a total of 74 patients have been treated in the study, including 58 patients on the q4w dosing schedule and 16 patients on the q2w dosing schedule. Patients have received between 1 and 13 doses of MEDI4736 and between 1 and 9 doses of tremelimumab. Details on the safety profile of MEDI4736 + tremelimumab combination therapy are summarized in Section 1.3.2.3. Refer to the MEDI4736 IB and Tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.7 for guidance on management of MEDI4736 + tremelimumab-related toxicities.

As of 27 January 2015 in Study D4190C00006, an approximately dose-proportional increase in PK exposure (maximum plasma concentration [C_{max}], trough plasma concentration [C_{trough}], and area under the plasma drug concentration-time curve from time zero to Day 28 post-dose) of both MEDI4736 and tremelimumab was observed over the dose range of 3 to 20 mg/kg MEDI4736 q4w or q2w and 1 to 10 mg/kg tremelimumab q4w. Four of 60 patients with ADA data available were ADA positive for either anti-MEDI4736 or anti-tremelimumab antibodies post-treatment; MEDI4736 PK was impacted in only 2 of these 4 patients. Complete soluble programmed cell death ligand 1 (sPD-L1) suppression was observed in all patients over the dose range of 3 to 20 mg/kg of MEDI4736 q4w or q2w.

1.1.5 Rationale for conducting this study

Current therapies for advanced MIBC have poor outcomes (1-year survival rate of approximately 25%, low 5-year survival of 15% for the United States), an ORR of 30% to 40%, and a median OS of approximately 14 months (Steinberg et al 2014). Cisplatin-based chemotherapy continues to be the standard first-line treatment in advanced surgically unresectable and metastatic cancers in patients fit enough to tolerate cisplatin. In first-line cisplatin/gemcitabine-based chemotherapy, the reported ORR is approximately 49%, represented by PR of approximately 37% and CR of approximately 12%. Approximately

33% of patients achieved SD, with a median time to PD of 7.4 months (95% CI, 6.6 to 8.1 months) and a median survival of 13.8 months (95% CI, 12.3 to 15.8 months) (

Von der Maase et al 2000). Patients unfit for cisplatin-based chemotherapy may be palliated with a carboplatin-based regimen or single-agent taxane or gemcitabine (Bellmunt et al 2014, NCCN Bladder Cancer Guidelines). It remains difficult to say with certainty which regimen should be the reference in unfit patients. At best, ORR values are approximately 30% to 40%, with median OS rarely exceeding 10 months (Fizazi 2013).

Thus, there is still a significant unmet medical need for additional treatment options for use in this patient population.

Despite the high rate of disease control (above 80%) in the first-line setting, disease progression invariably occurs after discontinuing chemotherapy, even in patients who initially respond to chemotherapy (

Von der Maase et al 2000).

Combining immunotherapy agents has been shown to result in improved response rates relative to monotherapy; for example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher ORRs than those obtained with single agent therapy. Importantly, responses appeared to be deep and durable (Wolchok et al 2013). The rationale for evaluating the combination of MEDI4736 with tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both may have additive or synergistic activity (Pardoll 2012). Similar results have been observed in an ongoing study of MEDI4736 + tremelimumab combination therapy in NSCLC (Antonia et al 2014a).

Based on the preliminary clinical data that include the safety and tolerability profile of MEDI4736 monotherapy observed in particular in the UC cohort of Study 1108 and the combination treatment observed in Study D4190C00006 with MEDI4736 + tremelimumab in NSCLC (see Section 1.1.4), data across multiple indications, and evidence of clinical activity observed by other mAbs currently in development that target the PD-L1/PD-1 pathway, AstraZeneca plans to determine the activity of MEDI4736 monotherapy and MEDI4736 in combination with tremelimumab in patients with UC and other indications. This Phase III study will determine the activity of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to Standard of Care (SoC; cisplatin + gemcitabine or carboplatin + gemcitabine) in the first-line treatment of patients with PD-L1 unselected tumors that contain histologically or cytologically documented, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3; or M1) transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra).

1.2 Rationale for study design, doses, and control arms

This study will utilize an open-label design due to the different treatment administration schedules and treatment durations.

1.2.1 MEDI4736 and tremelimumab dose and treatment regimen justification

1.2.1.1 MEDI4736 + tremelimumab combination therapy dose rationale

The MEDI4736 + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of MEDI4736 and tremelimumab that would yield sPD-L1, demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetics/Pharmacodynamics data

In order to reduce the dosing frequency of MEDI4736 to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/pharmacodynamics, safety, and efficacy profile, cohorts in Study D4190C00006 were narrowed to 15 and 20 mg/kg MEDI4736 q4w. PK simulations from the MEDI4736 monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w MEDI4736. The observed MEDI4736 PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of MEDI4736 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when MEDI4736 and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with MEDI4736 monotherapy. There was evidence of augmented pharmacodynamic activity relative to MEDI4736 monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg MEDI4736 plus 1 mg/kg tremelimumab combinations.

Clinical data

As of 15 April 2015, a total of 102 patients with advanced NSCLC have been treated with MEDI4736 and tremelimumab across 10 dose cohorts in Study D4190C00006. The 102 patients have received between 1 and 13 doses of MEDI4736. Various dose combinations were explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of MEDI4736 ranging from 3 to 20 mg/kg. Seventy-four of these patients were in the MEDI4736 q4w dosing schedule and 28 patients were in the MEDI4736 q2w dosing schedule, with the goal of identifying the dose combination that best optimizes the risk-benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious adverse events (SAEs), and severe AEs. Between the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab and 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg MEDI4736 + 3 mg/kg tremelimumab cohort than the 10 mg/kg MEDI4736 + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 mg/kg or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with MEDI4736. As a result, all combination doses utilizing either the 3 or 10-mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of MEDI4736 with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of MEDI4736 may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of MEDI4736.

In Study D4190C00006, of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab arm had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical activity. This cohort had a lower number of treatment-related Grade ≥3 AEs or treatment related SAEs. No dose-limiting toxicities (DLTs) were reported.

Preliminary clinical activity of the MEDI4736 and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg MEDI4736 q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with PR, 1 patient (20%) with SD, and 1 patient (20%) with PD. (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

Additionally, of all cohorts, the 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical activity. All together, the data suggested that a 20 mg/kg MEDI4736 + 1 mg/kg tremelimumab dose combination should be selected for further development.

1.2.1.2 Rationale for 4 cycles of combination therapy followed by MEDI4736 monotherapy

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

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

- Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis (Brahmer et al 2014, Drake et al 2013, Hodi et al 2014). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, CR, or toxicity) for up to 56 weeks at the time of data analysis (Topalian et al 2014).

- MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported (Herbst et al 2013, Wolchok et al 2013).

Similar long term results may be expected with use of other immune-mediated cancer therapeutics including anti-CTLA-4 antibodies such as tremelimumab, anti PD-L1 antibodies such as MEDI4736, or the combination of the 2.

The MEDI4736 + tremelimumab combination regimen will be administered for 4 doses followed by monotherapy MEDI4736 1.5 g q4w.

1.2.1.3 MEDI4736 monotherapy dose rationale

A dose of MEDI4736 dose of 20 mg/kg q4w is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors (ongoing first-time-in-humans study) and from a Phase I trial performed in Japanese patients with solid tumors (NCT01938612).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg q2w or 15 mg/kg q3w, MEDI4736 exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the MEDI4736 dosing frequency can be adapted to a particular regimen given the linearity seen at higher doses than 3 mg/kg. The expected

half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of MEDI4736 with PD-L1. Dose-related changes in a variety of peripheral biomarkers have been observed over the dose range of 0.1 to 15 mg/kg. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to MEDI4736. Of the 220 patients who received MEDI4736 monotherapy and for whom PK/ADA data were available as of14 July 2014, 5 were ADA positive, with an impact on PK/pharmacodynamics reported in 1 patient at 3 mg/kg.

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of MEDI4736 and tremelimumab) also show an approximately dose-proportional increase in PK exposure for MEDI4736 over the dose range of 3 to 20 mg/kg MEDI4736 q4w or q2w. (For further information on PK observations in Study D4190C00006, please refer to Section 1.2.1.1).

The observed MEDI4736 PK data from the combination study were well in line with the predicted monotherapy PK data (5^{th} median and 95^{th} percentiles) for a q4w regimen. (For further information on PK observations in Study D4190C00006, please refer to Section 1.2.1.1).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w.

Clinical data

As of 8 April 2015, there is initial safety data for 16 patients receiving the 20 mg/kg q4w dosing regimen (12 patients from Study 1108 and 4 patients from the Japan Phase I trial). The toxicities observed with 20 mg/kg q4w are consistent with the 10 mg q2w regimen, and there were no DLTs observed. Of the 12 patients in Study 1108, 42% of patients have experienced any grade AE, with 2 being Grade 3 and above (17%). None of the Grade 3 and higher events was considered treatment-related. No patients on the Japan Phase I trial have experienced a

Grade 3 or above AE. At present, the data do not suggest that the safety profile of MEDI4736 will be different in the 20 mg/kg q4w dosing regimen when compared to 10 mg/kg q2w regimen. In fact, as of 14 July 2014, 393 patients enrolled in Study 1108 have received MEDI4736, predominantly at 10 mg/kg q2w (either in the dose-escalation or dose-expansion phase of the study). Data presented at the European Society for Medical Oncology (ESMO) meeting 2014 with a later cutoff of 21 August 2014 showed that MEDI4736 was well tolerated at all doses in the NSCLC subset of patients enrolled into Study 1108, with drug-related Grade ≥3 AEs reported in 3% of patients and drug-related AEs leading to discontinuation reported in 1% of patients. No drug-related colitis or hyperglycemia of any grade, no Grade ≥3 pneumonitis and no drug-related AEs leading to death were reported (Antonia et al 2014b). No DLTs were observed up to a dose of 10 mg/kg q2w or 15 mg/kg q3w.

Efficacy data on the NSCLC patients in Study 1108, presented at ESMO 2014 (cutoff date of 21 August 2014), showed a DCR at 12 weeks of 41% and ORR of 16% among 162 evaluable patients, with activity observed in both squamous and non-squamous histologies. The ORR was higher (25%; 12 CR/PR; n=48) in patients with PD-L1-High tumors, defined as those with ≥25% of tumor cells with membrane staining for PD-L1, compared to patients with PD-L1-Low/Neg UC (10%; 7 CR/PR; n=74) (Antonia et al 2014b).

1.2.1.4 Rationale for fixed dosing

A population PK model was developed for MEDI4736 using monotherapy data from Study 1108 (Phase I study; N=292; doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). Population PK analysis indicated only a minor impact of body weight (WT) on the PK of MEDI4736 (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of MEDI4736 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 a median body WT of approximately 75 kg). A total of 1000 patients were simulated using a body WT distribution of 40 to 120 kg. Simulation results demonstrated that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with the fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase I through Phase III studies (N=654; doses=0.01 to 15 mg/kg q4w or every 90 days; metastatic melanoma; Wang et al 2014). A population PK model indicated minor impact of body WT on the PK of tremelimumab (coefficient of ≤0.5). The WT-based (1 mg/kg q4w) and fixed dosing (75 mg/kg q4w; based on a median body WT of approximately 75 kg) regimens were compared using predicted PK concentrations (5th, median, and 95th percentiles) using a population PK model in a simulated population of 1000 patients with a body WT distribution of 40 to 120 kg. Similar to MEDI4736, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less overall between-patient variability with the fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). 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 PK/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on an average body WT of 75 kg, a fixed dose of 1.5 g q4w MEDI4736 (equivalent to 20 mg/kg q4w) and 75 mg q4w tremelimumab (equivalent to 1 mg/kg q4w) is included in the current study.

1.2.2 Rationale for Standard of Care as a comparator

The choice of SoC options provided in this study includes cisplatin + gemcitabine or carboplatin + gemcitabine. Patients in the SoC arm will receive treatment based on their cisplatin eligibility, until progression per standard practice. The SoC options provided in this study include agents that are commonly used in unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3; or M1) transitional cell carcinoma (transitional cell and mixed transitional/ non-transitional cell histologies) of the urothelium and allow sufficient flexibility for Investigators and patients to select the agents that reflect their normal clinical practice and national guidelines (Bellmunt et al 2014).

1.2.3 Rationale for cisplatin-ineligible Interim Analysis

Cisplatin-based combination chemotherapy is widely considered standard therapy for first line advanced metastatic UC (Von der Maase et al 2000). However, roughly 40-50% of patients are ineligible for standard cisplatin based chemotherapy due to impaired renal function, advanced age, poor performance status or medical comorbidities (Galsky 2011). In addition, a review of US SEER database demonstrated that only 45% of patients with metastatic bladder cancer were able to receive treatment with any type of chemotherapy (Galsky 2015). Carboplatin-based regimens are widely used as treatment alternatives to cisplatin combination chemotherapy for patients unable to tolerate cisplatin, but are generally associated with poor response rates and shorter OS. Although no formal comparison can be made, first line UC patients who received carboplatin-based chemotherapy demonstrate lower ORR (30-40%) as compared to cisplatin- based chemotherapy, with OS rarely exceeding 10 months (De Santis et al 2012). It's expected that those patients who are unfit for cisplatin-containing chemotherapy or any chemotherapy would have much worse prognosis, i.e. lower response to chemotherapy or none, and much shorter survival. Taken together, the need for more efficacious and tolerable treatment alternatives for UC patients who are unable to tolerate cisplatin-based regimens highlights a significant unmet medical need.

Emerging clinical data suggests that PD-1/PD-L1 pathway inhibitors may be a reasonable treatment options for patient with UC cancer, including those unable to tolerate cisplatin-based therapy. Considering the short response duration and poor survival for patients which are treated with carboplatin based first-line chemotherapy and the encouraging activity with

PD-1/PD-L1 pathway inhibitors in UC, AstraZeneca plans to determine the activity of MEDI4736 monotherapy in UC patients that are cisplatin-ineligible.

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 + tremelimumab combination therapy, respectively, prior to the overall benefit/risk assessment.

1.3.1 Potential benefits

1.3.1.1 MEDI4736

Of the 414 patients treated with MEDI4736 (all dose levels) in all tumor types in Study 1108 as of 14 July 2014, a total of 169 patients were evaluable for response analysis, which included patients who had at least 24 weeks of follow-up as of 14 July 2014 and had either at least 1 post-baseline tumor assessment or experienced clinical PD or death. Nineteen patients (11.2%) had a best overall response of confirmed and unconfirmed CR/PR. The DCR (CR + PR + SD ≥12 weeks) was 32% (54 of 169 patients). PD-L1 status (based on Ventana assay) was known for 143 of 169 evaluable patients, of whom 30 had PD-L1-High tumors (defined by tumor staining >25%). A best overall response of CR/PR (confirmed and unconfirmed) was observed in 7 of 30 (23.3%) patients with PD-L1-High tumors and in 6 of 113 (5.3%) patients with PD-L1-Low/Neg tumors.

The most recent data from the UC cohort in Study 1108 as of 20 March 2015 included 20 previously treated (median of 2 prior systemic therapies) patients who had UC regardless of their PD-L1 expression status and who were treated with MEDI4736. Among the 16 patients with at least 1 post-baseline disease assessment (or death or disease progression prior to their first assessment), 4 patients have achieved a PR, 4 patients have maintained SD as of their last available disease assessment, and 8 patients have experienced PD. One of the patients with PD had an initial 46% increase in tumor burden at the first disease assessment, followed by a subsequent 21% tumor reduction relative to baseline (54% decrease from maximal tumor burden), which may be considered pseudoprogression. This patient remained on study at data cutoff. A retrospective analysis of the relationship between tumoral and immune cell PD-L1 expression and clinical activity is ongoing. Other mAbs targeting the PD-L1/PD-1 pathway have shown clinical activity in this indication, as summarized in Section 1.1.4.

1.3.1.2 Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, a response rate of 7% and a median OS of 10 months in the second-line setting (compared to approximately 6 months with BSC reported from a retrospective analysis; Korn et al 2008) were observed (Kirkwood et al 2010). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed a response rate of 11% and median OS of 12.58 months in the first-line setting compared to 10.71 months with standard

chemotherapy (Ribas et al 2013). Additionally, in a Phase II maintenance study, patients with NSCLC (Study A3671015), PFS at 3 months was 22.7% in the tremelimumab arm compared with 11.9% in the BSC arm. At this time there are no sources of tremelimumab monotherapy data in patients with UC. Currently AstraZeneca is planning a multi-indication Phase I/II study of tremelimumab monotherapy, including a UC patient cohort.

1.3.1.3 MEDI4736 + tremelimumab combination therapy

The preclinical and clinical justification for this combination as noted in Section 1.1.4 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma (Wolchok et al 2013). Further, preliminary efficacy data from Study D4190C00006 have demonstrated that this combination is clinically active and well tolerated. As of 27 January 2015, 53 patients were evaluable for response across various MEDI4736 + tremelimumab combination therapy dose regiments. Of these, 12 patients (23%) had a best response of PR and 14 patients (26%) had a best response of SD. In the MEDI4736 20 mg/kg plus tremelimumab 1 mg/kg q4w cohort, a total of 5 of 11 patients were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with PR, 1 patient (20%) with SD, and 1 patient (20%) with PD. (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

1.3.2 Potential risks

1.3.2.1 MEDI4736

Identified risks with MEDI4736 are diarrhea, increases in transaminases, pneumonitis, and colitis.

Potential risks include endocrinopathies (hypothyroidism and hyperthyroidism, hypophysitis/hypopituitarism, and adrenal insufficiency, type I diabetes mellitus and diabetes insipidus), hepatitis/hepatotoxicity, neurotoxicities, nephritis/increases in creatinine, pancreatitis, and dermatitis/rash, myocarditis, myositis/polymyositis. Additional important potential risks include infusion-related reactions, hypersensitivity reactions, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (e.g. Guillain Barre syndrome, myasthenia gravis). Further information on these risks can be found in the current version of the MEDI4736 IB.

In MEDI4736 monotherapy clinical studies, AEs at an incidence of $\geq$ 20% are fatigue, nausea, decreased appetite, dyspnea, cough Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of MEDI4736, and approximately 3.5% of patients experienced an SAE that was considered to be related to MEDI4736 by the study Investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and, in the case of events suspected to have an immune basis, the use of established

treatment guidelines for immune-mediated toxicity (see Dosing Modification and Toxicity Management Guidelines).

A detailed summary of MEDI4736 monotherapy AE data can be found in the most recent MEDI4736 IB.

1.3.2.2 Tremelimumab

Identified risks with tremelimumab monotherapy are gastrointestinal (GI) effects (colitis, diarrhea, enterocolitis, and intestinal perforation), endocrine disorders (hypothyroidism and hyperthyroidism, hypophysitis, and adrenal insufficiency), skin effects (rash and pruritus), and elevations in lipase and amylase.

Potential risks based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated reactions including other GI events, for example, ulcerative colitis, dehydration, nausea, and vomiting; hepatic events including hepatitis and liver enzyme elevations; pneumonitis and interstitial lung disease; clinical manifestations of pancreatitis; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré syndrome, and proximal muscle weakness; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions and hypersensitivity, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis, and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjögren's syndrome, and giant cell temporal arteritis and ulcerative colitis; hyperglycemia and diabetes mellitus; and. Further information on these risks can be found in the current version of the Tremelimumab IB.

With the use of pooled data from monotherapy clinical studies, AEs reported at an incidence of $\geq$ 20% 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.

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

1.3.2.3 MEDI4736 + tremelimumab combination therapy

The safety of MEDI4736 + tremelimumab combination therapy is being evaluated in the ongoing dose escalation and dose expansion Study D4190C00006, in patients with NSCLC, and has so far shown a manageable safety and tolerability profile.

The potential risks with the combination of MEDI4736 + tremelimumab are similar to those for MEDI4736 and tremelimumab monotherapy. Emerging data from Study D4190C00006 and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these potential immune-mediated toxicities.

As of 15 April 2015, a total of 102 patients with advanced NSCLC have been treated with MEDI4736 and tremelimumab across 10 dose cohorts in Study D4190C00006. The 102 patients have received between 1 and 13 doses of MEDI4736. Various dose combinations were explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of MEDI4736 ranging from 3 to 20 mg/kg. Seventy-four of these patients were in the MEDI4736 q4w dosing schedule, and 28 patients were in the MEDI4736 q2w dosing schedule, with the goal of identifying the dose combination that best optimizes the risk-benefit profile in an acceptable range of PK and pharmacodynamic values.

In Study D4190C00006, AEs (all grades) reported very commonly (≥10% of patients) were diarrhea, fatigue, nausea, dyspnea, pruritus, rash, increased amylase, decreased appetite, pyrexia, increased alanine aminotransferase (ALT), cough, colitis, and increased lipase. In this dose-finding study, all patients in the tremelimumab 3 and 10 mg/kg dose cohorts experienced AEs; patients in the MEDI4736 20 mg/kg and tremelimumab 1 mg/kg q4w cohort experienced the lowest AE rate (14 of 18 patients, 77.8%).

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 15% of patients experienced an SAE that was considered to be related to MEDI4736 and tremelimumab by the study investigator.

A detailed summary of MEDI4736 + tremelimumab combination AE data can be found in the current version of the MEDI4736 IB.

1.3.3 Overall benefit and risk assessment

There remains a significant unmet medical need for additional treatment options for treatment-naïve patients with histologically or cytologically documented, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3; or M1) transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium.

Treatment with agents targeting PD-1/PD-L1 (such as MEDI4736) 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 MEDI4736 monotherapy in the bladder cancer cohort have shown some clinical activity. Additionally, MEDI4736 + tremelimumab combination therapy has shown clinical activity in patients with recurrent or metastatic squamous cell cancer of the head and neck. Preliminary data generated from patients with NSCLC treated with MEDI4736 + 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 IPs (including MEDI4736, tremelimumab, and SoC).

The toxicity profile of the combination of MEDI4736 and tremelimumab included fatigue, colitis, diarrhea, aspartate aminotransferase (AST) or 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.

In particular, based on the specific mechanism of action of MEDI4736 and tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing immune-related adverse events (irAEs) during the conduct of this study. Potential irAEs 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 irAEs. 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 irAEs follow the guidelines outlined in Section 6.7.

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 MEDI4736 in this tumor type, and the strength of the scientific hypotheses under evaluation, the MEDI4736 monotherapy and MEDI4736 + 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 (QoL) and potentially extending survival. Furthermore, preclinical 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 MEDI4736 monotherapy and MEDI4736 + 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 a randomized, open-label, controlled, multi-center, global Phase III study to determine the efficacy and safety of MEDI4736 monotherapy (1.5 g intravenous [IV] q4w) and MEDI4736 (1.5 g IV q4w) in combination with tremelimumab (75 mg IV q4w) for up to 4 doses/cycle each followed by MEDI4736 1.5 g IV q4w) versus SoC (cisplatin + gemcitabine or carboplatin + gemcitabine doublet) first-line chemotherapy in treatment-naïve patients with histologically or cytologically documented, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3; or M1) transitional cell carcinoma (transitional cell and mixed

transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra). Crossover from SoC to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy will not be permitted. A schematic diagram and flow chart of the overall study design are shown in Figure 1 and Figure 2, respectively.

This study will randomize approximately 1005 patients globally. After the end of global enrollment (i.e. LSI, globally), recruitment into an expansion cohort will continue in China until approximately 180 Chinese patients have been randomized.

Patients will provide a tumor tissue sample at screening to determine PD-L1 status (defined by an immunohistochemistry [IHC] assay developed by Ventana, see Table 1) for stratification*.

Table 1 PD-L1 status defined by scoring of an IHC assay developed by Ventana for stratification in D419BC00001*

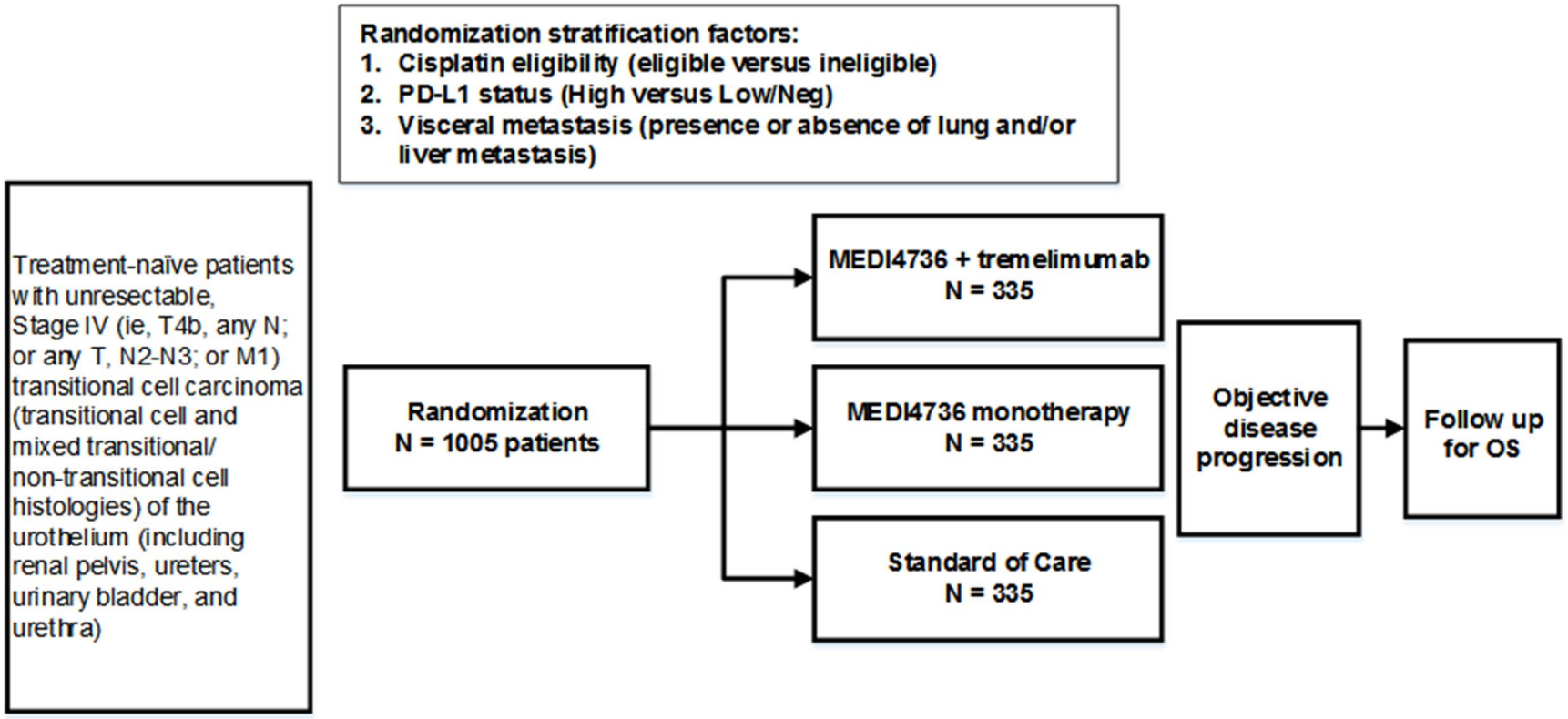
Interpretation	Staining description
PD-L1-High	≥25% tumor cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control OR ≥25% tumor associated immune cell positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control
PD-L1-Low/Neg	<25% tumor cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control AND <25% tumor associated immune cell positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control

IHC Immunohistochemistry; PD-L1 Programmed cell death ligand 1.
*Definition of PD-L1 high versus low/negative expression will be used for stratification. Different cutoff of PD-L1 expression may be utilized for analysis based on emerging data.

Note: PD-L1 High (>=25% tumor cell membrane positivity for PD-L1 or 1) IF IC area >1%: >=25% tumor associated immune cell positivity for PD-L1; 2) If IC area=1%: 100% tumor associated immune cell positivity for PD-L1). PD-L1 Low if criteria not met for PD-L1 High

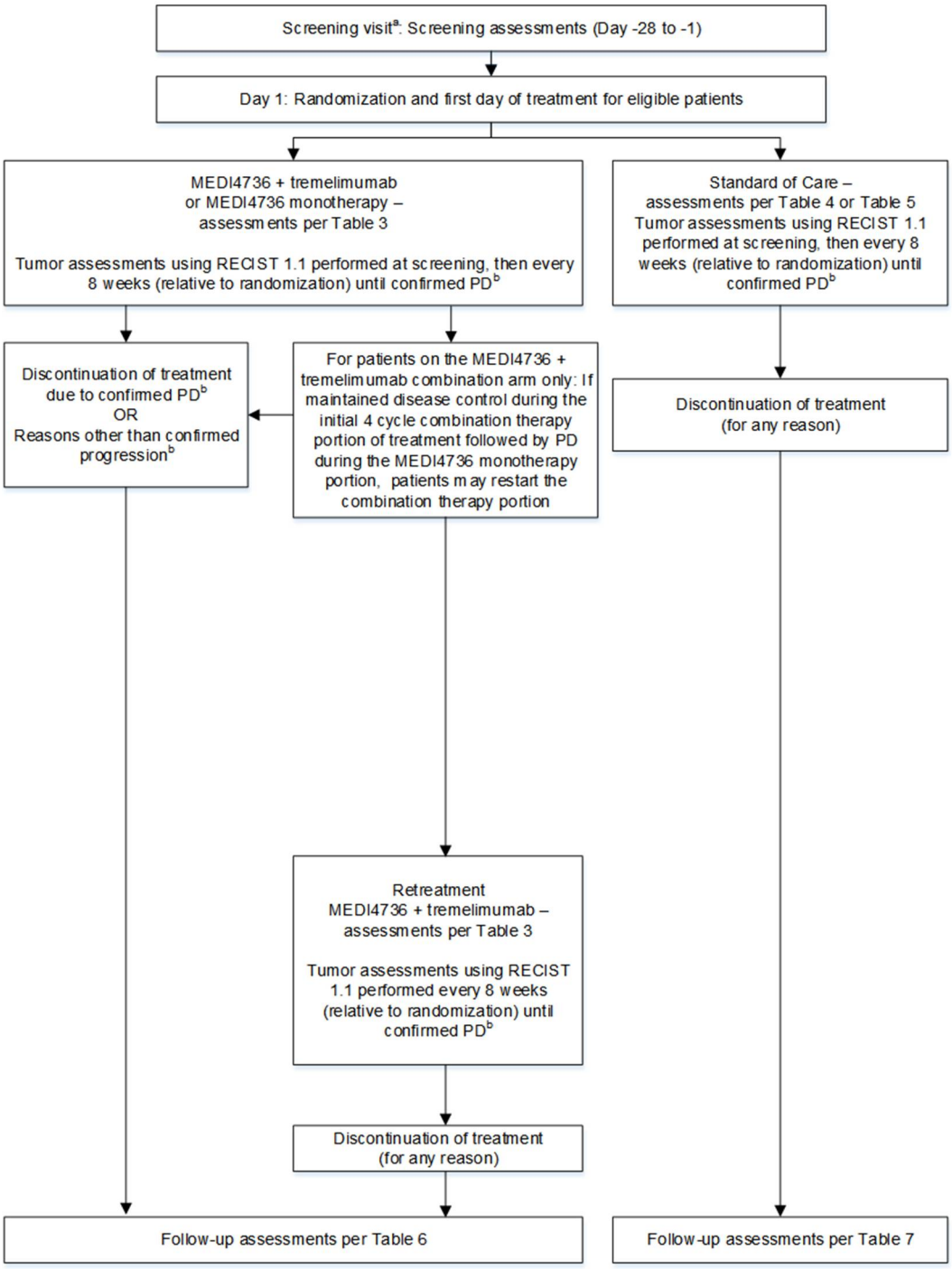
Patients enrolled in the study will be randomized (1:1:1) to treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC (cisplatin + gemcitabine or carboplatin + gemcitabine, based on cisplatin eligibility). Patients will be stratified according to cisplatin eligibility (eligible or ineligible; see Inclusion Criterion 7 in Section 3.1), PD-L1 status (High or Low/Neg, based on Ventana assay), and visceral metastasis (presence or absence of lung and/or liver metastasis). Doses and treatment regimens are described in Section 7.2. Assessments will be conducted as indicated in Table 3, Table 4, Table 5, Table 6, and Table 7.

Figure 1 Overall study design



OS Overall survival; PD-L1 Programmed cell death ligand 1.
Note: approximately 180 Chinese patients will be randomized in the same criteria (stratification factors and 1:1:1 fashion) as globally.

Figure 2 Study flowchart



[a] Informed consent may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization.

[b] In addition to PR and CR, a confirmatory scan is required following the initial demonstration of PD (patients enrolled in the SoC arm will discontinue study drug at the first assessment of disease progression). (See Section 5.1 for more information.)

CR Complete response; PD Progressive disease; PR Partial response; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SoC Standard of care.

2. STUDY OBJECTIVES

The assessments of OS will be considered primary objectives.

2.1 Primary objectives

Primary objectives:	Outcome measures:
To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of OS in patients with unresectable Stage IV UC	OS
To assess the efficacy of MEDI4736 monotherapy versus SoC in terms of OS in patients with unresectable Stage IV PD-L1-High UC	OS

OS Overall survival; SoC Standard of care; UC Urothelial cancer.

2.2 Secondary objectives

Secondary objectives:	Outcome measures:
To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of PFS in patients with PD-L1-High UC	PFS using Investigator assessments according to RECIST 1.1 [a]
To assess the efficacy of MEDI4736 + tremelimumab combination therapy versus SoC in terms of PFS in patients with UC	PFS using Investigator assessments according to RECIST 1.1 [a]
To assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of PFS and OS in patients with UC	PFS using Investigator assessments according to RECIST 1.1 [a] OS
To assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of PFS and OS in patients with PD-L1-Low/Neg UC	PFS using Investigator assessments according to RECIST 1.1 [a] OS
To assess the efficacy profile of MEDI4736 monotherapy in patients who are not cisplatin-eligible	ORR, DoR, DCR, TTR, and PFS, using BICR assessments according to RECIST 1.1 [b] OS

Secondary objectives:	**Outcome measures:**
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to MEDI4736 monotherapy in terms of PFS, OS, OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with PD-L1-Low/Neg UC and all patients with UC	OS OS24 PFS, APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with UC	OS24 APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1[a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with PD-L1-High UC	OS24 APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 monotherapy compared to SoC in terms of OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with UC	OS24 APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in terms of OS24, APF12, ORR, DoR, DCR, and PFS2 in patients with PD-L1-Low/Neg UC	OS24 APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] PFS2 as defined by local standard clinical practice
To further assess the efficacy of MEDI4736 + tremelimumab combination therapy compared to SoC in patients with PD-L1-High UC	PFS, APF12, ORR, DoR, and DCR using Investigator assessments according to RECIST 1.1 [a] OS and OS24 PFS2 as defined by local standard clinical practice
To assess disease-related symptoms and HRQoL in UC patients treated with MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared with SoC and each other using the FACT-BL questionnaire	FACT-BL: Fatigue, Pain, Derived NFBlSI-18 score, FACT-BL TOI, and FACT-BL Total score
To assess the PK of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Serum concentration of MEDI4736/tremelimumab PK parameters (such as peak concentration and trough, as data allow; sparse sampling)
To investigate the immunogenicity of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy	Presence of ADAs for MEDI4736 and tremelimumab (confirmatory results: positive or negative)

a The analysis will be based on programmatically derived investigator assessments according to RECIST 1.1. See Section 8 for further details.
b The analysis will be based on programmatically derived BICR assessments according to RECIST 1.1. See Section 8 for further details.

ADA Anti-drug antibody; APF12 Proportion of patients alive and progression free at 12 months from randomization; BICR Blinded Independent Central Review; DCR Disease control rate; DoR Duration of response; FACT-BL Functional Assessment of Cancer Therapy - Bladder Cancer; FACT-BL TOI Functional Assessment of Cancer Therapy - Bladder Cancer Trial Outcome Index; HRQoL Health-related quality of life; NFBlSI-18 National Comprehensive Cancer Network - FACT Bladder Symptoms Index-18; ORR Objective response rate; OS Overall survival; OS24 Proportion of patients alive at 24 months from randomization; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PFS2 Time from randomization to second progression; PK Pharmacokinetics; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SoC Standard of care; TTR Time to response; UC Urothelial cancer.

2.3 Safety objective

Safety objective:	Outcome measures:
To assess the safety and tolerability profile of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC	AEs, laboratory findings, vital signs, and ECGs
To assess the safety and tolerability profile of MEDI4736 monotherapy and SoC in patients who are not cisplatin-eligible	AEs, laboratory findings, vital signs, and ECGs

AE Adverse event; ECG Electrocardiogram; SoC Standard of care.

2.4 Exploratory objectives

Exploratory objectives:	Outcome measures:
To explore irRECIST as an assessment methodology for clinical benefit of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy versus SoC with assessment by BICR	PFS, APF12, ORR, DoR, and DCR using BICR assessment according to irRECIST
To assess AEs directly by patient self-reporting of specific PRO-CTCAE symptoms	Sixteen PRO-CTCAE symptoms considered relevant to study treatments
To assess disease-related symptoms and HRQoL in UC patients treated with MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy versus SoC and each other using the FACT-BL questionnaire	FACT-BL: PWB, SWB, EWB, FWB, BlCS, and FACT-G Total score

Exploratory objectives:	**Outcome measures:**
To investigate the relationship between PK exposure and clinical outcomes, efficacy, AEs, and/or safety parameters, if deemed appropriate	A graphical and/or a data modeling approach will be used to analyze PK exposure and the relationship with clinical outcomes, efficacy, AEs, and/or safety parameters, as deemed appropriate
To describe and evaluate resource use associated with assigned treatments and underlying disease during assigned treatment	Health resource utilization measures including hospitalization, outpatient visits, or emergency department visits, measured via the HOSPAD module
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L during assigned treatment	EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
To collect blood and tissue samples for defining biological responses to MEDI4736 and tremelimumab and for identifying candidate markers that may correlate with likelihood of clinical benefit	Protein expression detected by IHC (eg, PD-L1) miRNA/mRNA T-cell and MDSC phenotyping SNP genotyping Urine-derived factors, where applicable
To assess patients' overall impression of the change in their health status since the start of study treatment	Single-item PGIC measure

Note: Exploratory objective analyses may be reported separately from the main clinical study report.
AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months from randomization; BICR Blinded Independent Central Review; BlCS Bladder Cancer Subscale; DCR Disease control rate; DoR Duration of response; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; EWB Emotional well-being; FWB Functional well-being; FACT-BL Functional Assessment of Cancer Therapy - Bladder Cancer; FACT-G Functional Assessment of Cancer Therapy - General; FACT-BL TOI Functional Assessment of Cancer Therapy - Bladder Cancer Trial Outcome Index; HRQoL Health-related quality of life; IHC Immunohistochemistry; irRECIST Immune-related Response Evaluation Criteria in Solid Tumors; MDSC Myeloid-derived suppressor cells; miRNA Micro-ribonucleic acid; mRNA Messenger ribonucleic acid; ORR Objective response rate; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PGIC Patient Global Impression of Change; PK Pharmacokinetics; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; PWB Physical Well-Being; SNP Single nucleotide polymorphism; SoC Standard of care; SWB Social/family well-being; TFST Time to first subsequent therapy; TSST Time to second subsequent therapy or death; UC Urothelial cancer.

A further objective to meet China FDA requirement is to evaluate consistency in efficacy and safety among Chinese subjects for benefit-risk assessment of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy compared to SoC.

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

Each patient must meet all of the inclusion criteria (Section 3.1) and none of the exclusion criteria (Section 3.2) for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

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

1. Age ≥18 years at the time of screening.

2. 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.)

3. Patients with histologically or cytologically documented, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3 (Note: The Investigators will use their discretion to confirm the cause of N2 disease [reactive or inflammatory]); or M1) transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra) (see NCCN Bladder Cancer Guidelines), who have not been previously treated with first-line chemotherapy. (Patients who have received prior definitive chemoradiation, adjuvant or neoadjuvant treatment for locally advanced disease, are eligible, provided that progression to Stage IV disease has occurred >6 months from last therapy [for chemoradiation and adjuvant treatment] or >6 months from last surgery [for neoadjuvant treatment].)

4. At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with a computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements as per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) guidelines.

5. Eastern Cooperative Oncology Group (ECOG) PS 0 or 1

6. Life expectancy ≥12 weeks (in the opinion of the Investigator)

7. Patients eligible or ineligible for cisplatin-based chemotherapy. Cisplatin ineligibility is defined as meeting one of the following criteria:

- Creatinine clearance (CrCl) <60 mL/min calculated by Cockcroft-Gault equation (using actual body weight; see Appendix A) or by measured 24-hour urine collection. (In cases where both are performed, measured 24-hour urine collection will be used to determine eligibility, providing an adequate collection was performed.)*

- Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 audiometric hearing loss

- CTCAE Grade ≥2 peripheral neuropathy

- New York Heart Association ≥Class III heart failure

8. Tumor PD-L1 status, with IHC assay confirmed by a reference laboratory, must be known prior to randomization. As such, all patients must be able to provide a newly acquired tumor biopsy during screening (preferred) or provide an available tumor sample taken ≤3 years prior to screening. Tumor lesions used for newly acquired biopsies should not be target lesions, unless there are no other lesions suitable for biopsy. Samples with limited tumor content and fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component. The tumor specimen submitted to establish PD-L1 status should be of sufficient quantity to allow for PD-L1 IHC and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin embedded blocks.

9. Adequate organ and marrow function as defined below:

   - Hemoglobin ≥9 g/dL

   - Absolute neutrophil count ≥1500/mm3

   - Platelet count ≥100000/mm3

   - Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia [predominantly unconjugated bilirubin] in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with their physician and AstraZeneca.

   - ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT, and AST ≤5 × ULN

   - CrCl ≥30 mL/min calculated by Cockcroft-Gault equation (using actual body weight; see Appendix A) or by measured 24-hour urine collection for determination. (In cases where both are performed, measured 24-hour

measured urine collection will be used to determine eligibility, providing an adequate collection was performed.)*

10. Evidence of postmenopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered postmenopausal 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 postmenopausal 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 postmenopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

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

*Method used to determine CrCl for study eligibility will be the same method used to determine cisplatin eligibility at study entry. See Section 3.3 for detailed requirements regarding IVRS data entry for purposes of randomization.

Additional details pertaining to retreatment are presented in Section 7.2. Additional details pertaining to restrictions are presented in Section 3.8.

3.2 Exclusion criteria

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

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

2. Previous investigational product (IP) assignment in the present study

3. Concurrent enrollment in another clinical study, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study

4. Prior exposure to immune-mediated therapy (with exclusion of Bacillus Calmette Guerin), including but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines. Prior local intervesical chemotherapy or immunotherapy is allowed if completed at least 28 days prior to the initiation of study treatment.

5. Any unresolved toxicity National Cancer Institute (NCI) CTCAE Version 4.03 Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

   – Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with AstraZeneca.

   – Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with MEDI4736 or tremelimumab may be included after consultation with AstraZeneca.

6. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable. Note: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, local surgery or radiotherapy).

7. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 28 days of the first dose of study drug

8. 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.

9. History of allogenic organ transplantation that requires use of immunosuppressive agents.

10. Active or prior documented autoimmune or inflammatory disorders (including but not limited to inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, 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 3 years may be included but only after consultation with AstraZeneca.

    – Patients with celiac disease controlled by diet alone may be included but only after consultation with AstraZeneca.

11. Uncontrolled intercurrent illnesses, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, uncontrolled diabetes, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, 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. Other malignancy within 5 years before first dose of IP, except for the following pending a discussion with AstraZeneca:

    – Patients with a history of prostate cancer (tumor/node/metastasis stage) of stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention

    – Patients who have been adequately treated for a malignancy with a low potential risk for recurrence (eg, cervical carcinoma in situ, non-melanomatous carcinoma of the skin, or ductal carcinoma in situ of the breast that has been surgically cured).

13. History of leptomeningeal carcinomatosis

14. Brain metastases or spinal cord compression unless the patient's condition is stable (asymptomatic, no evidence of new or emerging brain metastases) and off steroids for at least 14 days prior to the start of study treatment. Patients with suspected or known brain metastases at screening should have an MRI (preferred)/CT, preferably with IV contrast to access baseline disease status.

15. QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated. Any clinically significant abnormalities detected require triplicate ECG results and a mean QTcF ≥470 ms calculated from 3 ECGs obtained over a brief period (eg, 30 minutes).

16. History of active primary immunodeficiency

17. 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, hepatitis C, or human immunodeficiency virus (HIV, positive HIV 1 or 2 antibodies). Active hepatitis B virus (HBV) infection is defined by a positive HBV surface antigen (HBsAg) result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core IgG antibody and the absence of HBsAg, deoxyribonucleic acid [DNA] negative) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).

18. Current or prior use of immunosuppressive medication within 14 days before the first dose of IP. 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
    - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

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 during the study and up to 30 days after the last dose of IP.

20. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy

21. Known allergy or hypersensitivity to IP or any IP excipient, or to other humanized mAbs

22. Any medical contraindication to platinum (cisplatin or carboplatin)-based doublet chemotherapy

23. Patient <30 kg in weight

For procedures for withdrawal of incorrectly enrolled patients, see Section 3.4.

3.3 Patient enrollment and randomization

Investigators should keep a record (ie, the patient screening log) of patients who entered screening.

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

1. Obtain signed informed consent before any study specific procedures are performed. (Informed consent may be obtained prior to the 28-day screening window in order to permit tumor biopsy sample acquisition which must be analyzed prior to randomization.)

2. Obtain a unique 7-digit enrollment number (E-code), through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) in the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the patient enrollment code at the center). This number is

the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

3. Obtain tumor sample and send for PD-L1 expression analysis. **(Obtaining the tumor biopsy sample should be given the highest priority and, as such, the sample may be obtained and sent for PD-L1 status evaluation prior to the 28-day screening window in order to permit analysis prior to randomization.)** PD-L1 status must be available in the IVRS/IWRS in order for the patient to be randomized, as it is a stratification factor.

4. Determine patient eligibility (see Sections 3.1 and 3.2)

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

Define the SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) treatment (based on cisplatin eligibility) that the patient would receive in the absence of randomized therapy. This must be completed for all patients. The information will be recorded in the IVRS/IWRS. **NOTE: If more than 1 evaluation of creatinine clearance has been obtained during the screening period, the creatinine clearance value closest to Cycle 1 Day 1 should be entered into the IVRS system for randomization purposes (see Section 3.1 for details).**

Method used to determine CrCl for study eligibility should be the same method used to determine IVRS randomization at study entry

5. Ensure PD-L1 status results are received by the IVRS/IWRS from the central laboratory prior to randomization.

6. Record the presence or absence of visceral metastases (as defined as metastatic disease in lung and/or liver) as a stratification factor in the IVRS/IWRS.

7. Obtain a unique randomization number via the IVRS/IWRS. Numbers will be assigned strictly sequentially by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 3 treatment arms.

If the patient is ineligible and not randomized, the IVRS/IWRS should be contacted to terminate the patient in the system.

It is strongly recommended that patients commence study drug on the same day as randomization by IVRS/IWRS. If same-day treatment is not possible, then the study treatment must occur within 3 working days of randomization. Patients must not be randomized unless all eligibility criteria have been met.

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

3.4 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study as a screen failure.

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

3.5 Methods for assigning treatment arms

Patients must not be randomized unless all eligibility criteria have been met.

At baseline, patients who satisfy all the entry criteria will be centrally assigned to study drug by the IVRS/IWRS, according to the randomization scheme generated by the Biostatistics Group, AstraZeneca, or delegate.

Patients enrolled in the study will be randomized (1:1:1) to treatment with MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC (cisplatin + gemcitabine or carboplatin + gemcitabine, based on cisplatin eligibility). Patients will be stratified according to cisplatin eligibility (ie, eligible or ineligible; see Inclusion Criterion 7 in Section 3.1), PD-L1 status (High or Low/Neg, based on Ventana assay), and visceral metastasis (presence or absence of lung and/or liver metastasis). PD-L1 status stratification will be based on natural prevalence rates. Randomization of cisplatin-eligible patients will be capped at a maximum 85% of the planned total number of patients.

The actual treatment given to patients will be determined by the randomization scheme in the IVRS/IWRS. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers.
One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment arm.

Patients will be identified to the Centralized Randomization Center per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization.

Every effort should be made to minimize the time between randomization and starting study drug. It is strongly recommended that patients commence study drug on the same day as randomization by IVRS/IWRS. If same-day treatment is not possible, then the study treatment must occur within 3 working days of randomization.

If a patient discontinues participation in the study, then their enrollment/randomization code cannot be reused.

3.6 Methods for ensuring blinding (not applicable)

Not applicable. This is an open-label study.

3.7 Methods for unblinding (not applicable)

Not applicable. This is an open-label study.

3.8 Restrictions

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

- **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 MEDI4736 + tremelimumab combination therapy or 90 days after receipt of the final dose of MEDI4736 or until alternate anti-cancer therapy is started. For patients on SoC, follow local prescribing information related to blood donations.

- **Patients in the MEDI4736 monotherapy or MEDI4736 + tremelimumab combination arms**: Female patients of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 2) from screening and must agree to continue using such precautions for 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy; cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should refrain from breastfeeding and egg cell donation throughout this period.

- It is strongly recommended for the male partner of a female patient to also use a male condom plus spermicide throughout this period.

  - Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menstruation without an alternative medical cause).

  - The acceptable methods of contraception are described in Table 2. A highly effective method of contraception is defined as 1 that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Not all methods of acceptable contraception are highly effective.

- Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from Day 1 and for 90 days after the last dose of MEDI4736 monotherapy or 180 days after the last dose of MEDI4736 + tremelimumab combination therapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this same period.

  - It is strongly recommended for the female partner of a male patient also use an effective method of contraception throughout this period

- **Patients in the SoC arm:** Follow the local prescribing information related to contraception, the time limits for such precautions, and any additional restrictions for agents in the SoC arm.

Table 2 Highly effective methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[a]	• *Etonogestrel implants: eg, Implanon or Norplan* • *Intravaginal device: eg, ethinylestradiol and etonogestrel* • *Medroxyprogesterone injection: eg, Depo-Provera* • *Normal and low-dose combined oral contraceptive pill* • *Norelgestromin/ethinylestradiol transdermal system* • *Cerazette (desogestrel)*

[a] This is also considered a hormonal method.

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 (MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC [cisplatin + gemcitabine or carboplatin + gemcitabine]) if any of the following occur in the patient in question:

1. Withdrawal of consent from further treatment with IP
2. An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing
3. Any AE that meets the criteria for discontinuation as defined in Section 6
4. Pregnancy or intent to become pregnant
5. Non-compliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal from study medication (eg, refusal to adhere to scheduled visits)
6. Initiation of alternative anticancer therapy including another investigational agent
7. Confirmed PD and Investigator determination that the patient is no longer benefiting from treatment with IP. Patients enrolled in the SoC arm will discontinue study drug at the first assessment of disease progression.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue the IP without prejudice to further treatment. A patient who decides to discontinue the IP will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. AEs will be followed up (see Section 6). AstraZeneca should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment. **Prior to discontinuing a patient from study therapy, it is strongly recommended that the patient's case be discussed with AstraZeneca in consultation with the treating physician.**

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 6 and Table 7). All patients will be followed up for survival until the end of the study. Details of any treatment for bladder cancer (including surgery) after the last dose of study treatment must be recorded in the eCRF, including the identity of subsequent anticancer therapies. Patients who decline to return to the site for evaluations should be contacted by telephone every 2 months as an alternative.

Patients who are permanently discontinued from receipt of IP should also be discontinued in the IVRS/IWRS.

3.10 Criteria for withdrawal from the study

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled and randomized. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for

screen failures (ie, not randomized patients). Patients can be rescreened a single time, but they cannot be re-randomized.

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.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn his or her 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. The patient will return electronic patient-reported outcomes (PRO) devices, if applicable.

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

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 3.11), 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 any evaluations should resume according to the protocol.

At the time of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- 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 in the 7 days following data cutoff. (The applicable CRF modules will be updated.)

- 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 in the 7 days following data cutoff. (The applicable CRF modules will be updated.)

3.11 Discontinuation of the study

The study may be stopped if, in the judgment 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 drug
- Are not considered to be consistent with continuation of the study

In addition, the study may be stopped based on the findings of the interim safety analysis conducted by the Independent Data Monitoring Committee (IDMC) (see Section 6.7.3).

Regardless of the reason for termination, all data available for the patients at the time of discontinuation or follow-up must be recorded in the eCRFs. All reasons for discontinuation of treatment must be documented.

In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the patients' interests. If this study is discontinued, all other studies involving MEDI4736 or tremelimumab will remain open to enrollment and screening, if deemed appropriate by AstraZeneca.

4. STUDY PLAN AND TIMING OF PROCEDURES

The procedures for the screening and treatment periods in this study are presented in Table 3, Table 4, and Table 5, and the procedures for the follow-up period are presented in Table 6 and Table 7. Patients who continue beyond C13 continue with all C13 assessments until termination of treatment (Table 3).

For all treatment arms

- PRO and tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (not the date of therapy).
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc required for dosing should be performed within 3 days prior to dosing.

For MEDI4736 monotherapy or MEDI4736 + 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-related AE.

- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
- Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of MEDI4736 and tremelimumab (see Sections 1.1.3 and 1.1.4, respectively).

Standard of Care Arm:

- Patients may delay and subsequently resume dosing per local standard clinical practice.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.

Table 3 Schedule of assessments for MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy treatment and retreatment periods (Patients who continue beyond C13 continue with all C13 assessments until termination of treatment)

*All scheduled assessments (safety, etc) must be performed within 3 days prior to the start of that dosing cycle, with the exception of tumor efficacy (RECIST) assessments (±7-day window, based on date of randomization regardless of dosing delays**). If more than 1 evalaution of creatinine clearance has been obtained during the screening period, the creatinine clearance value closest to Cycle 1 Day 1 should be entered into the IVRS system for randomization purposes (see Section 3.3 for details).**

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see CSP Section
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Informed consent															
Written informed consent	X[a]														3.3
Study procedures															
Physical examination (full)	X														5.2.2
Targeted physical exam (based on symptoms)		X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.2
ECG[b]	X	As clinically indicated													5.2.3
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.4
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Demography, including medical and surgical history and history of tobacco use	X														4.1
Laboratory assessments															
Serum or plasma chemistry (complete clinical chemistry panel) and hematology[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Hepatitis B and C and HIV	X														5.2.1

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see CSP Section
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Urine hCG or serum β-hCG[e] and coagulation parameters[c]	X	As clinically indicated													5.2.1
Pharmacokinetics															
MEDI4736 PK sample (serum)		X[f]	X[g]		X[f]			X[f]							5.4.1
Tremelimumab PK sample (serum; combination therapy arm only)		X[f]	X[g]		X[f]										5.4.1
Monitoring															
ECOG PS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	5.3.3
AE/SAE assessment	X[h]	All visits													6.3
Patient follow-up contact		Day 14 of Cycles 1, 2, and 3													5.2.5
IP administration[i]															
Monotherapy arm															
MEDI4736 (monotherapy)		X	X	X	X	X	X	X	X	X	X	X	X	X	7.2.1
Combination arm															
Tremelimumab[i]		X	X	X	X										7.2.1
MEDI4736 (combination therapy)[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	7.2.1
Quality-of-life assessments															
FACT-BL[j]		X		X		X		X		q8w					5.3.1
PRO-CTCAE[j]		q2w through Week 8			X	X	X	X	X	q4w					5.3.1
PGIC[j]				X		X				q16w					5.3.1
EQ-5D-5L[j]		X		X		X		X		q8w					5.3.1

	Screening	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	For details see CSP Section
Week	**-4 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation)		X	X		X			X[k]							5.4.2
Tumor biopsy (newly acquired or archival ≤3 years old)	X[a]														5.5
Tumor biopsy (archival, if available, is required for all patients who submit a newly acquired biopsy at screening for PD-L1 status)	X														5.5
Tumor assessment (CT or MRI)[l]	X	q8w (±7 days) relative to the date of randomization until confirmed disease progression													5.1
Health economics assessments															
Health resource use (HOSPAD module)[m]	To be completed at each hospitalization														8.5.10

[a] Informed consent includes consent for study procedures and biopsy for PD-L1 status. Informed consent may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization. For patients undergoing retreatment, if clinically feasible, a new biopsy should be obtained.

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

[c] For patients in the immunotherapy treatment arms vital signs will be evaluated prior to the start of the infusion and subsequent BP and pulse will be measured during and after infusion per institutional standard. Body weight will also be collected for all patients at each visit along with vital signs.

[d] If screening laboratory assessments are performed within 3 days prior to Day 1, then tests do not need to be repeated at Day 1. Serum or plasma chemistry, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated. Results for serum or plasma chemistry and LFT monitoring must be available and reviewed by the treating physician or Investigator prior to dosing. fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system. Coagulation tests include activated partial thromboplastin time and international normalized ratio. Gamma glutamyltransferase tested at screening, Cycle 1 Day 1, and as clinically indicated.

[e] Women of childbearing potential are required to have a pregnancy test within 3 days prior to the first dose of study drug. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

[f] Predose (may not exceed 6 hours prior to start of infusion) and within 1 hour of the end of infusion.

[g] Predose only (may not exceed 6 hours prior to the start of infusion).

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

[i] Patients will be randomly assigned to treatment with MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC (cisplatin + gemcitabine or carboplatin + gemcitabine). Tremelimumab will be administered first; MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion. If there are no clinically significant concerns after the first cycle, and at the discretion of the Investigator, then for all other cycles MEDI4736 can be given immediately after the tremelimumab infusion has finished.

[j] PRO assessment dates remain as originally scheduled, as they are based on the date of randomization (not the date of therapy) and are not affected by dose delays. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The FACT-BL will be administered first, followed by the PGIC, the EQ-5D-5L, and then the PRO-CTCAE. Patients will complete PROs using handheld electronic devices at study sites if the assessment timepoint coincides with a scheduled site visit; otherwise, patients will complete PROs at home. NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed within 3 days (-3 days) prior to dosing. PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***.

[k] ADAs for MEDI4736 only.

[l] RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of the chest, abdomen, and pelvis. Additional anatomy may be imaged based on signs and symptoms of individual patients. Baseline assessments, ideally, should be performed as close as possible prior to the start of study treatment. The confirmatory scans should preferably be performed at the next scheduled visit relative to the date of randomization and no less than 4 weeks after the initial assessment of CR/PR/PD. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

[m] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.

Note: For "retreatment" patients (only applicable to the MEDI4736 + tremelimumab combination arm), the schedule of assessments should be continued with the exception of PK and ADA assessments, Hepatitis B and C assessments, and HIV assessments which do not need to be collected a second time.

Note: Assessments to be performed at the times stipulated in the table (with ± windows as provided) and as clinically required in the management of the patient.

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

AE adverse event; ADA anti-drug antibody; β-hCG beta-Human chorionic gonadotropin; C Cycle; CSP Clinical study protocol; CT computed tomography; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; EQ-5D-5L EuroQol five-dimensional descriptive system; FACT-BL Functional Assessment of Cancer Therapy-Bladder Cancer; fT_3 Free triiodothyronine; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; HIV human immunodeficiency virus; LFT Liver function test; MRI magnetic resonance imaging; PD-L1 Programmed cell death ligand 1; PGIC Patient Global Impression of Change; PK pharmacokinetic; PRO Patient-reported outcome; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; PS performance status; q8w Every 8 weeks; SAE serious adverse event; TSH Thyroid-stimulating hormone.

Table 4 Schedule of assessments for cisplatin + gemcitabine 28-day cycle treatment period

*All scheduled assessments (safety, etc) must be performed within 3 days prior to the start of that dosing cycle, with the exception of tumor efficacy (RECIST) assessments (±7-day window, based on date of randomization regardless of dosing delays **If more than 1 evaluation of creatinine clearance has been obtained during the screening period, the creatinine clearance value closest to Cycle 1 Day 1 should be entered into the IVRS system for randomization purposes (see Section 3.3 for details).**

	Screening	C1				C2, C3, C4, and C5				C6[n]				For details see CSP Section
Week	**-4 to -1**	**0**	**0**	**1**	**2**	**4**	**4**	**5**	**6**	**20**	**20**	**21**	**22**	
Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	
Informed consent														
Written informed consent	X[a]													3.3
Study procedures														
Physical examination (full)	X													5.2.2
Targeted physical exam (based on symptoms)		X				X				X				5.2.2
ECG[b]	X	As clinically indicated												5.2.3
Vital signs	X	X				X[c]				X[d]				5.2.4
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Demography, including medical and surgical history and history of tobacco use	X													4.1
Laboratory assessments														
Serum or plasma chemistry (complete clinical chemistry panel) and hematology[e]	X	X		X	X	X		X	X	X		X	X	5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)[f]	X					X[c]								5.2.1
Hepatitis B and C, and HIV	X													5.2.1

	Screening	C1				C2, C3, C4, and C5				C6[n]				For details see CSP Section
Week	**-4 to -1**	**0**	**0**	**1**	**2**	**4**	**4**	**5**	**6**	**20**	**20**	**21**	**22**	
Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	
Urine hCG or serum β-hCG[g] and coagulation parameters[e]	X[g]	As clinically indicated												5.2.1
Monitoring														
ECOG PS	X	X				X				X				5.3.3
AE/SAE assessment	X[h]	All visits												6.3
IP administration														
Cisplatin			X				X				X			7.2.1
Gemcitabine		X		X	X	X		X	X	X		X	X	7.2.1
Quality of life assessments														
FACT-BL[i]		X	q8w											5.3.1
PRO-CTCAE[i]		X			X	X			X[j]	X				5.3.1
PGIC[i]						Weeks 8 and 16								5.3.1
EQ-5D-5L[i]		X	q8w											5.3.1
Other laboratory assessments and assays														
Tumor biopsy (newly acquired or archival ≤3 years old)	X[a]													5.5
Tumor biopsy (archival, if available, is required for all patients who submit a newly acquired biopsy at screening for PD-L1 status)	X													5.5
Tumor assessment (CT or MRI)[k]	X	q8w (±7 days) relative to the date of randomization until confirmed disease progression[l]												5.1
Health economics assessments														
Health resource use (HOSPAD module)[m]	To be completed at each hospitalization													8.5.10

[a] Informed consent includes consent for study procedures and biopsy for PD-L1 status. Informed consent may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization.

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

[c] Day 1 of Cycle 4 only.

[d] Day 1 of Cycle 6 only.

[e] If screening laboratory assessments are performed within 3 days prior to Day 1, then tests do not need to be repeated at Day 1, if applicable as per local routine practice. Hematology and chemistry results should be available and reviewed prior to chemotherapy administration on each dosing day and as per local routine practice. LFT results should be available and reviewed by the treating physician or Investigator prior to the start of each chemotherapy cycle and as per local routine practice. Chemistry, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated. Coagulation tests include activated partial thromboplastin time and international normalized ratio.

[f] fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[g] Women of childbearing potential are required to have a pregnancy test within 3 days prior to the first dose of study drug. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

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

[i] PRO assessment dates remain as originally scheduled, as they are based on the date of randomization (not the date of therapy) and are not affected by dose delays. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The FACT-BL will be administered first, followed by the PGIC, the EQ-5D-5L, and then the PRO-CTCAE. Patients will complete PROs using handheld electronic devices at study sites if the assessment timepoint coincides with a scheduled site visit; otherwise, patients will complete PROs at home. NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed within 3 days (-3 days) prior to dosing. PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***.

[j] Cycle 2 only.

[k] RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of the chest, abdomen, and pelvis. Additional anatomy may be imaged based on signs and symptoms of individual patients. Ideally, baseline assessments should be performed as close as possible prior to the start of study treatment. The confirmatory scans should preferably be performed at the next scheduled visit (±7 days relative to the date of randomization) and no less than 4 weeks after the initial assessment of CR/PR/PD. If an unscheduled assessment was performed and the patient's disease has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

[l] Patients enrolled in the SoC arm will discontinue study drug at the first assessment of disease progression.

[m] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.

[n] In a rare scenario, if at the Investigator's discretion, patients in the SoC arm who have not progressed continue the SoC treatment beyond 6 cycles, the exposure information will be reported in exposure form and the schedule of assessments beyond 6 cycles will be the same as the one for the treatments within 6 cycles.

Note: Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.

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

AE adverse event; β-hCG Beta-human chorionic gonadotropin; C Cycle; CSP Clinical study protocol; CT Computed tomography; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; EQ-5D-5L EuroQol five-dimensional descriptive system; FACT-BL Functional Assessment of Cancer Therapy-Bladder Cancer; fT_3 Free triiodothyronine; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; HIV human immunodeficiency virus; IP investigational product; LFT Liver function test;; MRI Magnetic resonance imaging; PD Progressive disease; PGIC Patient Global Impression of Change; PRO Patient-reported outcome; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; PS performance status; q8w Every 8 weeks; SAE serious adverse event; SoC Standard of care; TSH Thyroid-stimulating hormone.

Table 5 Schedule of assessments for cisplatin + gemcitabine 21-day cycle and carboplatin + gemcitabine treatment period

*All scheduled assessments (safety, etc) must be performed within 3 days prior to the start of that dosing cycle, with the exception of tumor efficacy (RECIST) assessments (±7-day window, based on date of randomization regardless of dosing delays **If more than 1 evaluation of creatinine clearance has been obtained during the screening period, the creatinine clearance value closest to Cycle 1 Day 1 should be entered into the IVRS system for randomization purposes (see Section 3.3 for details).**

	Screening	C1		C2		C3		C4		C5		C6[l]		For details see CSP Section
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	
Informed consent														
Written informed consent[a]	X[a]													3.3
Study procedures														
Physical examination (full)	X													5.2.2
Targeted physical exam (based on symptoms)		X		X		X		X		X		X		5.2.2
ECG[b]	X	As clinically indicated												5.2.3
Vital signs	X	X						X				X		5.2.4
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Demography, including medical and surgical history and history of tobacco use	X													4.1
Laboratory assessments														
Serum or plasma chemistry (complete clinical chemistry panel) and hematology[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1

	Screening	C1		C2		C3		C4		C5		C6[l]		For details see CSP Section
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	
Thyroid function tests (TSH, fT_3, and fT_4)[d]	X									X				5.2.1
Hepatitis B and C and HIV	X													5.2.1
Urine hCG or serum β-hCG[e] and coagulation parameters[c]	X	As clinically indicated												5.2.1
Monitoring														
ECOG PS	X	X		X		X		X		X		X		5.3.3
AE/SAE assessment[f]	X[f]	All visits												6.3
IP administration[g]														
Cisplatin + gemcitabine arm														
Cisplatin		X		X		X		X		X		X		7.2.1
Gemcitabine (+ cisplatin arm)		X	X	X	X	X	X	X	X	X	X	X	X	7.2.1
Carboplatin + gemcitabine arm														
Carboplatin		X		X		X		X		X		X		7.2.1
Gemcitabine (+ carboplatin arm)		X	X	X	X	X	X	X	X	X	X	X	X	7.2.1
Quality of life assessments														
FACT-BL[h]		X	q8w											5.3.1
PRO-CTCAE[h]		X	q2w through Week 8					q4w from Week 8						5.3.1
PGIC[h]								Weeks 8 and 16						5.3.1
EQ-5D-5L[h]		X	q8w											5.3.1
Other laboratory assessments and assays														
Tumor biopsy (newly acquired or archival ≤3 years old)	X[a]													5.5

	Screening	C1		C2		C3		C4		C5		C6[l]		For details see CSP Section
Week	**-4 to -1**	**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**13**	**15**	**16**	
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	
Tumor biopsy (archival, if available, is required for patients who submit a newly acquired biopsy at screening for PD-L1 status)	X													5.5
Tumor assessment (CT or MRI)[i]	X	q8w relative to the date of randomization until confirmed disease progression[j]												5.1
Health economics assessments														
Health resource use (HOSPAD module)[k]	To be completed at each hospitalization													8.5.10

[a] Informed consent includes consent for study procedures andbiopsy for PD-L1 status. Informed consent may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization.

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

[c] If screening laboratory assessments are performed within 3 days prior to Day 1, then tests do not need to be repeated at Day 1, if applicable as per local routine practice. Hematology and chemistry results should be available and reviewed by the treating physician or Investigator prior to chemotherapy administration on each dosing day and as per local routine practice. LFT results should be available and reviewed by the treating physician or Investigator prior to the start of each chemotherapy cycle and as per local routine practice. Chemistry, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated. Coagulation tests include activated partial thromboplastin time and international normalized ratio.

[d] fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[e] Women of childbearing potential are required to have a pregnancy test within 3 days prior to the first dose of study drug. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

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

[g] Patients randomized to the SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) arm will receive either cisplatin + gemcitabine or carboplatin + gemcitabine based on their cisplatin eligibility.

[h] PRO assessment dates remain as originally scheduled, as they are based on the date of randomization (not the date of therapy) and are not affected by dose delays. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The FACT-BL will be administered first, followed by the PGIC, the EQ-5D-5L, and then the PRO-CTCAE. Patients will complete PROs using handheld electronic devices at study sites if the assessment timepoint coincides with a scheduled site visit; otherwise, patients will complete PROs at home. NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed within 3 days (-3 days) prior to dosing. PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***.

[i] RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of the chest, abdomen, and pelvis. Additional anatomy may be imaged based on signs and symptoms of individual patients. Baseline assessments, ideally, should be performed as close as possible prior to the start of study treatment. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of randomization) and no less than 4 weeks after the initial assessment of CR/PR/PD. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

[j] Patients enrolled in the SoC arm will discontinue study drug at the first assessment of disease progression.

[k] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.

[l] In a rare scenario, if at the Investigator's discretion, patients in the SoC arm who have not progressed continue the SoC treatment beyond 6 cycles, the exposure information will be reported in exposure form and the schedule of assessments beyond 6 cycles will be the same as the one for the treatments within 6 cycles.

Note: Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.
Note: All assessments on treatment days are to be performed pre-infusion unless otherwise indicated.
AE adverse event; β-hCG Beta-human chorionic gonadotropin; C Cycle; CSP Clinical study protocol; CT computer tomography; FACT-BL Functional Assessment of Cancer Therapy-Bladder Cancer; fT_3 Free triiodothyronine; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; EQ-5D-5L EuroQol five-dimensional descriptive system; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; HIV human immunodeficiency virus; LFT Liver function test; MRI magnetic resonance imaging; PD-L1 programmed cell death 1; PGIC Patient Global Impression of Change; PRO Patient-reported outcome; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; PS performance status; q8w Every 8 weeks; SAE serious adverse event; TSH Thyroid-stimulating hormone.

Table 6 Schedule of study procedures: follow-up for patients in the MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy arms

Evaluation	Time since last dose of IP								For details see CSP Section
	Day (±3)	Months (±1 week)						12 months and every 6 months (±2 weeks)	
	30	2	3	4	6	8	10		
Physical examination (full)	X								5.2.2
Vital signs	X								5.2.4
Urine hCG or serum β-hCG[a]	X								5.2.1
AE/SAE assessment	X	X	X						6.3
Concomitant medications	X	X	X						7.7
ECOG PS[b]	X	X		X	X	X	X	X (every 2 months)	5.3.3
Survival status: for all patients, including phone contact with patients who refuse to return for evaluations and agree to be contacted[c]		X		X	X	X	X	X (every 2 months)	5.1
Subsequent anticancer therapy[d] and second progression assessment[e]	X	X	X	X	X	X	X	X	NA
Serum or plasma chemistry and hematology	X	X	X						5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)[f]	X								5.2.1
PK assessment			X						5.4.1
Immunogenicity assessment (ADA sampling [including ADA neutralizing antibodies] to identify ADA responses in patient circulation)			X						5.4.2
FACT-BL[g]	q8w up to Month 6 after disease progression								5.3.1
PRO-CTCAE[g]	q4w up to Month 6 after disease progression								5.3.1
EQ-5D-5L[g]	q8w up to Month 6 after disease progression								5.3.1

Evaluation	Time since last dose of IP								For details see CSP Section
	Day (±3)	Months (±1 week)						12 months and every 6 months (±2 weeks)	
	30	2	3	4	6	8	10		
Health resource use (HOSPAD module)[h]	X								8.5.10
Tumor assessment (CT or MRI)[i]	q8w (±7 days) relative to the date of randomization until confirmed disease progression								5.1

[a] For women of childbearing potential
[b] ECOG PS should be collected if available at the 2-monthly calls to obtain subsequent anticancer therapy and survival status.
[c] Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for bladder cancer (including surgery) after the last dose of study treatment must be recorded in the eCRF.
[d] Will be collected until the end of the clinical phase of the study (final study visit).
[e] Second disease progression (PFS2) assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. PFS2 should be collected after the progression used for the PFS endpoint.
[f] fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[g] PRO assessment dates remain as originally scheduled, as they are based on the date of randomization (not the date of therapy) and are not affected by dose delays. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The FACT-BL will be administered first, followed by the EQ-5D-5L and then the PRO-CTCAE. Patients will complete PROs using handheld electronic devices at study sites if the assessment timepoint coincides with a scheduled site visit; otherwise, patients will complete PROs at home. NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed within 3 days (-3 days) prior to dosing. PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***.
[h] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.
[i] RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of the chest, abdomen, and pelvis. Additional anatomy may be imaged based on signs and symptoms of individual patients. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of randomization) and no less than 4 weeks after the initial assessment of CR/PR/PD. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

AE adverse event; ADA anti-drug antibody; β- hCG beta-Human chorionic gonadotropin; CSP Clinical study protocol; CT computed tomography; eCRF electronic case report form; ECOG Eastern Cooperative Oncology Group; EQ-5D-5L EuroQol five-dimensional descriptive system; FACT-BL Functional Assessment of Cancer Therapy-Bladder Cancer; fT_3 Free triiodothyronine; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; IP investigational product; MRI magnetic resonance imaging; NA Not applicable; PK pharmacokinetic; PD progressive disease; PRO Patient-reported outcome; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; PS performance status; q8w Every 8 weeks; SAE serious adverse event; TSH Thyroid-stimulating hormone.

Table 7 Schedule of study procedures: follow-up for chemotherapy patients

Evaluation	Time since last dose of IP								For details see CSP Section
	Day (±3)	Months (±1 week)						12 months and every 6 months (±2 weeks)	
	30	2	3	4	6	8	10		
Physical examination (full)	X								5.2.2
Vital signs	X								5.2.4
Urine hCG or serum β-hCG[a]	X								5.2.1
AE/SAE assessment	X	X	X						6.3
Concomitant medications	X	X	X						7.7
ECOG PS[b]	X	X		X	X	X	X	X (every 2 months)	5.3.3
Survival status: for all patients, including phone contact with patients who refuse to return for evaluations and agree to be contacted[c]		X		X	X	X	X	X (every 2 months)	5.1
Subsequent anticancer therapy and second progression assessment[d]	X	X	X	X	X	X	X	X	NA
Serum or plasma chemistry and hematology	X	X	X						5.2.1
FACT-BL[e]	q8w up to Month 6 after disease progression								5.3.1
PRO-CTCAE[e]	q4w up to Month 6 after disease progression								5.3.1
EQ-5D-5L[e]	q8w up to Month 6 after disease progression								5.3.1
Health resource use (HOSPAD module)[f]	X								8.5.10
Tumor assessment (CT or MRI)[g]	q8w (±7 days) relative to the date of randomization until confirmed disease progression								5.1

[a] For women of childbearing potential.
[b] ECOG PS to be collected if available at the 2 monthly calls to obtain subsequent anticancer therapy and survival status.
[c] Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for bladder cancer (including surgery) after the last dose of study treatment must be recorded in the eCRF.
[d] Second disease progression (PFS2) assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. PFS2 should be collected after the progression used for the PFS endpoint.
[e] PRO assessment dates remain as originally scheduled, as they are based on the date of randomization (not the date of therapy) and are not affected by dose delays. PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The FACT-BL will be administered first, followed by the EQ-5D-5L

and then the PRO-CTCAE. Patients will complete PROs using handheld electronic devices at study sites if the assessment timepoint coincides with a scheduled site visit; otherwise, patients will complete PROs at home. NOTE: All PROs ***MUST*** be administered ***before*** ALL procedures including medication infusion(s). PROs must be completed within 3 days (-3 days) prior to dosing. PROs must be completed using ***ONLY the electronic devices***; paper questionnaires are ***not allowed***.

[f] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.

[g] RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of the chest, abdomen, and pelvis. Additional anatomy may be imaged based on signs and symptoms of individual patients. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of randomization) and no less than 4 weeks after the initial assessment of CR/PR/PD. If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

AE adverse event; β- hCG beta-Human chorionic gonadotropin; CSP Clinical study protocol; CT computed tomography; ECOG Eastern Cooperative Oncology Group; EQ-5D-5L EuroQol five-dimensional descriptive system; FACT-BL Functional Assessment of Cancer Therapy-Bladder Cancer; fT_3 Free triiodothyronine; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; IP investigational product; MRI magnetic resonance imaging; NA Not applicable; PRO Patient-reported outcome; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; PS performance status; q8w Every 8 weeks; SAE serious adverse event; TSH Thyroid-stimulating hormone.

4.1 Enrollment/screening period

All screening and enrollment procedures will be performed according to the assessment schedule in Table 3, Table 4, and Table 5.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply a sample of their tumor (archival or recently obtained biopsy for PD-L1 testing for study entry. Additionally, archival tissue (if available) is required for all patients who submit a newly acquired biopsy at screening for PD-L1 status. This consent is included in the main patient informed consent form (ICF).

All screening/baseline procedures, must be performed within 28 days before randomization (Days -28 to -1), with the exception of the patient's tumoral PD-L1 status (must be performed within -56 days before randomization). Informed consent may be obtained prior to the 28-day screening window in order to permit tumor biopsy sample acquisition, which must be analyzed prior to randomization.

The timing of ECGs and vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

If more than 1 evaluation of creatinine clearance has been obtained during the screening period, the creatinine clearance value closest to Cycle 1 Day 1 should be entered into the IVRS system for randomization purposes (see Section 3.3 for details).

4.2 Treatment period

All procedures to be conducted during the respective treatment periods for MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC will be performed according to the assessment schedules (see Table 3, Table 4, and Table 5). Note that patients randomized to the MEDI4736 ± tremelimumab combination or MEDI4736 monotherapy treatment arms may continue to be treated beyond Cycle 13. Patients in the MEDI4736 + tremelimumab combination arm who complete 4 dosing cycles and subsequently have PD during treatment with MEDI4736 alone may restart combination treatment if they meet eligibility criteria for retreatment (see Section 7.2.2) and are deemed to have clinical benefit per Investigator judgment.

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

4.3 Follow-up period

All procedures will be performed according to the assessment schedules (see Table 6 and Table 7). For patients who require IP treatment to be held for toxicity or other reasons and

subsequently discontinue therapy without restarting IP, all follow-up assessments will be based on the date of the last dose of IP.

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

5. STUDY ASSESSMENTS

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRF 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 (CSA). The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

The Investigator will record data on the observations, tests, and assessments specified in the protocol on the eCRFs provided by AstraZeneca. The eCRF will be accompanied with "Instructions for the Investigator," which should be followed. These instructions provide guidance for the recording of study data in the eCRF including how to change data incorrectly recorded.

5.1 Efficacy assessments

RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS, proportion of patients alive and progression free at 12 months from randomization (APF12), ORR, DoR, and DCR. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions and the objective tumor response criteria (CR, PR, SD, or PD) are presented in Appendix E. Time from randomization to second progression (PFS2) defined by local standard clinical practice, OS, and proportion of patients alive at 24 months from randomization (OS24) will also be evaluated.

The methods of assessment of tumor burden used at baseline are CT and MRI scans of the chest, abdomen, and pelvis. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. All on-study assessments should utilize the same mode of scanning (CT or MRI) as baseline scans for accurate comparisons.

Schedule of required RECIST assessments is based on the date of randomization, not on the date of C1D1. The baseline assessment should be performed no more than 28 days before randomization and ideally as close as possible to the start of the assigned IP. Efficacy for all patients will be assessed by objective tumor assessments every 8 weeks (q8w, ±7 days)

relative to the date of randomization and regardless of dosing delays until confirmed disease progression. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her originally scheduled visits (relative to the date of randomization).

For patients who discontinue treatment due to toxicity or other reasons in the absence of confirmed objective progression, objective tumor assessments per the scheduled assessments should be continued q8w (±7 days) relative to the date of randomization until confirmed disease progression.

In addition to the required confirmatory scan for PR and CR, a confirmatory scan is also required following the initial demonstration of PD. The confirmatory scan should occur preferably at the next regularly scheduled imaging visit (based on randomization date) and no earlier than 4 weeks after the prior assessment of radiological PD, by RECIST 1.1. In the absence of clinically significant deterioration after the initial assessment of disease progression, treatment with MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy will continue between the initial assessment of progression and confirmation of disease progression.

Immediate prior radiologic progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in the sum of diameters compared with nadir

- *and/or* significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan timepoint compared with the immediate prior timepoint (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan timepoint.)

- *and/or* additional new unequivocal lesions at the confirmatory scan timepoint

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to or after the initial assessment of progression, then the patient should continue to submit imaging assessments (q8w ±7 days) relative to the date of randomization until objective disease progression is confirmed.

Categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD, and PD. Target lesion progression will be calculated in comparison to when the tumor burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumor response (CR or PR) and SD will be calculated in comparison to the baseline tumor measurements obtained before starting treatment.

Objective tumor response (CR or PR) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed.

Following confirmed disease progression, all patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the study plan (Table 6 and Table 7). Patients enrolled in the SoC arm will discontinue study drug at the first assessment of disease progression. An exception is patients with PD who continue to receive MEDI4736 monotherapy or MEDI4736+tremelimumab combination arms at the discretion of the Investigator (after consultation with AstraZeneca); these patients will have scans for RECIST 1.1 assessments q8w (per Table 3, Table 4, and Table 5, based on randomization date) until confirmed disease progression. In addition, all patients will be contacted in the week following data cutoffs to confirm survival status.

Patients in the MEDI4736 + tremelimumab combination arm who complete 4 doses/dosing cycle (with clinical benefit per Investigator judgment) and subsequently have PD during treatment with MEDI4736 alone may restart combination treatment if they meet eligibility criteria for retreatment (see Section 7.2.2). **Patients who restart treatment after PD must have a baseline tumor assessment within 28 days of restarting treatment with MEDI4736 + tremelimumab combination therapy; all further scans should occur q8w (±7 days) relative to the date of first dose of retreatment until confirmed disease progression.**

It is important to follow the assessment schedule as closely as possible. Refer to the study plans (Table 3 [screening and the treatment period for MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy], Table 4 [screening and 28-day cycle treatment period for cisplatin + gemcitabine], Table 5 [screening and 21-day cycle treatment period for cisplatin + gemcitabine and carboplatin + gemcitabine], Table 6 [for follow-up of patients in the MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy arms] and Table 7 [for follow up of patients in the chemotherapy arm]), and Appendix E.

5.1.1 Central reading of scans

All imaging assessments, including unscheduled visit scans and scans from subsequent non-protocol therapy (if required per protocol), will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization. Central analysis of images will be used for analysis of efficacy profile of MEDI4736 monotherapy in patients who are not cisplatin-eligible. Results of these independent reviews will not be communicated to Investigators, and the management of patients will be based solely upon the results of the local assessments conducted by the Investigator.

5.1.2 Survival assessments

Assessments for survival must be made every 2 months following treatment discontinuation. Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the data cutoff for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the data cutoff.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 3 through Table 7).

If more than 1 evaluation of creatinine clearance has been obtained during the screening period, the creatinine clearance value closest to Cycle 1 Day 1 should be entered into the IVRS system for randomization purposes (see Section 3.3 for details). 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. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

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

The laboratory variables to be measured are presented in Table 8 (clinical chemistry), Table 9 (hematology).

Table 8 Clinical chemistry (serum or plasma)

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate (optional for Japan and other countries where available)	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein (optional for Japan and other countries where available)
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b] (optional for Japan and other countries where available)	Uric acid

[a] If total bilirubin is ≥2 × ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.
[b] At Screening, Cycle 1 Day 1, and as clinically indicated.
ULN upper limit of normal

Table 9 Hematology

Hemoglobin	Neutrophils
Lymphocytes	Platelet count
Monocytes	Total white cell count

Note: Coagulation parameters: activated partial thromboplastin time and international normalized ratio to be assessed at screening and as clinically indicated

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix D for further instructions. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria. All patients with an elevated AST, ALT, or bilirubin value (the latter at ≥1.5 × ULN) at the time of the last dose of study treatment should have a further liver chemistry profile (AST, ALT, bilirubin, and alkaline phosphatase) performed 30 days (±3 days) after permanent discontinuation of study treatment.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 6.3.6.

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

5.2.2 Physical examination

Physical examinations will be performed according to the assessment schedules (see Table 3 through Table 7). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured only at screening. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. All physical examinations will include body weight measurement. Situations in which physical examination results should be reported as AEs are described in Section 6.3.6.

5.2.3 ECG

Resting 12-lead ECGs will be recorded according to the assessment schedule (see Table 3, Table 4, and Table 5). ECGs should be obtained after the patient has been in a supine position for 5 minutes and should be recorded while the patient remains in that position.

At screening, ECGs will be obtained in which QTcF must be <470 ms.

Following screening, any clinically indicated ECGs must be performed within an hour prior to the start of the infusion and at least 1 timepoint 0 to 3 hours after the infusion.

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

Situations in which ECG results should be reported as AEs are described in Section 6.3.6.

5.2.4 Vital signs

For all treatment arms, vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules (see Table 3 through Table 7). Body weight is also recorded at each visit along with vital signs.

Supine or semi-supine BP will be measured using a BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes.

For patients in the MEDI4736 + tremelimumab combination and MEDI4736 monotherapy treatment arms:

For the first infusion (based on a 60-minute infusion):

- All vital signs (BP, pulse, respiratory rate, and temperature) will be collected prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])

- BP and pulse will be collected approximately 30 minutes during the infusion (halfway through infusion) (±5 minutes)

- BP and pulse will be collected at the end of the infusion (approximately 60 minutes ±5 minutes)

- A 1-hour observation period is required after the first infusion of tremelimumab or MEDI4736. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion.

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

On subsequent infusion days, patients in the MEDI4736 + tremelimumab combination and MEDI4736 monotherapy treatment arms will have all vital signs (BP, pulse, respiratory rate, and temperature) evaluated prior to the start of the infusion, and subsequent BP and pulse will be measured during and after infusion per institutional standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF page.

For patients in the SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) arm, all vital signs (BP, pulse, respiratory rate, and approximately 30 minutes before up to 0 minute). BP and pulse may additionally be evaluated as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 6.3.6.

5.2.5 Other safety assessments

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

(ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum beta-human chorionic gonadotropin [β-hCG]) samples will be performed for premenopausal women of childbearing potential at the times specified in the assessment schedule (see Table 3 through Table 7). Tests will be performed by the hospital's local laboratory. If results are positive, the patient is ineligible and must be discontinued from treatment. In the event of a suspected pregnancy during the study, the test should be repeated.

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, HIV antibodies, thyroid stimulating hormone, free triiodothyronine (fT_3), and free thyroxine (fT_4).

It is strongly recommended that patients are contacted 2 weeks after receiving the first 3 cycles of MEDI4736 + tremelimumab combination or MEDI4736 monotherapy (Cycle 1 Day 14, Cycle 2 Day 14, and Cycle 3 Day 14) of study drug(s) to ensure early identification and management of toxicities.

5.3 Other assessments

5.3.1 Patient-reported outcomes

PRO assessment dates remain as originally scheduled, as they are based on the date of randomization (not the date of therapy) and are not affected by dose delays. "PRO" is an umbrella term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become a significant endpoint when evaluating effectiveness of treatments in clinical studies. The following PROs will be administered in this study: Functional Assessment of Cancer Therapy-Bladder Cancer (FACT-BL); patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE); the Patient Global Impression of Change (PGIC); and the EuroQol 5-dimension, 5-level health state utility index (EQ-5D-5L; see Appendix F).

5.3.1.1 FACT-BL

The FACT-BL (Appendix F) is a disease-specific 39-item questionnaire included for the purpose of assessing health-related quality of life (HRQoL) and bladder cancer-specific symptoms. It is a well-established measure of HRQoL/health status commonly used in bladder cancer clinical studies. The FACT-BL was developed specifically for patients with advanced bladder cancer and has been found to be reliable and valid in this population (Cella et al 1993). The FACT-BL consists of 5 subscales: Physical Well-Being (PWB; 7 items), Functional Well-Being (FWB; 7 items), Emotional Well-Being (EWB; 6 items), Social Well-Being (SWB; 7 items), and Additional Concerns or Bladder Cancer Subscale (BlCS) specific to bladder cancer (12 items). The BlCS assesses 5 domains: urinary function (3 items), bowel function (2 items), sexual function (2 items; 1 item is not applicable to women), body image (1 item), weight loss/appetite (2 items), and the care of ostomy appliance or urinary diversion (2 items) (Cella et al 1993). Patients without any urinary diversion

procedure do not have to answer the ostomy appliance questions. Thus, specifically for the patients in the current study, the BlCS items are 10 and 9 for males and females, respectively. All FACT-BL questions are scored on a 5-point Likert scale from 0 to 4 (0 being not at all and 4 being very much). Negatively stated items are reversed by subtracting the response from 4. After reversing proper items, all subscale items are summed to a total, which is the subscale score. For all subscales, symptoms index, and individual item scores, the higher the score, the better the HRQoL/symptom. Thus, a score of 0 is a severely symptomatic patient, and the highest possible score is an asymptomatic patient.

5.3.1.2 PRO-CTCAE

The PRO-CTCAE (Appendix F) is included to address tolerability from the patients' perspective. It was developed by the NCI. The PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Basch et al 2009, Litwin et al 1998, Sprangers and Aaronson 1992). These symptoms have been converted to patient terms (eg, CTCAE term "myalgia" converted to "aching muscles"). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. These items have been extensively evaluated by patients with cancer to be clear, comprehensible, and measuring the symptom of interest. In this study, only items that are considered relevant for the trial, site of cancer, and cancer treatment are selected (see Appendix F).

5.3.1.3 PGIC

The PGIC item (Appendix F) is included to assess how a patient perceives his or her overall change in health status since the start of study treatment. Patients will choose from response options from "Very Much Improved" to "Very Much Worse." This item is included to assist with the interpretation of other PRO measures and for assessing the overall impact of treatment (see Appendix F).

5.3.1.4 EQ-5D-5L

The EQ-5D-5L (Appendix F) is a standardized measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple, descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. The questionnaire assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and extreme problems) that reflect increasing levels of difficulty (EuroQol Group 2013).

Since 2009, the EuroQol group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L) that expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011). Preliminary studies indicate that the EQ-5D-5L version improves upon the properties of the 3L measure in terms of reduced ceiling effect, increased reliability, and an improved ability to differentiate between different levels of health (Janssen et al 2008a, Janssen et al 2008b, Pickard et al 2007).

The patient will be asked to indicate his or her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analog scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state (see Appendix F).

5.3.2 Administration of the patient-reported outcome questionnaires

The PRO instruments will be self-administered by the patients as ePROs using handheld devices. All assessments should be completed without assistance from site staff or relatives/friends according to the assessment schedules (see Table 3 through Table 7), before any other study procedures are conducted at a given visit. Each center must allocate the responsibility for the administration of the PRO instruments to a specific individual (eg, a research nurse or study coordinator) and, if possible, assign a back-up person to cover if that individual is absent. PROs must be completed within 3 days (-3 days) prior to dosing. Study coordinators should ensure that patients have completed the PRO assessment for that visit before the patient is seen by a study nurse or physician. It takes approximately 15 to 30 minutes for patients to complete the questionnaires; therefore, the burden to the patient is moderate. Patients will complete PROs at study sites if the assessment timepoint coincides with a scheduled site visit; otherwise, patients will complete PROs at home. Similarly, during the post-progression period, patients should complete PROs at home or at the study site if a scheduled visit coincides with the timepoint. If patients have had scans or other tests at an outside facility or missed a scheduled data collection site visit, PRO questionnaires should still be completed by the patient at home on that scheduled visit date. Reminders should be sent to patients at home as needed to ensure compliance with the assessment schedules.

The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- PRO questionnaires must be completed prior to any other study procedures (following informed consent), including medication infusion(s), and before discussion of disease progression to avoid bias in patient's responses to the questions
- When each instrument is due to be completed, the following order should be observed; FACT-BL should be administered first followed by PGIC, EQ-5D-5L, and then PRO-CTCAE
- PRO questionnaires must be completed by the patient in private.

- The research nurse or appointed site staff must explain to patients the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the patients have any medical problems, they should discuss them with the doctor or research nurse separately from the ePRO assessment.

- The research nurse or appointed site staff must train the patient on how to use the ePRO device, using the materials and training provided by the ePRO vendor, and provide guidance on whom to call if there are problems with the device if the patient is completing the ePRO at home. All questionnaires must be completed using the ePRO device; paper questionnaires are not allowed in this study.

- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items.

- The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires. If a patient uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when he or she attends the clinic, the patient will be exempted from completing the PROs.

- Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient should be exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff.

- The patient should be given sufficient time to complete the PRO questionnaires at his or her own speed.

- The research nurse or appointed site staff must monitor compliance; minimizing missing data is a key aspect of study success. Compliance must be checked at each study visit and should be checked more frequently to identify problems early. If compliance drops below 85%, a check-in call from the site to ask the patient if he or she has any difficulties is highly recommended.

5.3.3 ECOG performance status

ECOG PS will be assessed at the times specified in the assessment schedules (see Table 3 through Table 7) based on the following:

- 0=Fully active; able to carry out all pre-disease activities without restrictions

- 1=Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work

- 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4=Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5=Dead

Any significant changes from baseline or screening must be reported as an AE.

5.4 Pharmacokinetics

5.4.1 Collection of samples and determination of drug concentration

Blood samples for determination of MEDI4736 and tremelimumab concentration in serum will be obtained according to the assessment schedules (see Table 3 and Table 6).

Samples for determination of MEDI4736 and tremelimumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

5.4.2 Collection of samples to measure the presence of ADAs

The presence of ADAs (including ADA neutralizing antibodies) will be assessed in serum samples taken according to the assessment schedules (see Table 3 and Table 6). Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual. Samples will be tested in AstraZeneca designated laboratory. The samples may need to be exported to USA for testing.

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for both IPs (MEDI4736 and tremelimumab) using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive-negative cut points previously statistically determined from drug-naïve validation samples will be used.

5.4.3 Storage and destruction of pharmacokinetic/ADA samples

PK and ADA samples, if not exhausted by analyses outlined herein, may be retained for 15 years from the patient's last visit date for research purposes.

PK and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the clinical study report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but will be reported separately in a Bioanalytical Validation Report.

Any residual back-up PK samples may be used for future exploratory biomarker research (in this case, residual back-up PK samples will be shipped to AstraZeneca-assigned Biobank; see details in the Laboratory Manual).

5.5 Biomarker analysis

The patient's consent to the use of donated biological samples is mandatory.

Pre-randomization tumor PD-L1 expression will be evaluated in all patients, and PD-L1 status is included as a stratification factor. Putative associations with clinical endpoints will be assessed. Baseline tumor requirements are briefly described in Section 5.5.1. Based on availability of tissue, additional exploratory biomarkers may also be evaluated as described in Section 5.5.1.1.

Comparisons of PD-L1 expression in tumor will be made between arms to determine if PD-L1 status is prognostic or predictive of outcomes associated with MEDI4736 monotherapy and/or MEDI4736 + tremelimumab combination therapy. These results may be pooled with biomarker data from other MEDI4736 and tremelimumab studies to evaluate biological responses across indications and to compare results in other monotherapy versus combination settings.

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 research relevant to evaluating biological and/or clinical response to immunotherapy.

5.5.1 Evaluation of candidate, predictive markers - tumor PD-L1

Provision of tissue for PD-L1 IHC is as follows:

- MANDATORY – Provision of a newly acquired tumor sample (preferred) OR formalin fixed and paraffin embedded archival tissue obtained within 3 years prior to screening. ONLY 1 sample (either newly acquired or archival tissue) will be used to determine PD-L1 status. Where multiple samples have been submitted for the same patient, the initial result will determine a patient's PD-L1 status.

- Samples should be collected via an image-guided core needle (18 gauge or larger) or be collected as an excisional or incisional tumor biopsy sample.

  Where institutional practice, in this setting, uses a smaller gauge needle, samples should be submitted in sufficient number to ensure that a valid result can be achieved.

When tissue is acquired for this study, effort should be made to maximize material for downstream analyses. Two cores using an 18 gauge or larger needle are required for establishing PD-L1 status. These should be placed in formalin and processed to a single paraffin embedded block, as described in the Pathology Manual. When a smaller gauge needle is used, the number of cores rises to 3 or 4. As a guidance, it is anticipated that 4 passes of a core needle will provide sufficient tissue for establishing PD-L1 status and for delivering protocol-defined exploratory objectives. Whenever feasible, additional cores (beyond those required to establish PD-L1 status) should be obtained and immediately frozen as described in the laboratory manual.

The tumor specimen submitted to establish PD-L1 status should be of sufficient quantity to allow for PD-L1 IHC analyses (see the pathology Manual). Samples with limited tumor content and fine needle aspirates are inadequate for defining tumor PD-L1 status.

Tumor lesions used for biopsies acquired during screening should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy, and in this instance, only core needle (not excisional/incisional) biopsy is allowed. For patients with a single target lesion, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.

- If a newly acquired tumor sample is submitted to determine PD-L1 status during screening, archived tumor tissue block (formalin-fixed paraffin-embedded) is required, when available and accessible, and where such samples exist in a quantity sufficient to allow for analysis. Tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. An archived tumor tissue block or sections may be delivered at any time during the study (when newly acquired tissue was used to establish PD-L1 status). Please consult the Laboratory Manual for specific instructions and guidelines regarding sections and acceptable tissue sampling.

- The collection of tumor biopsies at the time of progression and prior to retreatment is strongly encouraged. The biopsy procedure at retreatment should be omitted only if there is unacceptable clinical risk or the procedure is otherwise considered not feasible. The Investigator should consult with AstraZeneca prior to making the decision not to biopsy at retreatment.

- The collection of additional biopsies upon progression of patients in the MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy arms is strongly encouraged.

Tumor biopsies collected after determination of PD-L1 status for stratification will be used to evaluate potential predictive biomarkers and only for exploratory analyses.

Please review the Laboratory Manual for further details of requirements including sample quality control and shipping.

A brief description of exploratory tumor markers likely to be explored by IHC is provided in Section 5.5.1.1.

To meet the requirement of Food and Drug Administration (FDA) approval of a companion diagnostic, sections of the tumor will be retained at Ventana or a Ventana-approved laboratory for potential additional studies, as requested by the FDA, to support potential test approval.

5.5.1.1 Exploratory biomarker data

Blood samples already obtained will be used for exploratory biomarker analyses and tumor samples will be used for exploratory biomarker analyses in selected countries only. Details for tumor samples collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Pharmacodynamic changes in biomarker measures will be monitored, when applicable. Baseline measures (and early, on-treatment changes) will be correlated with outcomes. Data will be compared across treatment arms and times of treatment to determine if pharmacodynamic changes are specific to 1 treatment arm versus the other.

Additional sample collections and analyses may be completed at select study sites by site-specific amendments. All samples collected for such exploratory analyses will be stored at the site, a reference laboratory, or at Sponsor's facilities and may be used for subsequent research relevant to evaluating response to immunotherapy.

The exploratory biomarker plan is described by sample type below.

Tumor markers (in FFPET)

Tissue obtained as part of screening procedures (or at progression) for establishing PD-L1 status may be analyzed for additional markers by IHC. Markers evaluated may change based on the best available information at the time of the biomarker analysis. Markers of special interest include, but are not limited to, Ox40, GITR, PD-L2, Tim-3, CD137, and Lag-3.

Tissues obtained may also be assessed for somatic mutations, tumor burden, neo-antigen prediction, and/or for an interferon-gamma (IFN-γ) gene expression signature (eg, IFN-γ, *CXCL9*, *LAG3*, and *CD274*) by targeted RNAseq and/or other gene expression methodologies.

For geomic DNA which has been extracted, genotyping of immunomodulatory genes such as PD-1, PD-L1, CTLA-4, and human leukocyte antigen loci may be completed to determine whether natural variation within such genes is associated with likelihood of clinical benefit and/or with likelihood of drug-related AEs. Genes associated with solid tumor development, disease progression, or likelihood of tumor response to chemotherapy may, likewise, be investigated. Genotyping will occur retrospectively, data will not be shared with patients, and results will not impact treatment decisions.

For the whole blood samples which have been collected, total RNA may be prepared for quantification of RNA and/or micro-ribonucleic acid (miRNA) expression using reverse transcription quantitative polymerase chain reaction (RT-qPCR), microarray, sequencing, or similar methodology. Focus is likely to be given to the expression of immunomodulatory genes previously found to be up-regulated in response to MEDI4736 and/or tremelimumab (data not shown). Pretreatment expression of such genes may indicate active immune responses that may be augmented by checkpoint inhibitor immunotherapies; correlations with outcome data will be completed on select candidate predictive markers with the aim of characterizing useful expression thresholds for identifying patients likely to receive benefit. Similar procedures may be completed using select peripheral blood mononuclear cell (PBMC) samples described below.

Myeloid-derived suppressor cells

Recent collective findings suggest that a baseline measure of circulating myeloid-derived suppressor cells (MDSCs) may be used as a prognostic tool in different disease settings and may specifically predict the likelihood of response to ipilimumab (anti-CTLA-4 therapy) (Kitano et al 2014, Meyer et al 2014). Flow cytometry may be completed on available patient samples obtained to quantify pretreatment circulating MDSC subtypes and analyzed for their ability to predict clinical benefit from tremelimumab.

Peripheral blood mononuclear cells and soluble factors (plasma)

Whole blood samples may be collected for preparation of PBMCs and storage for potential downstream analyses, including: immune cell composition/activation status, epigenetic analyses, T-cell functional assays, and/or the assessment of the diversity and clonality of T-cell receptor gene rearrangements using DNA.

Plasma will be obtained to explore expression of cytokines and chemokines, including but not limited to IFN-γ, interleukin (IL)-18, CXCL9, and CXCL10.

Similarly, the concentrations of a battery of immune cell ligands or receptors may be assessed. Proteins of special interest include CTLA-4, PD-1, B7-1, B7-2, and IL6R.

Urine-based markers

Urine may be obtained before and after treatment from patients who have not undergone a full cystectomy and who have tumor lesion(s) present in the urothelium. These samples will be used to explore gene expression analyses by RT-qPCR or similar methodologies as well as cytokine/chemokine analyses.

5.5.2 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, any 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.

5.5.3 Storage, re-use, and destruction of biological samples

Biological samples for future research will be retained at AstraZeneca or its designee for a maximum of 15 years following last patient, last visit, after which they will be destroyed. The results of this biomarker research may be reported in the CSR itself, as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies involving MEDI4736 or tremelimumab to generate hypotheses to be tested in future research.

5.5.4 Labeling and shipment of biological samples

The Principal Investigator (PI) 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 materials in Category A 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.

5.5.5 Chain of custody of biological samples

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

The PI 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 by the AstraZeneca Biobank team during the entire life cycle.

5.5.6 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 will be documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The PI will:

- Ensure that AstraZeneca is immediately notified of the patient's 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 that the action is documented
- Ensure that the laboratory(ies) 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

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

6.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition (other than progression of the malignancy under evaluation) 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 or chest pain), signs (eg, tachycardia or enlarged liver), or the abnormal results of an investigation (eg, laboratory findings or electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, or follow-up) that fulfills 1 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 1 of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix A.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

AEs and SAEs for all treatment arms will be collected from the time the informed consent is signed through 90 days after the last dose of the last study treatment.

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

Any AEs that are unresolved 90 days after the last dose of study treatment are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) prior to the end of the study, if judged to be necessary.

6.3.2 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
- 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

- Whether the AE caused the patient's withdrawal from the study (yes or no)
- Outcome

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

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

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 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. An AE of severe intensity does not necessarily need to be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but it is not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would be an SAE if it satisfies the criteria shown in Section 6.2.

6.3.3 Causality collection

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

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

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

6.3.4 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 after an informed consent has been signed) 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.

6.3.5 Adverse events based on signs and symptoms

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

6.3.6 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the CSR. Deterioration, as compared with 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 if they are considered the reason for discontinuation of treatment with the IPs.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE, and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses 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 AE(s).

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.

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation. Occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law are shown in Appendix D.

6.3.8 Disease progression

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

6.3.9 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

6.3.10 Deaths

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

- Death clearly resulting from disease progression should be reported to the monitor at the next monitoring visit and should be documented in the eCRF. 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 monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign a single main cause as well as any contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. 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 Drug Safety or its representative within the usual timeframes.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IPs or to the study procedure(s). All SAEs, including supporting data, will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel should inform 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 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 should inform AstraZeneca representatives (and enter into the eCRF) of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate that an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigators or other study site personnel reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigators/study site personnel how to proceed.

The reference documents for definition of expectedness/listedness are the IBs for MEDI4736 and tremelimumab.

The PI 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.**

6.5 Overdose

Use of IP 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 IP, and possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigators or other site personnel should inform appropriate AstraZeneca representatives immediately or **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 provided to the AstraZeneca Patient Safety data entry site.

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

For patients randomized to the SoC arm, please refer to the local prescribing information for the treatment of cases of overdose. An overdose in the SoC arm with associated SAEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module. An overdose in the SoC arm without associated SAE symptoms should not be reported on the Overdose eCRF module.

6.6 Pregnancy

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

6.6.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 Investigators or other site personnel should inform 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 provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy, and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Male patients must refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 monotherapy. For patients receiving standard of care agents for chemotherapy, please follow the local prescribing information relating to contraception and the time limit for such precautions.

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, 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.

6.7 Management of IP-related toxicities

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 if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- 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.

6.7.1 Specific toxicity management and dose modification information – MEDI4736 and MEDI4736 + tremelimumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 monotherapy and MEDI4736 + tremelimumab are provided in Dosing Modification and Toxicity Management Guidelines.

The most current version of the TMGs is also available through the following link: https://tmg.azirae.com. In addition a version of the 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.

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.

Comprehensive toxicity management guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors, durvalumab [MED4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially 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 checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document 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),” and is maintained within the Site Master File. In addition, a current version of TMGs is available through the following link: https://tmg.azirae.com. Please contact the clinical study 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 MEDI4736 and tremelimumab should be permanently discontinued (see Section 3.9 of this protocol and Dosing Modification and Toxicity Management Guidelines).

Following the first dose of IP, subsequent administration of MEDI4736 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 judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to MEDI4736 monotherapy and the MEDI4736 + tremelimumab regimen by the reporting investigator.

Dose reductions are not permitted for the MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy. In case of doubt, the Investigator should consult with the Study Physician.

MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy adverse events of special interest

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

If any AESI occurs in the course of the study, then the Investigators or other site personnel should report to AstraZeneca by recording in the eCRF within 48 hours of when he or she becomes aware of it. AESIs for MEDI4736 ± tremelimumab combination therapy include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and that 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 MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy. In the event of irAE or suspected irAE, 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.

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

If the Investigator has any questions with regards to an AE being an irAE, the Investigator should immediately contact AstraZeneca.

AESI/imAEs observed with anti PD-L/PD-1 agents such as durvalumab and durvalumab in combination with 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-Barre 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 aetiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the MEDI4736 IB and the Tremelimumab IB. More specific guidelines for the evaluation and treatment of these AESIs are described in, the Dosing Modification and Toxicity Management Guidelines (please see Section 6.7.1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

6.7.2 Specific toxicity management and dose modification information - Standard of Care

Investigators should follow local standard clinical practice regarding dose modifications for agents used in the SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) arm. For specific information regarding the individual agent used in this study, please refer to the local prescribing information for the relevant agent.

6.7.3 IDMC

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

An IDMC will be established to perform an interim assessment of the safety of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy in this population. The IDMC will be comprised of independent experts. The committee will meet approximately 6 months after the study has started or after the randomization of 30 patients, whichever happens first. The second IDMC meeting will occur approximately 3 months after the first IDMC meeting or when 90 patients are enrolled, whichever occurs first. A subsequent IDMC meeting will occur 3 months after 90 patients are enrolled. Further IDMC meetings will occur every 6 months, unless otherwise requested by the IDMC. IDMC members will be consulted to ensure appropriate frequency. Following each meeting, the IDMC will report to AstraZeneca and may recommend changes in the conduct of the study.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

AstraZeneca will supply MEDI4736 and tremelimumab. Gemcitabine, cisplatin, and carboplatin will be supplied locally.

Investigational product	Dosage form and strength
MEDI4736	50 mg/mL solution IV
Tremelimumab	20 mg/mL solution IV
Standard of Care	
Gemcitabine[a]	IV (as sourced locally)
Cisplatin	IV (as sourced locally)
Carboplatin[a]	IV (as sourced locally)

[a] Under certain circumstances when local sourcing is not feasible, an SoC treatment may be supplied centrally through AstraZeneca.

IV intravenous; SoC standard of care

In Japan, a SoC treatment will be supplied from Astrazeneca K.K.

7.1.1 MEDI4736

MEDI4736 will be supplied by AstraZeneca as a 500-mg vial for solution for infusion after dilution. The solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume [w/v]) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

Preparation of MEDI4736 doses for administration with an IV bag

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

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

A dose of 1500 mg will be administered in IV bags containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2-µm or 0.22-µm in-line filter.

The calculated volume of MEDI4736 (30.0 mL for 1500-mg dose) is added to an appropriately sized IV bag such that final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limit, a new dose must be prepared using new vials. MEDI4736 does not contain preservatives, and any unused portion must be discarded.

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

No incompatibilities between MEDI4736 and polyvinylchloride or polyolefin IV bags have been observed.

Dose calculation

For 1500-mg fixed dose:

The volume of MEDI4736 (in mL) for a fixed dose of 1500 mg is 30.0 mL:

$$\text{Dose (30.0 mL)} = \frac{\text{MEDI4736 dose level (1500 mg)}}{\text{MEDI4736 concentration (50 mg/mL)}}$$

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

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. 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.

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 the following:

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

A dose of 75 mg will be administered using an IV bag containing 0.9% (w/v) saline and delivered through an IV administration set with a 0.2-µm or 0.22-µm in-line filter.

The calculated volume of tremelimumab (3.8 mL for 75 mg dose) is added to an appropriately sized IV bag such that final concentration is within 0.15 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limit, a new dose must be prepared using new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. However, administration sets containing cellulose-based filters should not be used with tremelimumab.

Dose calculation

For 75-mg fixed dose:

The volume of tremelimumab (in mL) for a fixed dose of 75 mg is 3.8 mL:

$$\text{Dose (mL)} = \frac{\text{Tremelimumab dose level (75 mg)}}{\text{Tremelimumab concentration (20 mg/mL)}}$$

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

7.1.3 Standard of Care

Each SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) agent will be sourced as commercially available material/locally sourced, prescribed according to local regulations, and will be administered according to prescribing information or treatment guidance in general use by the Investigating site. Under certain circumstances when local sourcing is not feasible, a SoC will be supplied centrally by AstraZeneca. This will be labeled with local language translated text in accordance with regulatory guidelines.

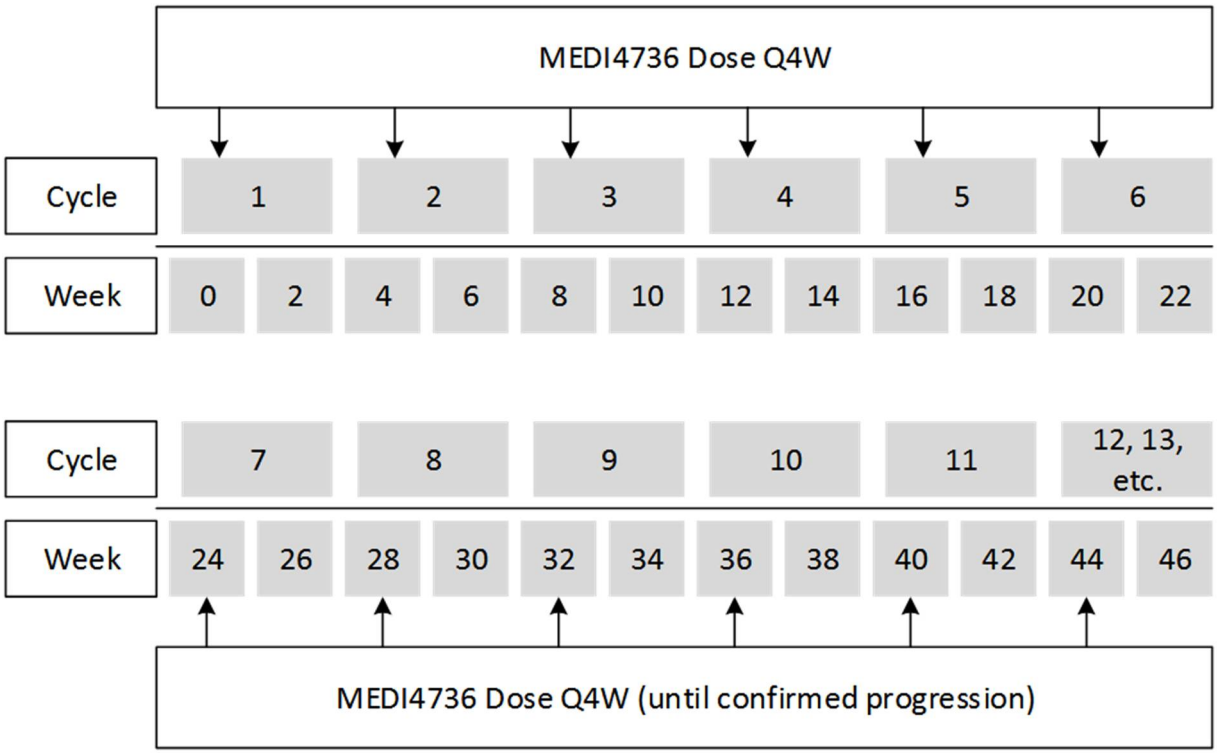
7.2 Dose and treatment regimens

7.2.1 Treatment regimens

MEDI4736 monotherapy

Patients in the MEDI4736 monotherapy treatment arm will receive 1.5 g MEDI4736 via IV infusion q4w at Week 0. See Figure 3.

Figure 3 MEDI4736 monotherapy dosing schedule



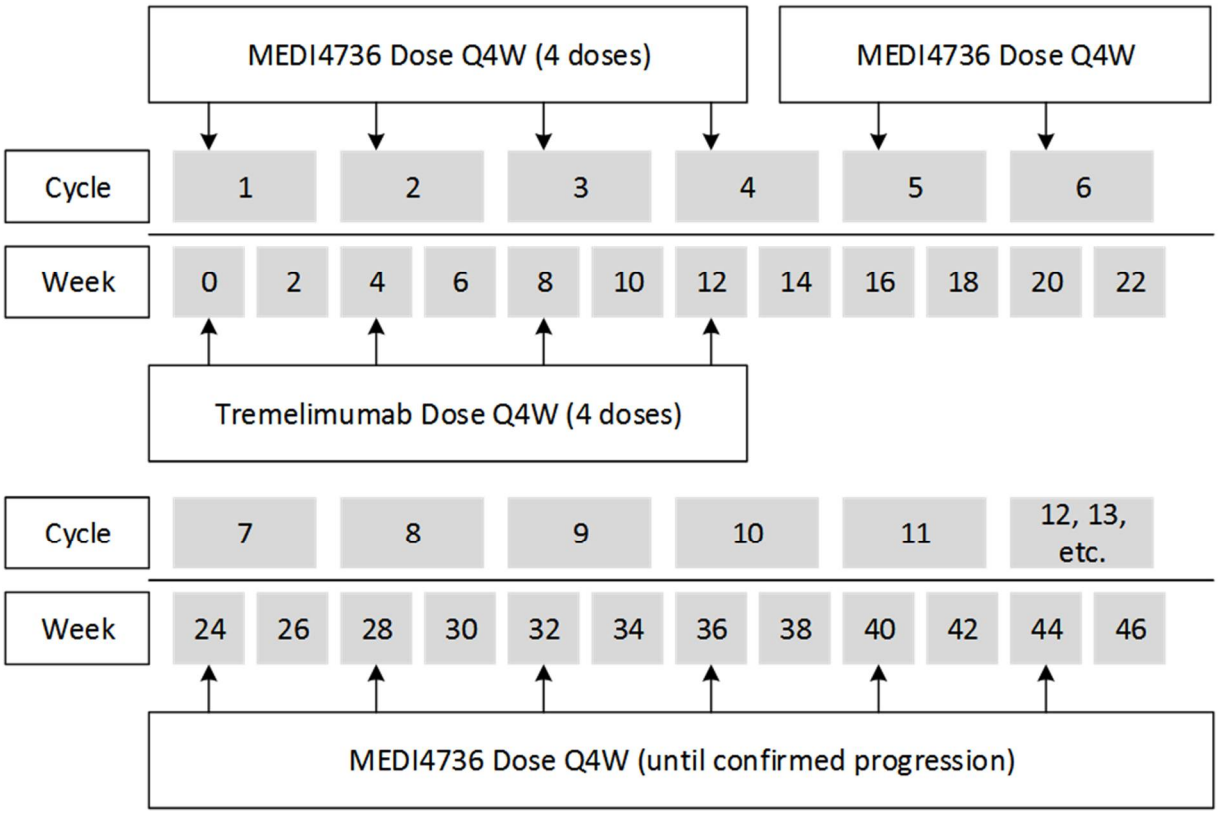
Q4W every 4 weeks

MEDI4736 + tremelimumab combination therapy

Patients in the MEDI4736 + tremelimumab combination therapy treatment arm will receive MEDI4736 (1.5 g IV q4w) over a 1-hour period in combination with tremelimumab (75 mg IV q4w) over a 1-hour period for up to 4 doses/cycle each, followed by MEDI4736 (1.5 g IV q4w) until confirmed disease progression or until other discontinuation criteria are met. The first MEDI4736 monotherapy dose at 1.5 g IV q4w will be 4 weeks after the final dose of MEDI4736 in combination with tremelimumab (see Figure 4).

Tremelimumab will be administered first; the MEDI4736 infusion will start approximately 1 hour after the end of the tremelimumab infusion. If there are no clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of MEDI4736 can be given immediately after the tremelimumab infusion has finished.

Figure 4 MEDI4736 + tremelimumab combination therapy dosing schedule



Q4W every 4 weeks

Standard of Care

Patients in the SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) arm who are eligible for cisplatin will receive 1 of 2 gemcitabine + cisplatin options:

1. IV infusions of cisplatin (70 mg/m^2) on Day 2 of each 28-day cycle + gemcitabine (1000 mg/m^2) on Days 1, 8, and 15 of each 28-day cycle, for up to 6 cycles or

2. IV infusions of cisplatin (70 mg/m^2) on Day 1 of each 21-day cycle + gemcitabine (1000 to 1250 mg/m^2) on Days 1 and 8 of each 21-day cycle, for up to 6 cycles.

Patients in the SoC arm who are ineligible for cisplatin will receive IV infusions of carboplatin at an AUC of 4.5 to 5 (AUC 4 is permitted only if required by local standard clinical practice) on Day 1 of each 21-day cycle + gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle, for up to 6 cycles.

Patients randomized to the SoC arm with cisplatin and gemcitabine who receive at least 1 cycle of cisplatin and gemcitabine and by physician's determination are unable to tolerate subsequent cisplatin cycles will be allowed to change from cisplatin to carboplatin 1 time.

The criteria justifying the change from cisplatin to carboplatin during study treatment must be documented in the eCRF.

In a rare scenario, if at the Investigator's discretion, patients in the SoC arm who have not progressed continue the SoC treatment beyond 6 cycles, the exposure information will be reported in exposure eCRF.

7.2.2 Duration of treatment, criteria for retreatment, and treatment through progression

Duration of treatment

Patients randomized to the MEDI4736 + tremelimumab combination therapy and the MEDI4736 monotherapy arms will begin treatment on Day 1 until PD is confirmed, unacceptable toxicity occurs, withdrawal of consent, or another discontinuation criterion is met. According to RECIST 1.1 modified for confirmation of progression, a confirmatory scan will be required following an overall timepoint assessment of progression, preferably at the next scheduled visit and no earlier than 4 weeks after the previous assessment of PD.

Patients randomized to treatment in the SoC arm (cisplatin + gemcitabine or carboplatin + gemcitabine) will begin treatment on Day 1 for up to 6 cycles until the first assessment of disease progression or until unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. A confirmatory scan will not be required if PD is identified on the SoC arm in order to discontinue treatment; however, a subsequent scan is required following an overall timepoint assessment of initial progression, even if a subsequent treatment is started and no earlier than 4 weeks after the previous assessment of PD. Retreatment is not permitted for patients in the SoC arm.

Retreatment

Patients randomized to the MEDI4736 + tremelimumab combination therapy arm who meet the retreatment criteria described below may receive retreatment 1 time at the Investigator's discretion. During retreatment, patients will follow the same schedule of assessments as the original treatment period (with the exception of the PK and ADA assessments, Hepatitis B and C assessments, and HIV assessments which do not need to be collected a second time):

- Patients who complete the 4 dosing cycles of the combination of durvalumab (MEDI4736) and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab (MEDI4736) monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

- Patients who restart treatment after PD must have a baseline tumor assessment within 28 days of restarting treatment with MEDI4736 + tremelimumab combination therapy; all further scans should occur q8w (±7 days) relative to the date of first dose of retreatment until disease progression.

Criteria for retreatment and treatment through progression

Treatment through progression in either the MEDI4736 monotherapy arm, MEDI4736 + tremelimumab combination therapy arm or retreatment in the MEDI4736 + tremelimumab combination therapy arm are at the Investigator's discretion. The Investigator will ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not provide further benefit to patients. Moreover, these patients must meet the following specific criteria for treatment in the setting of PD:

- Written informed consent for retreatment and/or treatment through progression in the setting of PD will specify that treatment beyond evidence of initial PD is not the SoC and that alternative treatment options, including either locally licensed treatments or other clinical trials, are available for this patient population

- Absence of clinical symptoms or signs (including worsening of laboratory values [eg, new or worsening hypercalcemia]) indicating clinically significant disease progression and no decline in ECOG performance status that can be attributed to disease progression

- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis or respiratory failure due to tumor compression or spinal cord compression) that cannot be managed by protocol-allowed medical interventions

- However, a patient in the MEDI4736 monotherapy arm with confirmed disease progression will not be permitted to continue therapy with MEDI4736 if disease progression occurred after confirmed response (CR or PR, as defined by RECIST 1.1) in the target lesions. Additionally, a patient randomized to the MEDI4736 + tremelimumab combination treatment arm with confirmed disease progression during the combination portion of therapy that occurred after confirmed response (CR or PR, as defined by RECIST 1.1), will not be permitted to continue immunotherapy if disease progression occurred in the target lesions that previously responded to immunotherapy

Patients whom AstraZeneca and the Investigator determined may not continue treatment after PD will enter follow-up. All patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed until confirmed disease progression and for survival.

7.3 Labeling

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

Japan and other countries where this is applicable: 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 investigational products.

Labels will be provided as either a single panel label or as multi-language booklet labels.

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 drugs (including IP) should be recorded in the appropriate sections of the eCRF.

Treatment compliance will be assured by site reconciliation of medication dispensed and returned.

7.6 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs

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

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The IP 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.

7.7 Concomitant and other treatments

The Investigator must be informed as soon as possible about any medication taken from the time of screening until 90 days after the last dose of IP (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF, in addition to the reason they were prescribed.

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 to Section 6.7 for guidance on management of IP-related toxicities. For agents in the SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) arm, also refer to the local prescribing information with regards to warnings, precautions, and contraindications.

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment	Should not be given while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be givenwhile the patient is on study treatment. Short-term use of immunosuppressive medications, including corticosteroids for the acute management of non-IP emergencies (eg, COPD, asthma) or IP-related emergent AEs, is permitted. In addition, immunosuppressive medication for palliative treatment for oncologic emergencies or prior to imaging procedures in patients with contrast allergies is acceptable. Use of inhaled, topical, and intranasal corticosteroids is permitted for all treatment arms. Immunosuppressive premedication is permitted only for patients randomized to the SoC arm.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Sunitinib	Should not be given to patients within 3 months of a dose of tremelimumab, as acute renal failure has been reported with combination therapy of tremelimumab and sunitinib

Prohibited medication/class of drug:	Usage:
EGFR TKIs	Should be used with caution in the 90 days after the last dose of durvalumab. Increased incidence of pneumonitis (with third-generation EGFR TKIs) and increased incidence of transaminase increases (with first-generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Drugs with laxative properties	Should be used with caution through 90 days after the last dose of tremelimumab during the study. In case of strong medical need, should be used with caution.
Herbal and natural remedies	Should be avoided while the patient is on study treatment(with the exception of homeopathic remedies, which may be used following discussion with AstraZeneca).

AE adverse event; CTLA-4 cytotoxic T lymphocyte-associated antigen 4; IP investigational product; PD-1 programmed cell death 1; PD-L1 programmed cell death ligand 1 SoC standard of care

Rescue/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
BSC (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

BSC best supportive care

7.7.1 Other concomitant treatment

Medication other than that described in Section 7.7 that is considered necessary for the patient's safety and well-being may be given at the discretion of the Investigator and recorded in the appropriate sections of the eCRF.

7.8 Post-study access to study treatment

Patients who continue to receive benefit from their assigned treatment at the scheduled data cutoff for final analysis of the global cohort and final database lock may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit or until meeting any other discontinuation criteria as defined in Section 3.9. For patients continuing to receive duravalumab or durvalumab + tremelimumab treatment following the scheduled data cutoff for final analysis of the global cohort, it is recommended that the patients continue the scheduled site visits. For those patients from China who are in the global cohort, final data cutoff and database lock will occur when the China cohort conducts its final data cutoff and final database lock.

Investigators should continue to monitor and document data for all study patients in the database after scheduled data cutoff for final analysis of the global cohort and final database lock. Dependent on the analysis results of the global cohort, a decision may be made to continue further data collection for a longer period with intent to analyze long-term OS and safety data to fulfill any other potential Health Authority requirements. Any additional long-term analysis may be further clarified through an addendum to the main statistical analysis plan, which will be developed before data cutoff for the long-term analysis. Data will be collected until any of following conditions are met:

- Until remaining patients in the study (including patients after discontinuation of study treatment) have discontinued the study; OR
- Remaining patients have been transferred into a roll-over study; OR
- If the Sponsor decides to stop data collection, patients remaining on study treatment at that time and deriving clinical benefit from their assigned treatment will be allowed to continue treatment and only SAEs will be collected

Patients moving to the the roll-over study will require a new Informed Consent. The OS data collected in the roll-over study may be combined with the OS data from the current Study D419BC00001 and evaluated as a combined dataset.

8. STATISTICAL ANALYSES BY ASTRAZENECA

8.1 Statistical considerations

All statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) within 3 months of the first randomized patient and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data.

Section 8.1 to 8.5 describes the statistical analyses that applies to global cohort data. For China cohort, same definitions of outcome measures (Section 8.4) and methods for statistical

analyses (Section 8.5) will be applied unless specified in Section 8.6 or SAP. The same OS treatment effect under the alternative hypothesis is assumed in the plan of China cohort analyses.

8.2 Sample size estimate

The study will plan to enroll approximately 1340 patients globally in order to randomize (1:1:1) approximately 1005 patients to MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, or SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) over a period of 16 months. Therefore, approximately 335 patients will be randomized to each of the treatment arms. Once global enrollment completes, recruitment to the expansion cohort will continue in China until approximately 180 Chinese patients have been randomized.

The global study is sized to characterize OS benefit of MEDI4736 in combination with tremelimumab versus SoC in patients with unresectable Stage IV UC and OS benefit of MEDI4736 versus SoC in patients with unresectable Stage IV PD-L1-High UC. The sizing assumes a 6-month delay in separation of the OS curves between each arm, hence the use of average hazard ratios (HRs).

Non-uniform accrual of patients (with k=2) is assumed when estimating the analysis times. The total proportion of patients randomized at time t [t≤16 months] following the start of the study is assumed to be $(t/16)^2$.

The final analysis of OS will be performed when approximately 327 target OS events (81% maturity) have occurred in PD-L1-High UC patients treated across the MEDI4736 monotherapy and SoC treatment arms.

For the co-primary OS endpoints in the intent-to-treat (ITT) population (MEDI4736 + tremelimumab combination therapy versus SoC), 1 interim analysis will also be undertaken; and the interim analysis for OS endpoint in the PD-L1-High population (MEDI4736 monotherapy versus SoC) will be conducted at the same time:

- The interim analysis will be conducted at the time when approximately 80% of the target OS events have occurred across the MEDI4736 + tremelimumab combination therapy and SoC treatment arms (440 events, 66% maturity); AND in the PD-L1-High population across the MEDI4736 monotherapy and SoC treatment arms (262 events, 65% maturity).

MEDI4736 + tremelimumab versus SoC (OS in all-comers UC)

The assumed OS treatment effect under the alternative hypothesis is an average HR of 0.73 for MEDI4736 + tremelimumab combination therapy versus SoC. The OS on the control arm is assumed to be characterized by an exponential distribution with a median OS of 11.3 months. The OS on the MEDI4736 + tremelimumab combination therapy treatment arm is therefore assumed to be characterized by a piece-wise exponential distribution with a median OS of 14.8 months. Assuming that the survival curves of the two treatment arms do not separate for 6 months then the HR after that point would need to be 0.61 to produce an average HR of 0.73 over the follow-up period.

The SoC control arm OS assumptions are based on a weighted average between median OS from gemcitabine/carboplatin (40% weighting) published in De Santis et al 2012 and gemcitabine/cisplatin published in Bellmunt et al 2012 (60% weighting). An exponential distribution was assumed with median OS of 0.4×9.3 months+0.6×12.7 months=11.3 months.

Final analysis of OS based on 550 events for the comparison of MEDI4736 + tremelimumab combination therapy versus SoC (82% maturity, 550/670), from all randomized patients, is expected to occur approximately 46 months after the first patient is randomized and will provide at least 87% power to demonstrate a statistically significant difference in OS at a 2-sided alpha level of 1.33% (with overall alpha for OS of 1.5%). With a minimum follow-up time of 30 months from the end of patient recruitment, this yields an anticipated overall average HR of 0.73, with a critical value for statistical significance of 0.81.

MEDI4736 versus SoC (OS in PD-L1-High UC)

It will be assumed that approximately 60% of patients will have PD-L1-High tumors.

The assumed OS treatment effect under the alternative hypothesis is an average HR of 0.71 for MEDI4736 monotherapy versus SoC, and the OS on the control arm is assumed to be the same regardless of PD-L1 status. The OS on the MEDI4736 monotherapy treatment arm is therefore assumed to be characterized by a piece-wise exponential distribution with a median OS of 15.3 months. Assuming that the survival curves of the two treatment arms do not separate for 6 months then the HR after that point would need to be 0.57 to produce an average HR of 0.71 over the follow-up period.

By the time of the final analysis of OS in the PD-L1-High population, it is expected that there will be around 327 OS events in PD-L1-High UC patients treated in the MEDI4736 monotherapy and SoC arms, from approximately 402 PD-L1-High patients in total (81% maturity, 327/402), which will provide at least 84% power to demonstrate a statistically significant difference in OS at a 2-sided alpha level of 3.03% (with overall alpha for OS of 3.5%). With a minimum follow-up time of 30 months from the last patient randomized, this yields an anticipated overall average HR of 0.71, with a critical value for statistical significance of 0.79.

MEDI4736 versus SoC (OS in all-comers UC)

The analysis of OS for MEDI4736 monotherapy versus SoC in all UC patients is a key secondary endpoint. For illustrative purposes, it will be assumed that the significance level applied to the test will be a 2-sided 5% significance level, that is, assuming the analysis of both coprimary endpoints are significant at the 1.5% and 3.5% alpha level, respectively.

The assumed OS treatment effect under the alternative hypothesis is an average HR of 0.75 for MEDI4736 monotherapy versus SoC, and the OS on the control arm is assumed to be the same regardless of PD-L1 status. The OS on the MEDI4736 monotherapy treatment arm is therefore assumed to be characterized by a piece-wise exponential distribution with a median OS of 14.4 months. Assuming that the survival curves of the two treatment arms do not separate for 6 months then the HR after that point would need to be 0.63 to produce an average HR of 0.75 over the follow-up period.

By the time of the analysis of the co-primary endpoints, it is expected that there will be around 553 OS events in UC patients treated in the MEDI4736 monotherapy and SoC arms, from 670 patients in total (83% maturity, 553/670), which will provide approximately 91% power to demonstrate a statistically significant difference in OS at a 2-sided 4.29% significance level (with overall alpha for OS of 5%). With a minimum follow-up time of 30 months from the end of patient recruitment, this yields an anticipated overall average HR of 0.75, with a critical value for statistical significance of 0.84.

This power calculation is illustrative only and relies on the assumptions specified above. Any results presented from these tests will consider the impact of the percent prevalence of PD-L1-High tumors and the significance level applied on the power of the test when interpreting the results.

8.3 Definitions of analysis sets

Definitions of the analysis sets for each outcome variable are provided in Table 10.

Table 10 Summary of outcome variables and analysis populations

Outcome variable	Population
Efficacy data	
OS	Full analysis set (ITT population) PD-L1-High analysis set PD-L1-Low/Neg analysis set MEDI4736 cisplatin ineligible population
PFS, OS24, APF12, ORR, DoR, DCR, PFS2, PROs, and symptom endpoints	Full analysis set (ITT population) PD-L1-High analysis set PD-L1-Low/Neg analysis set – ORR will be based on the subset of patients in each analysis set with measurable disease at baseline. – DoR will be based on the subset of patients in each analysis set which achieves objective tumor response. MEDI4736 cisplatin ineligible population – ORR, DoR, and DCR
Demography	Full analysis set (ITT population)
PK data	PK analysis set
Safety Data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
ECOG performance status	Safety analysis set
Vital signs	Safety analysis set

AE adverse event; APF12 proportion of patients alive and progression free at 12 months from randomization; DCR disease control rate; DoR duration of response; ECOG Eastern Cooperative Oncology Group; ITT Intent-to-treat; ORR objective response rate; OS overall survival; OS24 proportion of patients alive at 24 months from randomization; PD-L1 programmed cell death ligand 1; PFS progression-free survival; PFS2 time from randomization to second progression; PK pharmacokinetic; PRO patient-reported outcomes.

8.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients prior to the end of global recuriment. Any patients recruited in China, after global recruitment has ended, will not be included in the FAS (see Section 8.6). Unless otherwise specified, the FAS will be used for all efficacy analyses (including PROs). Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were

randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomized.

8.3.2 PD-L1-High analysis set

The PD-L1-High analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1-High as defined by an IHC assay developed by Ventana (see Table 1).

8.3.3 PD-L1-Low/Neg analysis set

The PD-L1-Low/Neg analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1-Low/Neg as defined by an IHC assay developed by Ventana (see Table 1).

8.3.4 Cisplatin ineligible analysis set

The Cisplatin ineligible analysis set will include the subset of patients in the FAS who are not eligible for cisplatin treatment at baseline (per eCRF).

8.3.5 MEDI4736 cisplatin ineligible population

All patients who have received MEDI4736 monotherapy and are not eligible for cisplatin treatment at baseline (per eCRF) will be included in this analysis set.

8.3.6 Safety analysis set

All patients recuited prior to the end of global recruitment who received at least 1 dose of IP will be included in the safety analysis set. Any patients recruited in China, after global recruitment has ended, will not be included in the safety anlysis set (see Section 8.6). The patients will be classified on the basis of the treatment actually received. When assessing safety and tolerability, summaries will be produced based on the safety analysis set.

The **cisplatin ineligible safety analysis set** will include the subset of patients in the safety anlysis set who are not eligible for cisplatin treatment at baseline (per eCRF) and have received either MEDI4736 monotherpay or SoC (carboplatin + gemcitabine).

8.3.7 PK analysis set

All patients who received at least 1 dose of MEDI4736 or tremelimumab per protocol and had at least one post-dose evaluable PK data of MEDI4736 or tremelimumab will be included in the PK analysis set. The population will be defined by AstraZeneca/MedImmune, the Pharmacokineticist, and the Statistician prior to any analyses being performed.

8.4 Outcome measures for analyses

8.4.1 Calculation or derivation of efficacy variables

The analysis of the secondary endpoints of PFS, APF12, ORR, DoR, and DCR on all analysis sets (excluding MEDI4736 cisplatin ineligible population) will be based on Investigator assessments according to RECIST 1.1. For analysis regarding MEDI4736 cisplatin ineligible population, see Section 8.5.15.

8.4.1.1 RECIST 1.1-based endpoints

Investigator RECIST 1.1-based assessments

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 28 days prior to randomization. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression, in which case the response will be assigned as PD). Endpoints (of PFS, APF12, ORR, DoR, and DCR) will be derived from the overall visit response data and the scan dates.

Please refer to Appendix E for the definitions of CR, PR, SD, and PD.

Blinded Independent Central Review of RECIST 1.1-based assessments

The BICR of all radiological imaging data will be carried out using RECIST 1.1. All radiological scans for cisplatin ineligible patients (including those at unscheduled visits or outside visit windows) will be provided to the BICR. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or not evaluable [NE]) and the relevant scan dates for each timepoint (ie, for visits where response or progression is/is not identified). If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of NE (unless there is evidence of progression in which case the response will be assigned as PD). Endpoints (such as PFS, ORR, and DoR) in the cisplatin ineligible patients will be derived from the overall visit response date and the scan dates. Further details of the BICR will be documented in the Imaging Charter.

8.4.1.2 Co-primary endpoints

OS in patients with UC, and OS in patients with PD-L1-High UC are the co-primary endpoints.

OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. In order to minimize confounding of OS, patients randomized to SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) will not be allowed to crossover to MEDI4736 monotherapy or MEDI4736 + tremelimumab combination therapy.

Note: Survival calls will be made in the week following the date of data cutoff for the analysis, and if patients are confirmed to be alive or if the death date is after the data cutoff

date, these patients will be censored at the date of data cutoff. Death dates may be found by checking publicly available death registries.

8.4.1.3 Secondary endpoints

Proportion of patients alive at 24 months

The OS24 will be defined as the Kaplan-Meier estimate of OS at 24 months.

Progression-free survival

PFS (per RECIST 1.1 as assessed by Investigator or BICR) will be defined as the time from the date of randomization until the date of first objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline.

The PFS time will always be derived based on scan/assessment dates and not visit dates.

RECIST 1.1 assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- The date of progression will be determined based on the earliest of the scan dates of the component that triggered the progression for the adjudicated reviewer selecting PD or of either reviewer where both select PD as a timepoint response and there is no adjudication for BICR data.
- For investigational assessments, the date of progression will be determined based on the earliest of the RECIST assessment/scan dates of the component that indicates progression.
- When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Note: For target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the target lesions, and similarly for non-target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the non-target lesions.

Proportion of patients alive and progression free at 12 months

The APF12 will be defined as the Kaplan-Meier estimate of PFS (per RECIST 1.1 as assessed by the Investigator) at 12 months.

Objective response rate

ORR (per RECIST 1.1 as assessed by Investigator) is defined as the number (%) of patients with at least 1 visit response of CR or PR and will be based on a subset of all randomized patients. The denominator is a subset of the ITT population who has measurable disease at Baseline. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression receive a subsequent therapy, and then respond will not be included as responders in the ORR.

For the definion of ORR (per RECIST 1.1 as assessed by BICR) used for the first interim analysis, see Section 8.5.15.1.

Duration of response

DoR (per RECIST 1.1 as assessed by Investigator) will be defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 PFS endpoint.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of CR or PR. If a patient does not progress following a response, then their DoR will be censored at the PFS censoring time. DoR will not be defined for those patients who do not have documented response.

For the definion of DoR (per RECIST 1.1 as assessed by BICR) used for the first interim analysis, see Section 8.5.15.1.

Disease control rate

DCR at 6 or 12 months is defined as the percentage of patients who have a best objective response (BoR) of CR or PR in the first 6 or 12 months, respectively, or who have demonstrated SD for a minimum interval of 24 or 48 weeks, respectively (-7 days, ie, 161 or 329 days, respectively), following the start of study treatment.

DCR will be determined programmatically based on RECIST 1.1 using Investigator data and all data up until the first progression event. This will use all data up until the progression event that is used for the analysis.

For the definion of DCR (per RECIST 1.1 as assessed by BICR) used for the first interim analysis, see Section 8.5.15.1.

Time from randomization to second progression

PFS2 will be defined as the time from the date of randomization to the earliest of the progression events subsequent to that used for the PFS endpoint or death. The date of second progression will be recorded by the Investigator in the eCRF and defined according to

local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Patients alive and for whom a second disease progression has not been observed should be censored at the last time known to be alive and without a second disease progression.

Best objective response

BoR is calculated based on the overall visit responses from each RECIST assessment, described in Appendix E. It is the best response a patient has had during their time in the study up until RECIST progression (or confirmed disease progression where applicable) or the last evaluable assessment in the absence of RECIST progression.

Categorization of BoR will be based on RECIST (Appendix E) using the following response categories: CR, PR, SD, PD, and NE.

BoR will be determined programmatically based on RECIST using all Investigator or BICR data up until the first progression event.

For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST assessments prior to death.

For patients who die with no evaluable RECIST assessments, if the death occurs ≤17 weeks (ie, 16 weeks ±7 days) after randomization, then BoR will be assigned to the PD category. For patients who die with no evaluable RECIST assessments, if the death occurs >17 weeks (ie, 16 weeks ±7 days) after randomization, then BoR will be assigned to the NE category.

Progression events that have been censored due to them being >17 weeks after the last evaluable assessment will not contribute to the BoR derivation.

8.4.2 Calculation or derivation of safety variables

8.4.2.1 Adverse events

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of IP (ie, the last dose of MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, or SoC [cisplatin + gemcitabine or carboplatin + gemcitabine]) may be included in the AE summaries, but the majority of those summaries will omit the AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of IP will be produced. These events will not be included in AE summaries.

8.4.2.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

8.4.2.3 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment.

The QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT).

QTcF=QT/RR^ (1/3) where RR is in seconds

Corrected calcium will be derived during creation of the reporting database using the following formulas:

Corrected calcium (mmol/L)=Total calcium (mmol/L) + ([40 – albumin (G/L)] × 0.02)

The denominator used in laboratory summaries will only include evaluable patients, in other words, those who had sufficient data to have the possibility of an abnormality.

For example:

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

The denominator in vital signs data should include only those patients with recorded data.

8.4.3 Calculation or derivation of patient-reported outcome variables

PROs will be assessed using the FACT-BL, PGIC, PRO-CTCAE, and EQ-5D-5L questionnaires. All items/questionnaires will be scored according to published scoring

guidelines or the developer's guidelines, if published guidelines are not available. All PRO analyses will be based on the FAS (ITT population), unless stated otherwise.

8.4.3.1 FACT-BL

Two total, 5 subscales, and a symptoms index score are computed using the FACT-BL questionnaire. Four of the 5 subscales are derived from the Functional Assessment of Cancer Therapy-General (FACT-G) component of the FACT-BL: PWB, FWB, EWB, and SWB. The fifth subscale, derived from Additional Concerns items of the FACT-BL form the Additional Concerns or BlCS subscale. The sum of the FACT-G subscales (PWB, FWB, EWB, and SWB) gives the FACT-G Total score. All the 5 subscales (PWB, FWB, EWB, SWB, and BlCS) are summed as the FACT-BL Total score, while the sum of PWB, FWB, and BlCS constitutes the FACT-BL TOI. The FACT-BL TOI is an efficient summary index of physical/functional outcomes used as a PRO endpoint in clinical trials because it is responsive to change in physical/functional outcomes. The National Comprehensive Cancer Network - FACT Bladder Symptoms Index-18 (NFBlSI-18) is based on the scores of 16 items available in the FACT-BL TOI (Jensen et al 2013).

In this study, the change from baseline in the following total/index scores will be evaluated as secondary endpoints: NFBlSI-18, FACT-BL TOI, and FACT-BL Total score. The change from baseline in the individual subscales (PWB, FWB, EWB, SWB, and BlCS), and the FACT-G Total score will also be examined as exploratory analyses. Fatigue and pain are prioritized as important symptoms of metastatic UC and will be evaluated as single items of the FACT-BL questionnaire. Time to improvement in fatigue (based the item GP1 "I have lack of energy") will be a relevant secondary endpoint as fatigue is expected to be present at baseline, improve with response to therapy, and then decline with progressive disease. Similarly, time to deterioration in pain (based on item GP4 "I have pain") is important as pain may arise from new bony metastasis upon progression. Details about each subscale/item will be provided in the SAP.

HRQoL visit responses

Scores for the FACT-BL will be derived using the developer instructions/manual (see Appendix F). If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

> Prorated subscale score=[Sum of item scores] × [N of items in subscale] ÷ [N of items answered]

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (a minimum of 4 of 7 items, 4 of 6 items, etc). The total score is then calculated as the sum of the unweighted subscale scores. The FACT scale is considered to be an acceptable indicator of patient QoL as long as overall item response rate is greater than 80% (eg, at least 22 of 27 FACT-G items completed). For individual subscale

item response rate, a subscale score is prorated for missing items if greater than 50% of items are answered. In addition, a total score should only be calculated if **all** of the component subscales have valid scores. If at least 50% of the items are missing, then that subscale will be treated as missing. Missing single items are treated as missing. The reason for any missing questionnaire will be identified and recorded. If there is evidence that the missing data are systematic, missing values will be handled to ensure that any possible bias is minimized. For the "Additional Concerns" subscale (BlCS) and the symptoms index, the procedures for scoring are the same as described above for the FACT-G. Again, over 50% of the items (eg, 7 of 12 items) must be completed in order to consider each subscale score valid.

The NFBlSI-18 is scored the same way as the FACT-BL (Jensen et al 2013).

8.4.3.2 PGIC

The response options of the PGIC are scored as follows: Very Much Improved (+3), Much Improved (+2), Minimally Improved (+1), No Change (0), Minimally Worse (-1), Much Worse (-2) and Very Much Worse (-3). Very Much Improved and Much Improved categories will be grouped together and compared with the other response categories grouped together.

8.4.3.3 PRO-CTCAE

The PRO-CTCAE items are not currently scored. The data will be descriptively summarized. Further details will be provided in the SAP.

8.4.3.4 Health state utility (EQ-5D-5L)

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems). A unique EQ-5D health state is referred to by a 5-digit code allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses). Where EQ-5D-5L values sets are not available, the EQ-5D-5L to EQ-5D-3L crosswalk will be applied (Oemar and Oppe 2013).

In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately. The evaluable population will comprise the FAS (ITT population).

8.4.4 Calculation or derivation of pharmacokinetic variables

8.4.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model may be developed using a non-linear mixed-effects modelling approach. The impact of physiologically-relevant patient characteristics (covariates) and

disease on PK may be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints may be evaluated. The results of such an analysis, if conducted, will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

8.4.4.2 Pharmacokinetic analysis

PK concentration data and summary statistics will be tabulated. PK parameters will be determined from raw data. The following PK parameters will be determined after the first and steady-state doses: peak and trough concentration (as data allow).

8.4.4.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against MEDI4736 and tremelimumab. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

8.4.5 Calculation or derivation of biomarker variables

Biomarker status, as defined in the secondary objectives, will be assessed for evaluable patients in each cohort according to prespecified criteria that will be detailed in the SAP.

8.4.6 Calculation or derivation of pharmacogenetic variables

For the genetic data already obtained, only the date that the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genetic data generated from the study will be stored in the AstraZeneca Laboratory Information Management System (LIMS) database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis. Data will be reported outside the CSR (please see Appendix C).

8.5 Methods for statistical analyses

In patients with UC, the following formal statistical analysis of OS (as co-primary endpoints) will be performed:

- H_0: No difference between MEDI4736 + tremelimumab combination therapy and SoC
- H_1: Difference between MEDI4736 + tremelimumab combination therapy and SoC

In patients with PD-L1-High UC, the following formal statistical analysis of OS (as co-primary endpoints) will be performed:

- H_0: No difference between MEDI4736 monotherapy and SoC
- H_1: Difference between MEDI4736 monotherapy and SoC

The study has been sized to characterize the OS benefit of MEDI4736 + tremelimumab combination therapy versus SoC in patients with UC, and the OS benefit of MEDI4736 monotherapy versus SoC in patients with PD-L1-High UC.

The final analysis of OS will be performed when approximately 327 target OS events (81% maturity) have occurred in PD-L1-High UC patients treated across the MEDI4736 monotherapy and SoC treatment arms.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables, baseline is defined as the last visit prior to randomization.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized on the safety analysis set.

All outputs will be summarized by treatment arm for all randomized patients (ITT) and where required, for all randomized patients within the PD-L1-Low/Neg subgroup.

Results of all statistical analysis will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

Table 11 details which endpoints are to be analyzed, together with preplanned sensitivity analyses indicating which analysis is regarded as primary for that endpoint.

Unless otherwise stated, data and endpoints derived from RECIST 1.1 tumor assessments will refer to Investigator assessed data.

Table 11 Preplanned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Overall survival	Co-primary analysis using a stratified log-rank test – MEDI4736 + tremelimumab combination therapy versus SoC (ITT population) – MEDI4736 monotherapy versus SoC (PD-L1-High population) Sensitivity analysis using a Kaplan-Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed – attrition bias Secondary analysis using stratified log-rank test: – MEDI4736 monotherapy versus SoC (ITT population) – MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1-Low/Neg population) – MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (PD-L1-Low/Neg population) – MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (ITT population) – MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1-High population) Secondary analysis of OS: – Median OS and 95% CI (MEDI4736 cisplatin ineligible population)
Progression free survival	Stratified log-rank tests for: Secondary analysis using site Investigator tumor data (RECIST 1.1): – MEDI4736 + tremelimumab combination therapy versus SoC (ITT population) – MEDI4736 monotherapy versus SoC (PD-L1-High population) – MEDI4736 monotherapy versus SoC (ITT population) – MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1-Low/Neg population) – MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (PD-L1-Low/Neg population) – MEDI4736 + tremelimumab combination therapy versus MEDI4736 monotherapy (ITT population) – MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1-High population) Secondary analysis using BICR tumor data (RECIST 1.1) – Median PFS and 95% CI (MEDI4736 cisplatin ineligible population)
Proportion of patients alive at 24 months	HR using the Kaplan-Meier estimates of survival at 24 months (following the method described by Section 8.5.38.5.4)
Proportion of patients alive and progression-free at 12 months	HR using the Kaplan-Meier estimates of patients alive and progression-free at 12 months (following the method described by Section 8.5.3)
Objective response rate	Logistic regression using Investigator data (RECIST 1.1) ORR and 95% CI using BICR data (MEDI4736 cisplatin ineligible population)

Endpoints analyzed	Notes
Duration of response	Analysis following the method described by Section 8.5.6 using Investigator data (RECIST 1.1) Analysis following the method described by Section 8.5.15.1 using BICR data
Disease control rate	Summarized by treatment arm n (%)
Time from randomization to second progression	Stratified log-rank test
Best objective response	N (%) using Investigator or BICR data (RECIST 1.1)
Change from baseline FACT-BL TOI, FACT-BL Total score, FACT-BL subscales, FACT-G Total score, and NFBlSI-18 score	Average change from baseline using a Mixed Model Repeated Measurements (MMRM) analysis
Time to improvement in fatigue, and Time to deterioration in pain	Stratified log-rank test
EQ-5D-5L (health state utility values and Visual Analog Scale)	Average change from baseline using a (MMRM) analysis. Summary statistics for health state utilities and visual analogue scale, including change from baseline.

BICR Blinded Independent Central Review; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; FACT-BL Functional Assessment of Cancer Therapy - Bladder Cancer; FACT-G Functional Assessment of Cancer Therapy - General; FACT-BL TOI Functional Assessment of Cancer Therapy - Bladder Cancer Trial Outcome Index; HR Hazard ratio; ITT Intent-to-Treat; MMRM Mixed Model Repeated Measurements; NFBlSI-18 National Comprehensive Cancer Network - FACT Bladder Symptoms Index-18; PD-L1 Programmed cell death 1; RECIST Response Evaluation Criteria In Solid Tumors; SoC Standard of care;

Multiple testing strategy

In order to strongly control the Type I error at 5% 2-sided, a multiple testing procedure (MTP) with gatekeeping strategy will be used across the co-primary endpoints (OS), analysis populations (ITT, PD-L1-High, and PD-L1-Low/Neg populations), and treatment regimens (MEDI4736 + tremelimumab combination therapy, MEDI4736 monotherapy, and SoC). If the higher level hypothesis in the MTP is rejected for superiority, the following hypotheses will then be tested as shown in Figure 5.

Hypotheses will be tested using a multiple testing procedure with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, hypotheses will be tested in a pre-defined order by first splitting the 5% alpha into 1.5%, and 3.5% for OS for MEDI4736 + tremelimumab combination therapy versus SoC (ITT population), and OS for MEDI4736 monotherapy versus SoC (PD-L1-High population), as outlined in Figure 5.

According to alpha (test mass) splitting and alpha recycling, the test mass that becomes available after each rejected hypothesis is recycled to secondary hypotheses not yet rejected.

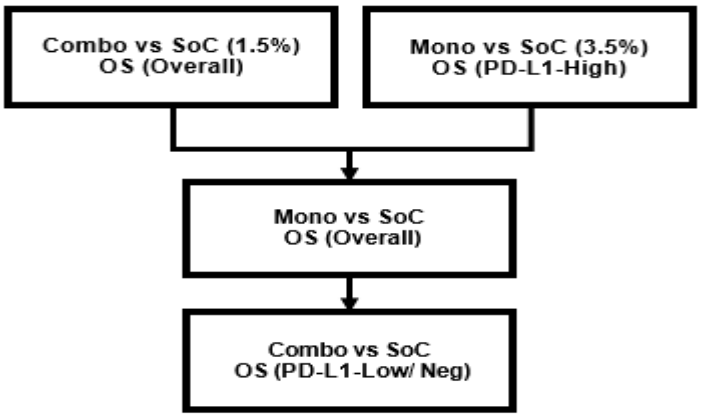
Since OS is tested at multiple timepoints (ie, 1 interim analysis and final analysis), the OS tests for the same comparison/population (ie, shown in 1 box in the MTP) will be considered as 1 test family. As long as 1 test in the family can be rejected, the family is rejected; thus, the assigned total alpha to the family can be recycled to the next MTP level. This testing procedure stops when the entire test mass is allocated to non-rejected hypotheses. Implementation of this pre-defined ordered testing procedure, including recycling, will strongly control type I error at 5% (2-sided), among all key hypotheses. Figure 5 shows the multiple testing framework for the co-primary endpoints and several key secondary endpoints. Once the hypothesis of OS for MEDI4736 monotherapy versus SoC (ITT) is rejected, the remaining alpha will be assigned to test MEDI4736 + tremelimumab combination therapy versus SoC (PD-L1-Low/Neg population). The details of the complete MTP and the alpha-exhaustive recycling procedure will be provided in the Statistical Analysis Plan.

Both OS co-primary endpoints will be tested at 1 interim timepoint and a final timepoint. The alpha level allocated to OS will be controlled at the interim and primary timepoints by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends on the proportion of information available.

For the co-primary OS endpoint in the ITT population (MEDI4736 + tremelimumab combination therapy versus SoC), the interim analysis will be conducted at the time when approximately 80% of the target OS events have occurred across the MEDI4736 + tremelimumab combination therapy and SoC treatment arms (440 events, 66% maturity). If exactly 80% of the target OS events are available at the time of the interim analysis (ie, 440/550 deaths have occurred), with an overall 2-sided alpha level of 1.5%, the 2-sided alpha to be applied at the OS interim analysis would be 0.56%. The 2-sided alpha to be applied for the final OS analysis would be 1.33%.

For the co-primary OS endpoint in the PD-L1-High population (MEDI4736 monotherapy versus SoC), the interim analysis will be conducted at the time when approximately 80% of the target OS events have occurred across the MEDI4736 monotherapy and SoC treatment arms in the PD-L1-High population (262 events, 65% maturity). If exactly 80% of the target OS events are available at the time of the interim analysis (ie, 262/327deaths have occurred), with an overall 2-sided alpha level of 3.5%, the 2-sided alpha to be applied at the OS interim analysis would be 1.58%. The 2-sided alpha to be applied for the final OS analysis would be 3.03%.

Figure 5 Multiple testing procedures for controlling the type I error rate



Combo MEDI4736 + tremelimumab combination therapy; Mono MEDI4736 monotherapy; OS, overall survival; PD-L1, Programmed cell death ligand 1; SoC Standard of care.

8.5.1 Overall survival

OS in the ITT population and PD-L1 subgroups will be analyzed using a stratified log-rank tests adjusting for cisplatin eligibility (ie, eligible or ineligible), PD-L1 status (High and Low/Neg), and visceral metastasis (presence or absence of lung and/or liver metastasis). The effect of treatment versus SoC treatement will be estimated by the HR together with its corresponding ([1-adjusted alpha] × 100%) CI and p-value. The HR and its CI will be estimated from the stratified Cox proportional hazards model (Cox 1972).

All of the secondary analyses will be performed using the same methodology as for the primary analyses described above.

Kaplan-Meier plots of OS will be presented by treatment arm. Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow up, and those who have withdrawn consent will be provided along with the median OS for each treatment.

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias, achieved by a Kaplan-Meier plot of time to censoring where the censoring indicator of OS is reversed.

Subgroup analyses will be conducted comparing OS between MEDI4736 + tremelimumab combination therapy (or MEDI4736 monotherapy) versus SoC in the following subgroups of the FAS (but not limited to):

- Sex (male versus female)
- Age at randomization (<65 versus ≥65 years of age)

- PD-L1 status (High versus Low/Neg)
- Visceral metastases (present versus absent, ie, lung or liver)
- Eligibility for cisplatin containing chemotherapy at randomization (eligible or ineligible)
- Race (Asian versus non-Asian)

Other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors.

No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of OS.

For each subgroup factor, the HR (MEDI4736 + tremelimumab:SoC) and HR (MEDI4736 monotherapy:SoC) and 95% CI will be calculated from a single model that contains treatment within each subgroup. These will be presented on a forest plot including the HR and 95% CI from the overall population.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and OS will not be formally analyzed. In this case, only descriptive summaries will be provided.

For the analysis method of OS used in the interim analysis, see Section 8.5.15.2.

8.5.2 Progression-free survival

The PFS analysis will be based on the programmatically derived RECIST 1.1 using Investigator data. The analysis will be performed in the corresponding population using a stratified log-rank test based on the same methodology as described for the OS endpoint. The effect of treatment versus SoC treatment will be estimated by the HR together with its corresponding 95% CI and p-value.

Kaplan-Meier plots of PFS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each treatment.

In addition, as a sensitivity analysis, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy.

For the analysis method of PFS used in the interim analysis, see Section 8.5.15.1.

8.5.3 Overall survival at 24 months

The OS24 will be summarized (using the Kaplan-Meier curve) and presented by treatment arm. OS24 will be compared between treatments by using the Kaplan-Meier estimator of OS at 24 months for each treatment to obtain the HR. The HR and CI will be presented using the following approach (Klein et al 2007):

- The *HR(group1:group2)* is estimated as $\frac{\ln \hat{S}_1(t)}{\ln \hat{S}_2(t)}$
- The variance for *ln(HR)* is estimated as $\frac{\hat{\sigma}_1(t)^2}{\ln^2 S_1(t)} + \frac{\hat{\sigma}_2(t)^2}{\ln^2 S_2(t)}$

where $\hat{\sigma}_i(t)^2 = \sum_{t_i \le t} \frac{d_i}{n_i(n_i - d_i)}$ is the variance for ln(S(t)) derived from Greenwood's formula for the variance of *S(t)* and can be estimated from standard software packages, where d_i and n_i refer to the number of deaths and patients at risk for each risk set.

The *ln(HR)* and its variance in each strata will be estimated and combined by weighting inversely proportionately according to each within stratum variance (Whitehead and Whitehead 1991).

8.5.4 Proportion of patients alive and progression free at 12 months

APF12 will be summarized using the same methodology as OS24 (see Section 8.5.3).

8.5.5 Objective response rate

The ORR will be based on the programmatically derived RECIST using the Investigator data. The ORR will be compared between MEDI473 + tremelimumab combination therapy versus SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) and MEDI4736 monotherapy versus SoC using logistic regression models adjusting for the same factors as the primary endpoint. The results of the analysis will be presented in terms of an odds ratio together with its associated profile likelihood 95% CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model).

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). Overall visit response data will be listed and summarized over time for all patients (ie, the FAS). For each treatment arm, BoR will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

For the analysis method of ORR used in the first interim analysis, see Section 8.5.15.1.

8.5.6 Duration of response

Descriptive data will be provided for the DoR in responding patients, including the associated Kaplan-Meier curves (without any formal comparison of treatment arms or p-value attached).

For the analysis method of DoR used in the first interim analysis, see Section 8.5.15.1.

8.5.7 Disease control rate

The DCR will be summarized (ie, number of patients).

8.5.8 Time from randomization to second progression

Second progression (PFS2) will be analyzed using identical methods as outlined for the analysis of PFS and stratifying for the same set of covariates. Medians and Kaplan–Meier plots will be presented to support the analysis. The sensitivity analysis outlined in Section 8.5.2 will not be repeated for PFS2 with the exception of a Kaplan-Meier plot of the time to censoring where the censoring indicator of PFS2 is reversed.

For supportive purposes, the time to the start of subsequent therapy will be analyzed using the same methodology and model. The HR for the treatment effect together with its 95% CI will be presented. In addition, a Kaplan-Meier plot of the time to the start of subsequent therapy will be presented by treatment arm and the time between progression and starting subsequent therapy will be assessed. No multiplicity adjustment will be applied as these are viewed as supportive endpoints.

A summary table of first subsequent therapies by treatment arm will be provided, as well as response to first subsequent therapy by treatment arm.

This analysis will be performed in the ITT population and PD-L1 status subsets.

8.5.9 Patient reported outcomes

8.5.9.1 FACT-BL

A separate family of endpoints is defined in order of importance (highest to lowest) for the secondary endpoints of NFBlSI-18 (a bladder symptoms index), FACT-BL TOI, and FACT BL Total score. The mean change in score from baseline will be analyzed for each measure using a mixed model for repeated measures. Full details of this and appropriate sensitivity analyses will be described in full in the SAP.

Additionally, the endpoints of PWB, FWB, EWB, SWB, and BlCS subscales as well as the FACT-G Total score may also be analyzed in a similar way as exploratory analyses. Data will be summarized at each visit and graphical presentations may also be produced as appropriate.

Time to improvement in fatigue and time to deterioration/worsening in pain as time to event analyses using the same analysis methods described for OS will be done. Depending on the baseline scores, consideration will also be given to analyzing the data (NFBlSI-18, FACT-BL TOI and FACT-BL Total score) using time to worsening or time to improvement as time to

event analysis using the same analysis methods described for OS. This will be an exploratory analysis, and further details will be provided in the SAP.

8.5.9.2 PGIC

PGIC data will be presented using summaries and descriptive statistics based on the FAS. Further details will be provided in the SAP.

8.5.9.3 PRO-CTCAE

PRO-CTCAE data will be presented using summaries and descriptive statistics based on the FAS. Further details will be provided in the SAP.

8.5.9.4 EQ-5D-5L

Descriptive statistics, graphs and listings will be reported for health state utility index values (United Kingdom base case) and visual analogue scale by visits as well as change in these scores from baseline. To support future economic evaluations of the study treatment, additional appropriate analyses may be undertaken, for example, mean health state utility pre- and post-treatment, and pre- and post-progression.

8.5.10 Healthcare resource use (HOSPAD)

Using the HOSPAD module, an exploratory health economic analysis of hospital episodes including type of contact (hospitalization, outpatient, or day case), reason, length of stay by ward type (including intensive care unit), procedures, and tests may be undertaken to examine the impact of disease and treatment on resource use to primarily support the economic evaluation of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy in comparison to SoC (cisplatin + gemcitabine or carboplatin + gemcitabine). The module is for all non-study protocol-related hospital admissions; any routine hospital visits for study protocol-related requirements do not need to be captured. This would include providing descriptive statistics as appropriate, including means, median, and ranges.

8.5.11 Safety data

Safety and tolerability data will be presented by treatment arm using the safety population.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced. Any safety summaries examining retreatment with MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy will be produced separately.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to MEDI4736 monotherapy, MEDI4736 + tremelimumab combination therapy, and SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) will be summarized. Time on study, MEDI4736 monotherapy, MEDI4736 +

tremelimumab combination therapy, and SoC dose delays/interruptions and dose reductions in the SoC arm will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

8.5.12 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day, and a summary provided for all evaluable patients.

8.5.12.1 Immunogenicity analysis

Immunogenicity results will be listed by patient and a summary will be provided of the number and percentage of patients who develop detectable anti-MEDI4736 and anti-tremelimumab antibodies. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-MEDI4736 and anti-tremelimumab antibodies.

The effect of immunogenicity on PK, pharmacodynamics, efficacy, and safety will be evaluated if data allow.

8.5.13 Pharmacokinetic/pharmacodynamic relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modelling approach.

8.5.14 Biomarker data

The relationship of PD-L1 status determined by the Ventana IHC assay and if applicable, of exploratory biomarkers to OS, OS24, APF12, ORR, DoR, and PFS2 will be presented for a subset of patients in the ITT population who are evaluable for each biomarker.

This will be assessed using similar summary and graphical representations to those that are outlined for the efficacy outputs in Section 8.5.2 to Section 8.5.3.

PD-L1 status determined by the Ventana IHC assay will be reported in the CSR. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

8.5.15 Interim analyses

Two interim analyses will be performed. The first interim (Interim 1) will focus on ORR and DoR in patients who are not cisplatin-eligible and treated with MEDI4736 monotherapy (Section 8.5.15.1), and the second interim (Interim 2) will focus on co-primary OS endpoints (Section 8.5.15.2). Interim 1 will be conducted when all patients in the global cohort have at least 6 months follow-up.

8.5.15.1 Interim analysis focusing on ORR and DoR

This interim analysis will take place when all patients in the global cohort have at least 6 months follow-up. Results of this interim analysis will be used for potential interaction with

regulatory agencies regarding future development of MEDI4736 monotherapy in patients who are ineligible for cisplatin treatment. OS will remain as the co-primary endpoints in this study. The evaluation in MEDI4736 cisplatin ineligible population will be considered as a secondary analysis outside of the MTP. Hence, there are no plans to stop the study early based on any results from this interim analysis and no formal statistical adjustments are planned, and no alpha adjustment on the primary analyses and secondary analyses in the MTP due to the evaluation of MEDI4736 cisplatin ineligible population is planned.

In order to maintain the integrity of this ongoing study, the interim results will be reviewed by the IDMC. If IDMC recommends the interim analysis indicate favorable benefit:risk profile of MEDI4736 monotherapy in cisplatin-ineligible patients, the interim results will be shared with a separate unblinded internal (AstraZeneca) committee, consisting of personnel who are not involved in the day-to-day study conduct. The details of IDMC and internal committee process and decision criteria will be detailed in the IDMC Charter. Finally, results will not be communicated externally, except with regulators for a potential discussion on registration in the cisplatin-ineligible population.

Details of this interim analysis, such as analysis set definition, endpoint definition (if different from which used in Section 8.3) and analysis methods will be specified in the following sections.

8.5.15.1.1 Analysis set

For the analysis sets used for this interim analysis, see Section 8.3.5 and Section 8.3.6.

8.5.15.1.2 Sample size

In the case of 130 patients in the MEDI4736 cisplatin ineligible population, the maximum width between the observed ORR and its lower limit of the exact 95% CI will be no more than 9%.

8.5.15.1.3 Analysis endpoints

ORR (per RECIST 1.1 as assessed by the BICR) is defined as the number (%) of patients with a confirmed overall response of CR or PR and will be based on MEDI4736 cisplatin ineligible population. A confirmed response of CR/PR means that a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Therefore, data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Any patient who discontinues treatment without progression, receives a subsequent therapy and then responds will not be included as responders in the ORR.

Duration of response (per RECIST 1.1 as assessed by the BICR) will be defined as the time from the date of first documented response (which is subsequently confirmed) until the first date of documented progression or death in the absence of disease progression.

Time to response (per RECIST 1.1 as assessed by the BICR) is defined as the time from the date of randomisation until the date of first documented response. The date of first documented response should coincide with that used for the DoR endpoint. TTR will not be defined for those patients who do not have documented response.

DCR and PFS (per RECIST 1.1 as assessed by the BICR), and OS will also be evaluated as secondary endpoints.

ORR, DoR, TTR, DCR and PFS will be obtained using the algorithm described above for the RECIST1.1 site investigator tumor data.

PK and ADA will be assessed in patients who are in the MEDI4736 cisplatin ineligible population with the corresponding samples taken.

Safety will be evaluated in the Cisplatin ineligible safety analysis set.

8.5.15.1.4 Analysis methods

ORR will be estimated with a 95% exact CI by Clopper-Pearson method. The primary analysis will be based on the programmatically derived ORR based on BICR assessments, and using all scans regardless of whether they were scheduled or not. The primary analysis population for ORR will be the MEDI4736 cisplatin ineligible population.

A sensitivity analysis excluding patients who do not have measurable disease at baseline per BICR will be presented.

An analysis of ORR using the results of the programmatically derived RECIST site investigator tumor data from all scans will be conducted as a sensitivity analysis to confirm the results of the primary analysis.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR). The number (%) of patients with a confirmed response and the number (%) of patients with a single visit response (ie, an unconfirmed response) will also be presented.

Kaplan Meier plots of DoR based on the BICR assessment of RECIST will be presented. Median DoR will also be summarized. Only patients who have a response will be included in this summary table. DoR will also be analyzed based upon the site investigator tumor data.

Descriptive summary statistics (ie, minimum, maximum, and median) will also be presented for TTR based on BICR assessments. TTR will also be summarised based upon the site investigator tumor data.

The DCR based upon the BICR assessment of RECIST will be summarized (ie, number of patients [%]). DCR will also be summarized based upon the site investigator tumor data.

Kaplan-Meier plots of PFS (per BICR assessment) will be presented. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with median PFS. The proportion of patients alive and

progression free at 3, 6, 9 and 12 months will be summarized (using the Kaplan-Meier curve) and presented. This analysis will be repeated for site investigator data.

Kaplan-Meier plots of OS will be presented. Summaries of the number and percentage of patients who have died, are still in survival follow-up, are lost to follow-up and have withdrawn consent will be provided along with median OS. The proportion of patients alive at 6, 9, and 12 months will be summarized (using the Kaplan-Meier curve).

Analyses of safety, PK and ADA data will be conducted as outlined in Section 4.

Demographic and baseline characteristic will be presented.

Subgroup analyses will be conducted using the factors specified in Section 8.5.2 as appropriated.

8.5.15.2 Interim analysis of overall survival endpoints

One interim analysis of OS will be carried out for superiority:

- The interim analysis will be conducted at the time when approximately 80% of the target OS events have occurred across the MEDI4736 + tremelimumab combination therapy and SoC treatment arms (440 events, 66% maturity); AND across the MEDI4736 monotherapy and SoC treatment arms in PD-L1-High population (262 events, 65% maturity), projected approximately 16 months after the last patient being randomized.

This analysis will be assessed by an IDMC. Details of the plan and communication process will be provided in the statistical analysis plan and the IDMC charter.

The criterion for superiority in the OS co-primary endpoint is a statistically significant improvement in OS. The alpha level that is to be spent at the interim and final analyses for the OS analyses in the ITT population and PD-L1-High population will be calculated using the Lan DeMets spending function separately.

For the co-primary OS endpoint in the ITT population (MEDI4736 + tremelimumab combination therapy versus SoC), if exactly 80% of the target OS events are available at the time of the interim analysis (ie, 440/550 deaths have occurred), with an overall 2-sided alpha level of 1.5%, the 2-sided alpha to be applied at the OS interim analysis would be 0.56%. The 2-sided alpha to be applied for the final OS analysis would be 1.33%.

For the co-primary OS endpoint in the PD-L1-High population (MEDI4736 monotherapy versus SoC), if exactly 80% of the target OS events are available at the time of the interim analysis (ie, 262/327 deaths have occurred), with an overall 2-sided alpha level of 3.5%, the 2-sided alpha to be applied at the OS interim analysis would be 1.58%. The 2-sided alpha to be applied for the final OS analysis would be 3.03%.

If the interim analysis indicates superiority, then subsequent analyses of the further secondary endpoints will be performed in accordance with the hierarchical multiple testing strategy. If the interim results do not meet the criterion of stopping for superiority, then follow-up will continue until final OS analysis.

8.6 China cohort

China cohort consists of all patients from China sites and Taiwan sites accredited by China regulation recruited prior to the end of global recruitment and after the completion of global recruitment. The global cohort includes Chinese patients recruited prior to the end of global recruitment. Once global enrollment has completed, recruitment into an expansion cohort continues. Hence a patient randomized in China cohort prior to the end of global recruitment will be included in both the (globally recruited) FAS and the China FAS. A patient randomized in China after the end of global recruitment will be included only in the China FAS.

Per China FDA guidance, in addition to the evaluation of global cohort data for primary, secondary and safety objectives, evaluation of consistency in efficacy and safety in China and Asia population is required to facilitate the benefit-risk assessment for Chinese patients. Hence, the safety and efficacy data in China cohort will be analyzed separately where the same endpoint definitions (as detailed in Section 8.4) and the same analysis methods (as detailed in Section 8.5) are applied.

The China full analysis set (China FAS) will include all patients randomized in China cohort and will be used for all China only efficacy analyses.

The China safety analysis set will consist of all patients recruited in China cohort who received at least 1 dose of study treatment and for whom post-dose data are available.

Efficacy analyses for China cohort will be performed when the OS data from the China patients is of similar maturity where significant clinical efficacy is established in the global cohort, e.g. if OS efficacy is established at the second OS interim analysis, a similar maturity to this will be used for consistency evaluation.

All statistical analyses will be considered exploratory and only performed if sufficient numbers of events or patients are available (e.g. ≥20 OS events) unless specified, otherwise descriptive statistics only will be presented. No adjustment for multiplicity will be made and so the procedure for hierarchical testing detailed in Section 8.5 will not be followed. OS efficacy evaluation for China cohort will be performed only once.

Details of China cohort and Asia population analysis, including vendor to perform the analysis, will be specified in China supplementary SAP, which is to be finalized before global cohort data lock for analysis.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca 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 IVRS/IWRS, WBDC, and any electronic PRO systems to be utilized.

The PI 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 PI 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 representative will have regular contact 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 eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs 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 or destroyed accordingly, and the action is documented and reported to the patient

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

9.2.1 Source data

Refer to the CSA for the location of source data.

Source data are any data generated as a result of the patient's inclusion in the study (including run-in and/or follow-up related to the study) and includes all related medical examinations and other records.

9.2.2 Direct access to source data in Japan only

The Head of the study site and the PI/Investigator will cooperate with monitoring and auditing by AstraZeneca and accept inspection by the Institutional Review Board (IRB) or regulatory authorities. All study documents, such as raw data, will be open for direct access to source data at the request of the monitor and the auditor of AstraZeneca, the IRB, or regulatory authorities.

The monitor(s) will verify data from the eCRFs against source data before the PI signs the eCRFs to ensure accuracy and completeness of documentation, and assure that the PI has submitted the eCRFs to AstraZeneca. If the Investigator wishes to amend the collected eCRFs, the monitor will ensure that the PI has recorded the amendment with signature and date and provided this to AstraZeneca.

9.2.3 Study agreements

The PI at each center should comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this clinical study protocol and the CSA, the terms of clinical study protocol shall prevail with respect to the conduct of the study and the treatment of patients. In all other respects not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

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

9.2.4 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

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 study is expected to start in Q3 2015 and to end by Q3 2019.

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 MEDI4736 or tremelimumab.

Refer to Section 7.8 for details regarding study treatment access, data collection, and patient follow-up at the end of study.

9.4 Data management by AstraZeneca

Data management will be performed by a chosen vendor according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version of MedDRA. Medications will be classified according to the AstraZeneca Drug Dictionary. Classification coding will be performed by the chosen vendor.

The 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 the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan 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, a clean file will be declared. Any treatment-revealing data may thereafter be added and the final database will be locked.

Serious adverse event reconciliation

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

Data management of genotype data

Data management of genotype data is described in Appendix C.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratories internal or external to AstraZeneca.

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.

The applicable regulatory requirements in Japan are "Good Clinical Practice for Trials on Drugs" (Ministry of Health, Labor, and Welfare [MHLW] Ordinance No. 28, 27 March 1997, partially revised by MHLW Ordinance and their related notifications.

10.2 Patient data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document.

Patient data protection for genetic data is described in Appendix C.

10.3 Ethics and regulatory review

An ethics committee (EC)/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 Investigator will ensure the distribution of these documents to the applicable EC/IRB and to the study site staff.

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

The EC/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.

If required by local regulations, the protocol should be re-approved by the EC/IRB 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/IRBs, and PIs with safety updates/reports according to local requirements.

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

Japan and other countries where this is applicable:

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 enrolment of any patient should into the study.

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

AstraZeneca should approve any modifications to the ICF, which 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 1 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 enrolment 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 provide regulatory authorities, IRB, the head of the study site, and the PIs 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 relative safety information reported by AstraZeneca.

10.4 Informed consent

The PI(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 her or 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/IRB.

For Japan and other countries where this is applicable:

If any new information on the study medication becomes available that may influence the decision of the patient to continue the study, the Investigator(s) should inform the patient of such information immediately, record this in a written form, and confirm with the patient if he or she wishes to continue their participation in the study. In addition, if the Investigator(s) deem it necessary to revise the ICF, they should revise it immediately (refer to Section 10.5). The Investigator(s) should re-explain to the patients using an updated ICF even if the patients have already been informed of the new information verbally. Written informed consent to continue participation in the study should be provided separately.

10.5 Changes to the protocol and informed consent form

For sites outside Japan:

Study procedures will not be changed without the mutual agreement of the PI 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 (clinical study protocol).

The amendment is to be approved by the relevant EC/IRB and if applicable, also the national regulatory authority, 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 PI(s). For distribution to EC/IRB see Section 10.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's EC/IRB 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/IRB.

For Japan sites only:

Study procedures will not be changed without the mutual agreement of the PI 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. 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 representatives of AstraZeneca, a regulatory authority, or an EC/IRB 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, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

For Japan sites only: All study data may undergo a reliability review and onsite-GCP inspection by the regulatory authorities.

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Appendix A Additional Safety Information

Further guidance on the definition of a serious adverse event (SAE)

Life threatening

"Life-threatening" means that the patient was at immediate risk of death from the adverse event (AE) as it occurred, or it is suspected that use or continued use of the product would result in the patient's death. "Life-threatening" does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity but may jeopardize the patient or may require medical intervention to prevent 1 or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation, but requires intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A guide to interpreting the causality question

When making an assessment of causality, consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of "related" is made if, following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related."

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as "no reasonable possibility."

Creatinine calculation

Cockcroft-Gault equation

Males:

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

Females:

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

MEDI4736 and tremelimumab

There is no information to date on drug-drug interactions with MEDI4736 or tremelimumab, either pre-clinically or in patients. As MEDI4736 and tremelimumab are monoclonal antibodies and therefore proteins, they will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that MEDI4736 or tremelimumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions.

No formal drug-drug interaction studies have been conducted with tremelimumab. However, in renal cell carcinoma studies, acute renal failure has been reported with the combination of tremelimumab and sunitinib.

The mechanism of action of MEDI4736 involves binding to programmed cell death ligand 1 (PD-L1), and the mechanism of action of tremelimumab involves binding to cytotoxic T lymphocyte-associated antigen 4 (CTLA-4); therefore, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labeling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, B, C, D, and E viruses and Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations, which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Pharmacogenetics Research

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system

Below information is only applicable for the blood samples for the genetic research have been obtained.

Background and rationale

AstraZeneca intends to perform genetic research in the MEDI4736 and MEDI4736+ tremelimumab clinical development program to explore how genetic variations may affect the clinical parameters associated with MEDI4736, MEDI4736+ tremelimumab, and/or agents used as comparators. Collection of deoxyribonucleic acid (DNA) samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to MEDI4736, MEDI4736+ tremelimumab, and/or agents used as comparators, but also susceptibility to the disease for which MEDI4736 and/or MEDI4736+ tremelimumab may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

Genetic research objectives

The objective of this research is to collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) and/or susceptibility to disease to MEDI4736, MEDI4736+ tremelimumab, and/or agents used as comparators.

Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.9 of the main Clinical Study Protocol.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of

15 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrollment/randomization code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and trace samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

Patient data protection

AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, patient family members, general physician or any other third party, unless required to do so by law.

Extra precautions are 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.

Data management

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyze the samples.

The results from this genetic research may be reported in the clinical study report for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

References

None

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

Introduction

This appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Sections 5.2.1 and of the protocol and in the Toxicity Management Guidelines.

During the course of the study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree on whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug induced liver injury (DILI) caused by the Investigational Product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) ≥3 × Upper limit of normal (ULN) **together with** Total bilirubin (TBL) ≥2 × ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN

- AST ≥3 × ULN
- TBL ≥2 × ULN

If a central laboratory is used

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Request a repeat of the test (new blood draw) by the central laboratory.
- Complete the appropriate unscheduled laboratory case report form (CRF) module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see earlier section of this appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

If a local laboratory is used

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see earlier section of this appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF.

Follow-up

Potential Hy's Law criteria not met

If the patient does not meet PHL criteria the Investigator will:

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

Potential Hy's Law criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

AstraZeneca contacts the Investigator, to provide guidance, discuss and agree on an approach for the study patient's 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 AstraZeneca. If a central laboratory is used, this includes deciding which of the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available.
- If at any time (in consultation with AstraZeneca) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and assessment of Potential Hy's Law cases

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, AstraZeneca 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 IP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject 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 an 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 AstraZeneca 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.

Actions required when Potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patient's condition[#] compared with the last visit where PHL criteria were met[#]

  - If there is no significant change, no action is required.

  - If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in the Section "Potential Hy's Law criteria met" of this appendix.

[#] 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 AstraZeneca if there is any uncertainty.

Actions required for repeat episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in the section "Actions required when Potential Hy's Law criteria are met before and after starting study treatment?"

If No: follow the process described in the section "Potential Hy's Law criteria met "of this appendix.

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in the section "Potential Hy's Law criteria met "of this appendix.

[#] 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 AstraZeneca if there is any uncertainty.

References

FDA Guidance for Industry. Drug-induced liver injury: Premarketing clinical evaluation, July 2009. Available from:http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix E Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for the D419BC00001 study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study.

Definition of measurable, non-measurable, target and non-target lesions

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined (by RECIST 1.1) as the presence of at least 1 measurable lesion which has not been previously irradiated. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Measurable:

A lesion, not previously irradiated per the protocol prior to enrollment, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and that is suitable for accurate repeated measurements. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline[1]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions that have not demonstrated progression[2]
- Brain metastasis

[1] The short axis is defined as the longest axis perpendicular to the long axis of the tumor. Nodes with <10 mm short axis are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).
[2] Localized post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated and have not demonstrated progression will not be considered measurable and must be selected as NTL at baseline and followed up as part of the NTL assessment.

Special cases:

- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability. Blastic lesions are considered non-measurable.

- Cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected as target lesions (TLs).

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved and suitable for accurate repeated measurement, should be identified as TLs at baseline. Lymph nodes, in any location, are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral, segmented, or multi-lobular organ is considered as a single organ.

Non-target lesions:

All other lesions (or sites of disease) not recorded as TLs should be identified as non-target lesions (NTLs) at baseline.

Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and recorded lesion at baseline and during follow-up visits.

A summary of the methods to be used for RECIST 1.1 assessment is provided in Table E12, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

Table E12 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Clinical examination	Clinical examination
	X-ray, Chest X-ray	X-ray, Chest X-ray
		Ultrasound
		Bone scan
		FDG-PET

CT Computed tomography; FDG-PET ^{18}F-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging; Clinical examination refers to manually palpable tumor lesions.

CT and MRI

CT and MRI, each preferably with intravenous (IV) contrast, are generally considered to be the best currently available and reproducible methods to measure TLs selected for response assessment and to assess NTLs and identify any new lesions.

In this study, it is recommended that IV contrast-enhanced CT examinations of the chest, abdomen, and pelvis be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. In patients who are sensitive to IV CT contrast, a non-contrast CT examination of the chest and an MRI with IV contrast of the abdomen and pelvis are appropriate. In patients with severely compromised renal function, a non-contrast CT examination of the chest, abdomen, and pelvis is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over contrast-enhanced CT. It is strongly recommended to maintain use of the same imaging modality (CT or MRI), acquisition protocol, facility, and scanner across all imaging timepoints per patient.

Clinical examination

In this study, clinical examination will not be used for assessment of TL. Clinically detected lesions can be selected as TLs if they are assessed by CT or MRI scans. Clinical examination can be used to assess NTL and to identify the presence of new lesions.

Chest X-ray

In this study, chest X-ray assessment will not be used for assessment of TL as they will be assessed by CT or MRI examination. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

In this study plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Ultrasound

In this study, ultrasound examination will not be used for assessment of TLs and NTLs as it is not a reproducible method, does not provide an accurate assessment of tumor size and it is subjective and operator dependent. Ultrasound examination can, however, be used to identify the presence of new lesions. If new clinical symptoms occur and an ultrasound is performed, new lesions should be confirmed by CT or MRI examination.

Endoscopy and laparoscopy

In this study, endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers

In this study, tumor markers will not be used for tumor response assessments as per RECIST 1.1.

Cytology and histology

In this study, histology on biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. In such circumstances, the cytology is necessary for the Investigator to differentiate between response/stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). Where cytology findings are not available, any effusion that significantly worsens (from trace to large) or gives the appearance of clinically significant effusion (requiring change in drug therapy) during the study treatment will be considered to be NTL progression or disease progression due to new lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTL and followed by the same method as per baseline assessment.

In this study, isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. New lesions will be recorded where a positive hot-spot that was not present on the baseline bone scan assessment is identified on a bone scan performed at any time during the study. The Investigator should consider the positive hot-spot to be a significant new site of malignant disease and represent true disease progression in order to record the new lesion. Confirmation by CT, MRI and X-ray is recommended where bone scan findings are equivocal.

FDG-PET scan

In this study, ^{18}F-Fluoro-deoxyglucose positron emission tomography (FDG-PET) scans may be used as a method for identifying new lesions in accordance with the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[3] not present on baseline FDG-PET scan or in a location corresponding to a new lesion on CT/MRI at the same follow-up visit. If there is no baseline FDG-PET scan available, and no evidence of new lesions on CT/MRI scans, then follow-up CT/MRI assessments should be continued as scheduled per protocol or clinically indicated in order to confirm new lesions.

[3] A positive FDG-PET scan lesion should be reported only when an uptake greater than twice that of the surrounding tissue is observed.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed as part of a PET/CT examination is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 measurements. However, this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

Tumor response evaluation

Schedule of evaluation

RECIST 1.1 assessments will be performed using contrast-enhanced CT/MRI assessments of chest, abdomen, and pelvis. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before start of study treatment, and ideally should be performed as close as possible to the start of study treatment (see Schedules of Assessments tables in Section 4 of the Clinical Study Protocol). Follow-up assessments will be performed every 8 weeks (relative to the date of randomization) until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping treatment or subsequent therapy).

Additional assessments will be performed post confirmed objective disease progression for patients remaining on assigned treatment, retreatment, or until subsequent cancer therapy according to the clinical study protocol.

Any other anatomical sites at which new disease is suspected should also be adequately imaged at follow-up.

If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits. This schedule is to be followed in order to minimize any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Target lesions

Documentation of target lesions

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TL at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline, the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TLs measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.
- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.
- If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.
- If a TL splits into two or more parts, then record the sum of the diameters of those parts.
- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).
- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.
- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion.
- When a TL has had any intervention eg, radiotherapy, embolization, surgery, during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 electronic case report form.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TLs (see Table E13).

Table E13 Evaluation of target lesions

Complete Response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit. Note: if the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.

TL Target lesion.

Non-target lesions

Evaluation of non-target lesions

All other lesions (or sites of disease) not recorded as TL should be identified as NTL at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit, an overall assessment of the NTL response should be recorded by the Investigator. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit (see Table E14).

Table E14 Evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non CR/Non PD	Persistence of one or more NTL.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: for patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.

NTL Non-target lesion; TL Target lesion.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of stable disease or partial response in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status.

New lesions

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

If a new lesion is equivocal, for example because of its small size, the treatment and tumor assessments should be continued until the new lesion has been confirmed. If repeat scans confirm there is a new lesion, then the progression date should be declared using the date of the initial scan.

Symptomatic deterioration

Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.

Patients with "symptomatic deterioration" requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo regularly scheduled tumor assessments where possible until objective disease progression is observed.

Evaluation of overall visit response

The overall visit response will be derived using the algorithm shown in Table E15.

Table E15 Overall visit response

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NE	Non PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NA Not applicable (only relevant if there were no non-target lesions at baseline).

Confirmation of progression

Confirmation of progression guidelines are set for the following reasons:

- For patient management and treatment decisions
- In the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression (in MEDI4736 monotherapy and MEDI4736 + Tremelimumab immunotherapy treatment arms)
- When scans are evaluated by Investigator and by BICR, to reduce informative censoring by Investigator assessments (when Investigator assesses PD and collects no additional scans, and BICR does not assess PD by RECIST 1.1).

Objective disease progression refers to one of the following scenarios:

- **For All Treatment Arms:** Clinical progression/deterioration followed by a radiologic scan, if clinically feasible.

- **For MEDI4736 monotherapy and MEDI4736 + Tremelimumab Treatment Arms (confirmed objective disease progression):** In the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 is considered confirmed if an immediate subsequent scan has PD assessed according to the specific confirmation of progression criteria listed below. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

  Note: In the absence of clinical progression/deterioration, in order to have confirmed objective disease progression, there should be 2 consecutive radiologic PDs, the first radiologic PD by RECIST 1.1 and the second radiologic PD using the confirmation of progression criteria below. If the first radiologic PD by RECIST 1.1 is not confirmed (unconfirmed), continue with assessments until the next radiologic PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

- **For Standard of Care Arm:** In the absence of significant clinical deterioration, at least 1 scan documenting unequivocal radiographic progression.

Criteria for confirmation of progression:

Immediate prior radiologic progression would be considered confirmed if the following criteria are met:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in the sum of diameters compared with nadir

- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan timepoint compared with the immediate prior timepoint (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan timepoint.)

- *and/or* additional new unequivocal lesions at the confirmatory scan timepoint

For patients in the MEDI4736 monotherapy and MEDI4736 + Tremelimumab Treatment Arms:

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

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

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.** If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

Central review

The Contract Research Organization (CRO) appointed by AstraZeneca to perform the independent central review for this study will provide specification for radiological imaging protocols in standard acquisition guidelines documentation.

All images will be collected, quality checked, and stored centrally by an Imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. The management of patients will be based solely on the local assessments conducted by the Investigator.

Further details of the Blinded Independent Central Review will be documented in the Independent Review Charter (also referred to as "Imaging Charter").

References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix F Patient-reported Outcomes Questionnaires

FACT-Bl (Version 4)

NCI- PRO-CTCAE ITEMS

PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

EQ-5D-5L, Health Questionnaire, English version for the UK

FACT-Bl (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-BI (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Bl (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BL1	I have trouble controlling my urine	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BL5	(For men only) I am able to have and maintain an erection	0	1	2	3	4
Q2	Do you have an ostomy appliance? No___ Yes___ If yes, answer the following two items: ↓					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult	0	1	2	3	4

NCI- PRO-CTCAE ITEMS

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ⓧ in the one box that best describes your experiences over the past 7 days…

1. FATIGUE, TIREDNESS OR LACK OF ENERGY				
What was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

2. DECREASED APPETITE				
What was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

3. LOOSE OR WATERY STOOLS (DIARRHEA)				
How OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly

4. NAUSEA				
How OFTEN do you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

5. VOMITING				
How OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

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NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

6. NUMBNESS OR TINGLING IN YOUR HANDS OR FEET				
What was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

7. SHORTNESS OF BREATH				
What was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much does your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

8. ITCHY SKIN				
What was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

9. RASH	
Did you have any RASH?	
O Yes	O No

10. ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)				
How OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTEREFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

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NCI- PRO-CTCAE ITEMS

Please think back over the past 7 days…

11. PROBLEMS WITH TASTING FOOD OR DRINK				
What was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

12. CONSTIPATION				
What was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

13. COUGH				
What was the SEVERITY of your COUGH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much does your COUGH INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

14. DIZZINESS				
What was the SEVERITY of your DIZZINESS at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did DIZZINESS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

15. HEADACHE				
How OFTEN did you have a HEADACHE?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your HEADACHE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did your HEADACHE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

16. PAIN IN THE ABDOMEN (BELLY)				
How OFTEN did you have PAIN IN THE ABDOMEN (BELLY)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
What was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
How much did PAIN IN THE ABDOMEN (BELLY) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

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PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Since the start of the treatment I have received in this study, my overall health status is:

Please tick (✓) one box only:

- ☐ Very Much Improved
- ☐ Much Improved
- ☐ Minimally Improved
- ☐ No Change
- ☐ Minimally Worse
- ☐ Much Worse
- ☐ Very Much Worse

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

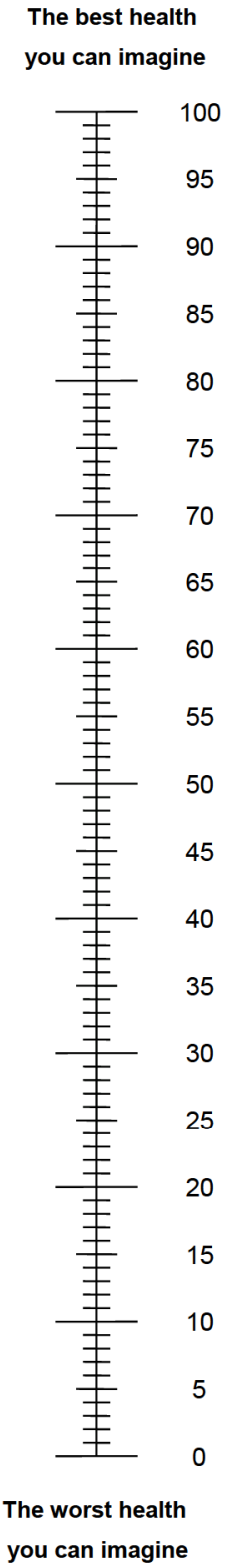
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix H Amendment 1 Summary of Changes

Clinical Study Protocol Amendment

Amendment Number	01
Drug Substance	MEDI4736 + Tremelimumab
Study Code	D419BC00001
Date	7 August 2015
Protocol Dated	9 June 2015

A Phase III, Randomized, Open-label, Controlled, Multi-Center, Global Study of First-Line MEDI4736 Monotherapy and MEDI4736 in Combination with Tremelimumab Versus Standard of Care Chemotherapy in Patients with Unresectable Stage IV Urothelial Bladder Cancer

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Centers affected by the Amendment: All centers

The protocol for the study is to be amended as follows:

Change 1 Deletion of the "peer review" text "This clinical study 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."

The following section of the protocol has been amended to reflect this change:

1. The bottom of the cover page

Change 2 The deletion of "bone" to the list of example of visceral metastasis to read "(presence or absence, ie, lung or liver)."

The following sections of the protocol have been amended to reflect this change:

1. PROTOCOL SYNOPSIS, Study design
2. PROTOCOL SYNOPSIS, Statistical methods
3. PROTOCOL SYNOPSIS, MEDI4736 + tremelimumab combination therapy versus SoC (primary endpoint)
4. INTRODUCTION, Section 1.4 Study design, Figure 1
5. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.3 Patient enrollment and randomization
6. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.5 Methods of assigning treatment groups
7. STATISTICAL ANALYSIS BY ASTRAZENECA, Section 8.5 Methods for statistical analysis, Table 12
8. STATISTICAL ANALYSIS BY ASTRAZENECA, Section 8.5.1 Analysis of the primary variable (2 occurrences)

Change 3 Addition of the statement "(patients enrolled in the platinum gemcitabine arm will discontinue study drug at the first assessment of disease progression)" or the statement "Patients randomized to treatment in the SoC arm will discontinue study drug at the first assessment of disease progression." or similar

The following sections of the protocol have been amended to reflect this change:

1. PROTOCOL SYNOPSIS, Study design
2. PROTOCOL SYNOPSIS, Duration of treatment
3. INTRODUCTION, Figure 2 footnotes

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.9 Discontinuation of investigational product

5. STUDY PLAN AND TIMING OF PROCEDURES, Table 3 footnotes

6. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 footnotes

7. STUDY ASSESSMENTS, Section 5.1 Efficacy assessments

8. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS, Section 7.2.2 Duration of treatment and criteria for retreatment

Change 4 Addition of the word "first" to define PFS as "...the time from the date of randomization until the first date of objective disease progression or death..."

The following sections of the protocol have been amended to reflect this change:

1. PROTOCOL SYNOPSIS, Statistical methods

2. STATISTICAL ANALYSIS BY ASTRAZENECA, Section 8.4.1.2 Primary endpoint

Change 5 Addition of the statement "Randomization of cisplatin-eligible patients will be capped at a maximum of 85% of the planned total number of patients."

The following sections of the protocol have been amended to reflect this change:

1. PROTOCOL SYNOPSIS, Statistical methods

2. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.5 Methods of assigning treatment groups

Change 6 Addition of the text "Among the overall fatal cases (67.7%) reported in the patients treated with tremelimumab monotherapy, the most frequent cause of death was ascribed to the patient's underlying malignant disease (61.8%), whereas the remaining causes included other or unknown/missing (7.1%), and due to investigational product (IP; 0.5%)."

The following section of the protocol has been amended to reflect this change:

1. INTRODUCTION, Section 1.3.2.2 Tremelimumab

Change 7 Deletion of the text "(newly acquired or archived sample <3 months old [if not available, a sample <6 months old may be provided with Sponsor approval])" or "When a tumor sample taken <3 months prior to screening is not available for any

reason, a sample <6 months old may be provided, only after Sponsor approval." or similar (including change from "<3 years" to "<3 months"). Note: Change 8 and Change 10 are related to this change.

The following sections of the protocol have been amended to reflect this change:

1. INTRODUCTION, Section 1.4 Study design

2. STUDY PLAN AND TIMING OF PROCEDURES, Table 2 footnotes

3. STUDY ASSESSMENTS, Section 5.5.1 Evaluation of candidate, predictive markers - tumor PD-L1

Change 8 Addition of Table 1, PD-L1 status defined by scoring of an IHC assay developed by Ventana for stratification in D419BC00001

The following section of the protocol has been amended to reflect this change:

1. INTRODUCTION, Section 1.4 Study design

Change 9 Addition of the note "(Note: The Investigators will use their discretion to confirm the cause of N2 disease **[reactive or inflammatory]**)"

The following section of the protocol has been amended to reflect this change:

1. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.1 Inclusion criteria

Change 10 Change from "As such, all patients must be able to undergo a fresh tumor biopsy during screening or to provide an available tumor sample taken <3 months prior to screening. When a tumor sample taken <3 months prior to screening is not available for any reason, a sample <6 months old may be provided, only after Sponsor approval."

to

"As such, all patients must be able to provide a newly acquired biopsy during screening (preferred) or provide an available tumor sample taken <3 years prior to screening."

The following sections of the protocol have been amended to reflect this change:

1. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.1 Inclusion criteria

2. STUDY PLAN AND TIMING OF PROCEDURES, Table 3 footnote

3. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 footnotes

4. STUDY PLAN AND TIMING OF PROCEDURES, Table 4

5. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 footnote a

6. STUDY PLAN AND TIMING OF PROCEDURES, Table 5 footnote a

Change 11 Addition of the text "(with exclusion of Bacillus Calmette Guerin, BCG)" from exclusion criterion 4; addition of the text ", or to other humanized mAbs" in exclusion criterion 22; change from "No" to "Any" to read "Any medical contraindication to platinum..." for exclusion criterion 23; and addition of "Patient <30 kg in weight" for exclusion criterion 24

The following section of the protocol has been amended to reflect this change:

1. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.2 Exclusion criteria

Change 12 Deletion of the text "or without" to read "Male or female condom with spermicide" and addition of the text "Progesterone T"

The following section of the protocol has been amended to reflect this change:

1. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.8 Restrictions, Table 1

Change 13 Addition of "Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion."

The following sections of the protocol have been amended to reflect this change:

1. STUDY PLAN AND TIMING OF PROCEDURES, Table 3 footnotes

2. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 footnotes

3. STUDY PLAN AND TIMING OF PROCEDURES, Table 5 footnotes

4. STUDY PLAN AND TIMING OF PROCEDURES, Table 6 footnotes

5. STUDY PLAN AND TIMING OF PROCEDURES, Table 7 footnotes

Change 14 Changes to cycle timing; changes to timing of vital signs assessment, thyroid function tests, QoL assessments, serum PD-L1 concentration, circulating soluble factors, PBMCs, and miRNA/mRNA, and urine for exploratory biomarkers; correction from "<3 months" to "<3 years" for tumor biopsy; and correction from "Tumor biopsy (archival ≥ months old, if available)" to "Tumor biopsy (archival if available, for patients who submit a fresh biopsy at screening for PD-L1 status)."

The following section of the protocol has been amended to reflect this change:

1. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 and Table 4 footnotes

Change 15 Clarification of "serum chemistry" to "chemistry" or addition of "or plasma"

The following sections of the protocol have been amended to reflect this change:

1. STUDY PLAN AND TIMING OF PROCEDURES, Table 3
2. STUDY PLAN AND TIMING OF PROCEDURES, Table 3 footnote c
3. STUDY PLAN AND TIMING OF PROCEDURES, Table 4
4. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 footnote e
5. STUDY PLAN AND TIMING OF PROCEDURES, Table 5
6. STUDY PLAN AND TIMING OF PROCEDURES, Table 5 footnote c
7. STUDY PLAN AND TIMING OF PROCEDURES, Table 6
8. STUDY PLAN AND TIMING OF PROCEDURES, Table 7
9. STUDY ASSESSMENTS, Section 5.2 Safety assessments

Change 16 Replacement of "X" with "q8w up to Month 6 after disease progression" to EQ-5D-5L on Day 30 (±3)" and addition of the text "(±7 days)" to read "q8w **(±7 days)** relative to the date of randomization until confirmed progression"

The following sections of the protocol have been amended to reflect this change:

1. STUDY PLAN AND TIMING OF PROCEDURES, Table 6
2. STUDY PLAN AND TIMING OF PROCEDURES, Table 7

Change 17 Replacement of "IP" with "MEDI4736 monotherapy or MEDI4736 + tremelimumab combination arms"

The following section of the protocol has been amended to reflect this change:

1. STUDY ASSESSMENTS, Section 5.1 Efficacy assessments

Change 18 Changes to provisions of tissue for PD-L1 IHC and clarifications to related text

The following section of the protocol has been amended to reflect this change:

1. STUDY ASSESSMENTS, Section 5.5.1 Evaluation of candidate, predictive markers - tumor PD-L1

Change 19 Addition of the text "after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 monotherapy. For patients receiving standard of care agents for chemotherapy, please follow the local prescribing information relating to contraception and the time limit for such precautions."

to read

"Male patients must refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 monotherapy. For patients receiving standard of care agents for chemotherapy, please follow the local prescribing information relating to contraception and the time limit for such precautions."

The following section of the protocol has been amended to reflect this change:

1. SAFETY REPORTING AND MEDICAL MANAGEMENT, Section 6.6.Paternal exposure

Change 20 Addition of "[MEDI4736 and MEDI4736 + tremelimumab, only; for SOC refer to Section 6.7.2])."

The following section of the protocol has been amended to reflect this change:

1. SAFETY REPORTING AND MEDICAL MANAGEMENT, Section 6.7.Management of IP-related toxicities

Change 21 Addition of "Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the MEDI4736 and tremelimumab safety profile and require close monitoring and rapid communication by the Investigator to AstraZeneca. MEDI4736 and tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of these IPs." and deletion of "adverse events of special interest and deletion of "adverse events of special interest" in the following paragraph to read as "Information on MEDI4736 and MEDI4736 + tremelimumab AESIs and guidelines..."""

The following section of the protocol has been amended to reflect this change:

1. SAFETY REPORTING AND MEDICAL MANAGEMENT, Section 6.7.1 MEDI4736 and MEDI4736 + tremelimumab

Change 22 Clarifications in the text regarding the IDMC

The following section of the protocol has been amended to reflect this change:

1. SAFETY REPORTING AND MEDICAL MANAGEMENT, Section 6.8 Study governance and oversight

Change 23 Addition of the following prohibited medications/classes of drugs: Sunitinib, usage - Should not be given to patients within 3 months of a dose of tremelimumab, as acute renal failure has been reported with combination therapy of tremelimumab and sunitinib; Drugs with laxative properties and herbal or natural remedies for constipation, usage - Should be avoided through 90 days after the last dose of tremelimumab during the study, if possible. In case of strong medical need, should be used with caution.

The following section of the protocol has been amended to reflect this change:

1. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS, Section 7.7 Concomitant and other treatments

Change 24 Deletion of "Treatment through PD in the SoC group is at the Investigator's discretion; however, a" to read "A confirmatory scan is required for all patients in the SoC group, even if a subsequent treatment is started."

The following section of the protocol has been amended to reflect this change:

1. STATISTICAL ANALYSIS BY ASTRAZENECA, Section 8.4.1.2 Primary endpoint

Change 25 Typographical errors have been corrected, and minor text clarifications have been made throughout the document. These minor changes do not affect patient safety or study assessments and, therefore, are not further described in this Amendment.

The specific modifications to the protocol implemented by Changes 1 through 24 are presented on the following pages.

Change 1

Section of protocol affected:

1. The bottom of the cover page

Deleted text:

This clinical study 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.

[...]

Reason for Amendment:

This edit was made due to template language modifications.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 2

Sections of protocol affected:

1. PROTOCOL SYNOPSIS, Study design
2. PROTOCOL SYNOPSIS, Statistical methods
3. PROTOCOL SYNOPSIS, MEDI4736 + tremelimumab combination therapy versus SoC (primary endpoint)
4. INTRODUCTION, Section 1.4 Study design, Figure 1
5. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.3 Patient enrollment and randomization
6. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.5 Methods of assigning treatment groups
7. STATISTICAL ANALYSIS BY ASTRAZENECA, Section 8.5 Methods for statistical analysis, Table 12

8. STATISTICAL ANALYSIS BY ASTRAZENECA, Section 8.5.1 Analysis of the primary variable (2 occurrences)

Previous text:

ie, bone, lung, or liver

[...]

Revised text:

ie, lung or liver

[...]

Reason for Amendment:

This correction was made based on comments from the Food and Drug Administration (FDA) in its review of the protocol.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 3

Sections of protocol affected:

1. PROTOCOL SYNOPSIS, Study design
2. PROTOCOL SYNOPSIS, Duration of treatment
3. INTRODUCTION, Figure 2 footnotes
4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.9 Discontinuation of investigational product
5. STUDY PLAN AND TIMING OF PROCEDURES, Table 3 footnotes
6. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 footnotes
7. STUDY ASSESSMENTS, Section 5.1 Efficacy assessments
8. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS, Section 7.2.2 Duration of treatment and criteria for retreatment

Previous text:

Not applicable

[...]

Revised text:

Tumor assessments will be performed every 8 weeks until **confirmed progression (patients enrolled in the platinum gemcitabine arm will discontinue study drug at the first assessment of disease progression)** according to objective tumor response by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1).

or

Unless specific treatment discontinuation criteria are met, treatment will continue for a 12-month period for the MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy groups and for up to 6 cycles for the SoC (cisplatin + gemcitabine or carboplatin + gemcitabine) group.

Patients randomized to treatment in the SoC arm will discontinue study drug at the first assessment of disease progression.

Patients randomized to treatment with MEDI4736 monotherapy may undergo retreatment if they

or similar

[...]

Reason for Amendment:

Text was amended for clarification.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 4

Sections of protocol affected:

1. PROTOCOL SYNOPSIS, Statistical methods

2. STATISTICAL ANALYSIS BY ASTRAZENECA, Section 8.4.1.2 Primary endpoint

Previous text:

Statistical methods

PFS (per RECIST 1.1, using site Investigator tumor assessments) will be defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression.

[...]

Revised text:

Statistical methods

PFS (per RECIST 1.1, using site Investigator tumor assessments) will be defined as the time from the date of randomization until the date of **first** objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomized therapy or receives another anticancer therapy prior to progression.

[...]

Reason for Amendment:

This text was revised to clarify a definition.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 5

Sections of protocol affected:

1. PROTOCOL SYNOPSIS, Statistical methods

2. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.5 Methods of assigning treatment groups

Previous text:

Approximately 525 patients will be randomized 1:1:1 to MEDI4736 + tremelimumab, MEDI4736 monotherapy, or SoC. The randomization will be stratified according to cisplatin

eligibility (eligible or ineligible), PD-L1 status (positive and negative), and visceral metastases (presence or absence, ie, bone, lung, or liver).

[...]

Revised text:

Approximately 525 patients will be randomized 1:1:1 to MEDI4736 + tremelimumab, MEDI4736 monotherapy, or SoC. The randomization will be stratified according to cisplatin eligibility (eligible or ineligible), PD-L1 status (positive and negative), and visceral metastases (presence or absence, ie, lung or liver). **Randomization of cisplatin-eligible patients will be capped at a maximum 85% of the planned total number of patients..**

[...]

Reason for Amendment:

This correction was made based on comments from the FDA in its review of the protocol.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 6

Section of protocol affected:

1. INTRODUCTION, Section 1.3.2.2 Tremelimumab

Previous text:

Tremelimumab

The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the IB data cutoff date of 12 November 2014 (for all studies except D4190C00006 that has a cutoff date of 04 December 2014, and not including 497 patients who have been treated in the ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. The frequency of any AEs and Grade ≥3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 28 days and

15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of investigational product (IP), and deaths.

[...]

Revised text:

Tremelimumab

The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the IB data cutoff date of 12 November 2014 (for all studies except D4190C00006 that has a cutoff date of 04 December 2014, and not including 497 patients who have been treated in the ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. **Among the overall fatal cases (67.7%) reported in the patients treated with tremelimumab monotherapy, the most frequent cause of death was ascribed to the patient's underlying malignant disease (61.8%), whereas the remaining causes included other or unknown/missing (7.1%), and due to investigational product (IP; 0.5%).** The frequency of any AEs and Grade ≥3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 28 days and 15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of IP, and deaths.

[...]

Reason for Amendment:

Text was added to clarify the most frequent cause of death in this population.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 7

Sections of protocol affected:

1. INTRODUCTION, Section 1.4 Study design

2. STUDY PLAN AND TIMING OF PROCEDURES, Table 2 footnotes

3. STUDY ASSESSMENTS, Section 5.5.1 Evaluation of candidate, predictive markers - tumor PD-L1

Previous text:

Study design

Patients will provide a tumor tissue sample at screening **(newly acquired or archived sample <3 months old [if not available, a sample <6 months old may be provided with Sponsor approval])** to determine PD-L1 status (defined by an immunohistochemistry [IHC] assay developed by Ventana) for stratification.

[...]

Revised text:

Study design

Patients will provide a tumor tissue sample at screening to determine PD-L1 status (defined by an immunohistochemistry [IHC] assay developed by Ventana, see Table 1) for stratification.

[...]

Reason for Amendment:

The text was amended to clarify tumor biopsy sampling.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 8

Section of protocol affected:

1. INTRODUCTION, Section 1.4 Study design

Previous text:

Table not present

[...]

Revised text:

Table 1 PD-L1 status defined by scoring of an IHC assay developed by Ventana for stratification in D419BC00001

Interpretation	Staining description
Positive for PD-L1	≥25% tumor cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control OR ≥25% tumor associated immune cell positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control
Negative for PD-L1	<25% tumor cell membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control AND <25% tumor associated immune cell positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative control

IHC Immunohistochemistry; PD-L1 Programmed cell death ligand 1.
[...]

Reason for Amendment:

The table was included to increase the visibility of the cutoff utilized for PDL1.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 9

Section of protocol affected:

1. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.1 Inclusion criteria

Previous text:

Section 3.1 Inclusion criteria

3. Patients with histologically or cytologically documented, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3; or M1) transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra), who have not been

previously treated with first-line chemotherapy. (Patients who have received prior definitive chemoradiation for locally advanced disease, adjuvant treatment, or neoadjuvant treatment are eligible, provided that progression has occurred >6 months from last therapy [for chemoradiation and adjuvant treatment] or >6 months from last surgery [for neoadjuvant treatment].)

[...]

Revised text:

Section 3.1 Inclusion criteria

3. Patients with histologically or cytologically documented, unresectable, Stage IV (ie, T4b, any N; or any T, N2-N3 **(Note: The Investigators will use their discretion to confirm the cause of N2 disease [reactive or inflammatory]); or M1)** transitional cell carcinoma (transitional cell and mixed transitional/non-transitional cell histologies) of the urothelium (including renal pelvis, ureters, urinary bladder, and urethra), who have not been previously treated with first-line chemotherapy. (Patients who have received prior definitive chemoradiation for locally advanced disease, adjuvant treatment, or neoadjuvant treatment are eligible, provided that progression has occurred >6 months from last therapy [for chemoradiation and adjuvant treatment] or >6 months from last surgery [for neoadjuvant treatment].)

[...]

Reason for Amendment:

This correction was made based on comments from the FDA in its review of the protocol.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

<u>Change 10</u>

Sections of protocol affected:

1. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.1 Inclusion criteria

2. STUDY PLAN AND TIMING OF PROCEDURES, Table 3 procedures

3. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 procedures

Previous text:

Section 3.1 Inclusion criteria

8. Tumor PD-L1 status, with IHC assay confirmed by a reference laboratory, must be known prior to randomization. As such, all patients must be able to undergo a fresh tumor biopsy during screening **or to provide an available tumor sample taken <3 months prior to screening. When a tumor sample taken <3 months prior to screening is not available for any reason, a sample <6 months old may be provided, only after Sponsor approval.** Tumor lesions used for fresh biopsies should not be target lesions, unless there are no other lesions suitable for biopsy. Fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component. The tumor specimen submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin embedded blocks.

[...]

Revised text:

Section 3.1 Inclusion criteria

8. Tumor PD-L1 status, with IHC assay confirmed by a reference laboratory, must be known prior to randomization. As such, all patients must be able **provide a newly acquired** tumor biopsy during screening (**preferred) or provide an available tumor sample taken <3 years prior to screening.** Tumor lesions used for **newly acquired** biopsies should not be target lesions, unless there are no other lesions suitable for biopsy. **Samples with limited tumor content and** fine needle aspirate specimens are not acceptable. Specimens from metastatic bone lesions are typically unacceptable unless there is a significant soft tissue component. The tumor specimen submitted to establish **PD-L1 status** should be of sufficient quantity to allow for PD-L1 IHC and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin embedded blocks.

[...]

Reason for Amendment:

The text was amended to provide clarification of tumor biopsy sampling.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 11

Section of protocol affected:

1. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.2 Exclusion criteria

Previous text:

Section 3.2 Exclusion criteria

4. Prior exposure to immune-mediated therapy, including but not limited to, other anti-CTLA 4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines

12 Other malignancy within 5 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin or ductal carcinoma in situ of the breast that has been surgically cured. Cancer patients with incidental histologic findings of prostate cancer (tumor/node/metastasis stage of T1a or T1b or prostate specific antigen <10) who have not received hormonal treatment may be included, pending a discussion with the Study Physician

17 Known history of clinical diagnosis of tuberculosis

22. Known allergy or hypersensitivity to IP or any IP excipient

23. **No** medical contraindication to platinum (cisplatin or carboplatin)-based doublet chemotherapy

[...]

Revised text:

Section 3.2 Exclusion criteria

4. Prior exposure to immune-mediated therapy **(with exclusion of Bacillus Calmette Guerin, BCG),** including but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, including therapeutic anticancer vaccines

12 Other malignancy within 5 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin, **localized prostate cancer treated with curative intent and absence of PSA relapse** or ductal carcinoma in situ of the breast that has been surgically cured. Cancer patients with incidental histologic findings of prostate cancer (tumor/node/metastasis stage of T1a or T1b or prostate specific antigen <10) who

have not received hormonal treatment may be included, pending a discussion with the Study Physician

17 **Active** tuberculosis

22. Known allergy or hypersensitivity to IP or any IP excipient**, or to other humanized mAbs**

23. **Any** medical contraindication to platinum (cisplatin or carboplatin)-based doublet chemotherapy

24. Patient <30 kg in weight

[...]

Reason for Amendment:

The criteria were amended for clarity and completeness.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 12

Section of protocol affected:

1. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION, AND WITHDRAWAL, Section 3.8 Restrictions, Table 1

Previous text:

Table 1 Effective methods of contraception

Barrier/Intrauterine methods	Hormonal methods
• Male or female condom with **or without** spermicide[a,b,c] • Cap, diaphragm, or sponge with spermicide[a,b,c] • Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[d]	• Implants • Hormone shot or injection • Combined pill • Minipill[b] • Patch

[...]

Revised text:

Table 2 Effective methods of contraception

Barrier/Intrauterine methods	Hormonal methods
• Male or female condom with spermicide[a,b,c] • Cap, diaphragm, or sponge with spermicide[a,b,c] • Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[d] • **Progesterone T[d]**	• Implants • Hormone shot or injection • Combined pill • Minipill[b] • Patch

[...]

Reason for Amendment:

The protocol contraceptive language was reviewed and updated to be consistent with similar AstraZeneca clinical trials.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 13

Sections of protocol affected:

1. STUDY PLAN AND TIMING OF PROCEDURES, Table 3 footnote d
2. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 footnotes
3. STUDY PLAN AND TIMING OF PROCEDURES, Table 5 footnotes
4. STUDY PLAN AND TIMING OF PROCEDURES, Table 6 footnotes
5. STUDY PLAN AND TIMING OF PROCEDURES, Table 7 footnotes

Previous text:

Table 2, footnote d

For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[...]

Revised text:

Table 3, footnote d

For women of childbearing potential **are required to have a pregnancy test within 7 days prior to the first dose of study drug. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.**

[...]

Reason for Amendment:

The pregnancy language was modified to provide clarity.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 14

Section of protocol affected:

1. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 and Table 4 footnotes

Previous Text: Table 3 Schedule of assessments for cisplatin + gemcitabine 28-day cycle treatment period

	Screening	C1				C2				C3, C4, C5, and C6				For details see CSP Section
		(±3 days, tumor assessment ±7 days)												
Week	**-4 to -1**	**0**	**0**	**1**	**2**	**4**	**4**	**5**	**6**	**8**	**8**	**9**	**10**	
Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	
Informed consent														
Written informed consent	X[a]													3.3
Study procedures														
Physical examination (full)	X													5.2.2
Targeted physical exam (based on symptoms)		X				X				X				5.2.2
ECG[b]	X	As clinically indicated												5.2.3
Vital signs	X	X								**X**[c,d]				5.2.4
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Demography, including medical and surgical history and history of tobacco use	X													4.1
Laboratory assessments														
Serum chemistry (complete clinical chemistry panel) and hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Liver enzyme panel[e]	X	X				X				X				5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)[f]	X									**X**[c]				5.2.1
Urinalysis[e], hepatitis B and C, and HIV	X													5.2.1
Urine hCG or serum β-hCG[g] and coagulation parameters[e]	X	As clinically indicated												5.3.3
Monitoring														
ECOG PS	X	X				X				X				5.3.3
AE/SAE assessment	X[h]	All visits												6.3
IP administration														

	Screening	C1				C2				C3, C4, C5, and C6				For details see CSP Section
		(±3 days, tumor assessment ±7 days)												
Week	**-4 to -1**	**0**	**0**	**1**	**2**	**4**	**4**	**5**	**6**	**8**	**8**	**9**	**10**	
Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	
Cisplatin			X				X				X			7.2.1
Gemcitabine		X		X	X	X		X	X	X		X	X	7.2.1
Quality of life assessments														
FACT-BL[i]		X	q8w											5.3.1
PRO-CTCAE[i]		X			X	X			X	X	**q4w from Week 8**			5.3.1
PGIC[i]										Weeks 8, 16**, 32, and 48**				5.3.1
EQ-5D-5L[i]		X	q8w											5.3.1
Other laboratory assessments and assays														
Serum PD-L1 concentration		X								**X[c]**				5.5
Circulating soluble factors, PBMCs, and miRNA/mRNA		X				X				**X[c,j]**				5.5
Urine for exploratory biomarkers[k]		X				X				**X[c]**				5.5
SNP genotyping		X												5.5
MDSCs		X												5.5
Tumor biopsy (recently acquired (within 3 months) or archival <3 years old)	X[a]													5.5
Tumor biopsy (archival if available, for patients who submit a (recently acquired (within 3 months) biopsy at screening for PD-L1 status)	X													5.5
Tumor assessment (CT or MRI)[l]	X	q8w relative to the date of randomization until **confirmed progression**												5.1
PGx sample (optional [DNA element])		X												5.6
Health economics assessments														
Health resource use (HOSPAD module)[m]	**X**	To be completed at each hospitalization												8.5.10

[a] Informed consent includes consent for study procedures, biopsy for PD-L1 status, and optional genetic sampling and analysis. Informed consent may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization. **When a tumor sample taken <3 months prior to screening is not available for any reason, a sample <6 months old may be provided, only after Sponsor approval.**

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

[c] Day 1 of Cycle 4 only.

[d] Day 1 of Cycle 6 only.

[e] If screening laboratory assessments are performed within 3 days prior to Day 1, then tests do not need to be repeated at Day 1, if applicable as per local routine practice. Hematology and **serum** chemistry results should be available and reviewed prior to chemotherapy administration on each dosing day and as per local routine practice. LFT results should be available and reviewed by the treating physician or Investigator prior to the start of each chemotherapy cycle and as per local routine practice. **Serum chemistry**, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated. Coagulation tests include activated partial thromboplastin time and international normalized ratio.

[f] fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[g] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.

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

[i] PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The FACT-BL will be administered first, followed by the PGIC, the EQ-5D-5L, and then the PRO-CTCAE. Patients will complete PROs using handheld electronic devices at study sites if the assessment timepoint coincides with a scheduled site visit; otherwise, patients will complete PROs at home.

[j] Circulating soluble factors only.

[k] Urine for exploratory biomarkers will be obtained only in patients who have not undergone a full cystectomy and who have tumor lesion(s) present in the urothelium.

[l] RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of the chest, abdomen, and pelvis. Additional anatomy may be imaged based on signs and symptoms of individual patients. Baseline assessments, ideally, should be performed as close as possible prior to the start of study treatment. The confirmatory scans should preferably be performed at the next scheduled visit (relative to the date of randomization) and no less than 4 weeks after the initial assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

[m] HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.

Note: Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.

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

β-hCG Beta-human chorionic gonadotropin; C Cycle; CSP Clinical study protocol; EQ-5D-5L EuroQol five-dimensional descriptive system; FACT-BL Functional Assessment of Cancer Therapy-Bladder Cancer; fT_3 Free triiodothyronine; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; LFT Liver function test; MDSC Myeloid-derived suppressor cells; miRNA Micro-ribonucleic acid; mRNA Messenger ribonucleic acid; PBMC Peripheral blood mononuclear cells; PGIC Patient Global Impression of Change; PGx Pharmacogenetic; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; q8w Every 8 weeks; SNP Single nucleotide polymorphism; TSH Thyroid-stimulating hormone.

[…]

Revised text:

Table 4 Schedule of assessments for cisplatin + gemcitabine 28-day cycle treatment period

	Screening	C1				C2, C3, C4, and C5				C6				For details see CSP Section
		(±3 days, tumor assessment ±7 days)												
Week	**-4 to -1**	**0**	**0**	**1**	**2**	**4**	**4**	**5**	**6**	**20**	**20**	**21**	**22**	
Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	
Informed consent														
Written informed consent	X[a]													3.3
Study procedures														
Physical examination (full)	X													5.2.2
Targeted physical exam (based on symptoms)		X				X				X				5.2.2
ECG[b]	X	As clinically indicated												5.2.3
Vital signs	X	X				**X**[c]				X[d]				5.2.4
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Demography, including medical and surgical history and history of tobacco use	X													4.1
Laboratory assessments														
Serum or plasma chemistry (complete clinical chemistry panel) and hematology[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	5.2.1
Liver enzyme panel[e]	X	X				X				X				5.2.1
Thyroid function tests (TSH, fT_3, and fT_4)[f]	X					**X**[c]								5.2.1
Urinalysis[c], hepatitis B and C, and HIV	X													5.2.1

	Screening	C1				C2, C3, C4, and C5				C6				For details see CSP Section
		(±3 days, tumor assessment ±7 days)												
Week	**-4 to -1**	**0**	**0**	**1**	**2**	**4**	**4**	**5**	**6**	**20**	**20**	**21**	**22**	
Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	
Urine hCG or serum β-hCG[g] and coagulation parameters[e]	X	As clinically indicated												5.2.1
Monitoring														
ECOG PS	X	X				X				X				5.3.3
AE/SAE assessment	X[h]	All visits												6.3
IP administration														
Cisplatin			X				X				X			7.2.1
Gemcitabine		X		X	X	X		X	X	X		X	X	7.2.1
Quality of life assessments														
FACT-BL[i]		X	q8w											5.3.1
PRO-CTCAE[i]		X			X	X			X[r]	X				5.3.1
PGIC[i]										Weeks 8 and 16				5.3.1
EQ-5D-5L[i]		X	q8w											5.3.1
Other laboratory assessments and assays														
Serum PD-L1 concentration		X				**X[c]**								5.5
Circulating soluble factors, PBMCs, and miRNA/mRNA		X				**X[l, m]**								5.5
Urine for exploratory biomarkers[n]		X				**X[l]**								5.5
SNP genotyping		X												5.5
MDSCs		X												5.5
Tumor biopsy (**newly acquired** or archival <3 years old)	X[a]													5.5

	Screening	C1				C2, C3, C4, and C5				C6				For details see CSP Section
		(±3 days, tumor assessment ±7 days)												
Week	**-4 to -1**	**0**	**0**	**1**	**2**	**4**	**4**	**5**	**6**	**20**	**20**	**21**	**22**	
Day	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**15**	
Tumor biopsy (archival, if available, for patients who submit a **newly acquired** biopsy at screening for PD-L1 status	X													5.5
Tumor assessment (CT or MRI)[o]	X	q8w relative to the date of randomization until **progression**[p]												5.1
PGx sample (optional [DNA element])		X												5.6
Health economics assessments														
Health resource use (HOSPAD module)[q]		To be completed at each hospitalization												8.5.10

[a] Informed consent includes consent for study procedures, biopsy for PD-L1 status, and optional genetic sampling and analysis. Informed consent may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization.

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

[c] Day 1 of Cycle 4 only.

[d] Day 1 of Cycle 6 only.

[e] If screening laboratory assessments are performed within 3 days prior to Day 1, then tests do not need to be repeated at Day 1, if applicable as per local routine practice. Hematology and chemistry results should be available and reviewed prior to chemotherapy administration on each dosing day and as per local routine practice. LFT results should be available and reviewed by the treating physician or Investigator prior to the start of each chemotherapy cycle and as per local routine practice. Chemistry, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated. Coagulation tests include activated partial thromboplastin time and international normalized ratio.

[f] fT_3 and fT_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[g] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. **Pregnancy test may occur on the day of dosing, but results must be available and reviewed by the physician prior to the first dose of study drug**.

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

[i] PRO-CTCAE will only be administered in those countries where a linguistically validated version exists. The FACT-BL will be administered first, followed by the PGIC, the EQ-5D-5L, and then the PRO-CTCAE. Patients will complete PROs using handheld electronic devices at study sites if the assessment timepoint coincides with a scheduled site visit; otherwise, patients will complete PROs at home.

[j] **Starting at Cycle 3; every 4 weeks**

[k] **For Cycle 3 and 4 only**

[l] **Day 1 of Cycle 2 and 4 only;**

[m] Circulating soluble factors only **for Cycle 4**

[n] Urine for exploratory biomarkers will be obtained only in patients who have not undergone a full cystectomy and who have tumor lesion(s) present in the urothelium.

[o] RECIST assessments will be performed using contrast-enhanced CT/MRI assessments of the chest, abdomen, and pelvis. Additional anatomy may be imaged based on signs and symptoms of individual patients. Baseline assessments, ideally, should be performed as close as possible prior to the start of study treatment. The confirmatory

scans should preferably be performed at the next scheduled visit (relative to the date of randomization) and no less than 4 weeks after the initial assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits (relative to the date of randomization). All confirmatory scans should be recorded on the database.

p **Patients enrolled in the SOC arm will discontinue study drug at the first assessment of disease progression.**

q HOSPAD module should be completed by site staff whenever the patient has attended or been admitted in to the hospital. A reminder will be provided at each clinic visit.

r Week 2 only

Note: Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.
Note: All assessments on treatment days are to be performed pre-infusion unless otherwise indicated.
β-hCG Beta-human chorionic gonadotropin; C Cycle; CSP Clinical study protocol; EQ-5D-5L EuroQol five-dimensional descriptive system; FACT-BL Functional Assessment of Cancer Therapy-Bladder Cancer; fT_3 Free triiodothyronine; fT_4 Free thyroxine; hCG Human chorionic gonadotropin; LFT Liver function test; MDSC Myeloid-derived suppressor cells; miRNA Micro-ribonucleic acid; mRNA Messenger ribonucleic acid; PBMC Peripheral blood mononuclear cells; PGIC Patient Global Impression of Change; PGx Pharmacogenetic; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; q8w Every 8 weeks; SNP Single nucleotide polymorphism; TSH Thyroid-stimulating hormone.

[...]

Reason for Amendment:

Table header was reorganized for clarity, as a result, C3, C4, and C5 that had been previously grouped with C6 were regrouped with C2. As a result some of the operations at various timepoints shifted, resulting in updates to superscript lettering and footnotes. In addition, language regarding tissue biopsies was clarified and updated in the table.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 15

Sections of protocol affected:

1. STUDY PLAN AND TIMING OF PROCEDURES, Table 3
2. STUDY PLAN AND TIMING OF PROCEDURES, Table 3 footnote c
3. STUDY PLAN AND TIMING OF PROCEDURES, Table 4
4. STUDY PLAN AND TIMING OF PROCEDURES, Table 4 footnote e
5. STUDY PLAN AND TIMING OF PROCEDURES, Table 5
6. STUDY PLAN AND TIMING OF PROCEDURES, Table 5 footnote c
7. STUDY PLAN AND TIMING OF PROCEDURES, Table 6
8. STUDY PLAN AND TIMING OF PROCEDURES, Table 7
9. STUDY ASSESSMENTS, Section 5.2 Safety assessments

Previous text:

Serum chemistry (complete clinical chemistry panel) and hematology

[...]

Revised text:

Serum **or plasma** chemistry (complete clinical chemistry panel) and hematology

[...]

Reason for Amendment:

Text was revised to indicate that serum or plasma could be used for chemistry analyses.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 16

Sections of protocol affected:

1. STUDY PLAN AND TIMING OF PROCEDURES, Table 6

2. STUDY PLAN AND TIMING OF PROCEDURES, Table 7

Previous text:

X

and

q8w relative to the date of randomization until confirmed progression

Revised text:

q8w up to Month 6 after disease progression

and

q8w **(±7 days)** relative to the date of randomization until confirmed progression

Reason for Amendment:

Text was revised and updated to clarify timepoints for post-disease progression assessments.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 17

Section of protocol affected:

1. STUDY ASSESSMENTS, Section 5.1 Efficacy assessments

Previous text:

Section 5.1 Efficacy assessments

Following confirmed progression, patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the study plan (Table 5 and Table 6). An exception is patients with PD who continue to receive **IP** at the discretion of the Investigator (after consultation with AstraZeneca); these patients will have scans for RECIST 1.1 assessments q8w (per Table 2, Table 3, and Table 4) until confirmed progression. In addition, all patients will be contacted in the week following data cutoff to confirm survival status.

[...]

Revised text:

Section 5.1 Efficacy assessments

Following confirmed progression, patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the study plan (Table 6 and Table 7). Patients enrolled in the SOC arm will discontinue study drug at the first assessment of disease progression). An exception is patients with PD who continue to receive **MEDI4736 monotherapy or MEDI4736 + tremelimumab combination arms** at the discretion of the Investigator (after consultation with AstraZeneca); these patients will have scans for RECIST 1.1 assessments q8w (per Table 3, Table 4, and Table 5) until confirmed progression. In addition, all patients will be contacted in the week following data cutoff to confirm survival status.

[...]

Reason for Amendment:

Text was updated to provide clarity with regards to medication referred to as IP in paragraph.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 18

Section of protocol affected:

1. STUDY ASSESSMENTS, Section 5.5.1 Evaluation of candidate, predictive markers - tumor PD-L1

Previous text:

Provision of tissue for PD-L1 IHC is as follows:

- MANDATORY – Provision of a recent tumor biopsy formalin fixed and embedded in paraffin. A freshly collected tumor biopsy is strongly preferred; however, if not clinically feasible, an archival muscle invasive tumor biopsy sample taken <3 **months** prior to screening may be submitted. **When a tumor sample taken <3 months prior to screening is not available for any reason, a sample <6 months old may be provided, only after Sponsor approval.**

  Samples should be collected via an image-guided core needle (18 gauge or larger) or be collected as an excisional or incisional tumor biopsy sample.

  When tissue is **newly** obtained for **the purpose of entry into the study,** 2 cores should be placed in formalin and processed to a single paraffin embedded block, as described in the **Laboratory Manual**.

  The tumor specimen submitted to establish eligibility should be of sufficient quantity to allow for PD-L1 IHC analyses (see the Laboratory Manual). Newly acquired or archival specimens with limited tumor content and fine needle aspirates are inadequate for defining tumor PD-L1 status.

  Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy. If a RECIST 1.1 target lesion is used for biopsy, the lesion must be ≥2 cm in the longest diameter and must be biopsied outside of the screening period.

- If **available and accessible,** archived tumor tissue block greater than 6 months old (formalin-fixed paraffin-embedded) is requested, where such samples exist in a quantity sufficient to allow for analysis. Tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. An archived tumor tissue block or sections may be delivered at any time during the study. Please consult the Laboratory Manual for specific instructions and guidelines regarding sections.

- The collection of tumor biopsies at the time of progression and prior to retreatment is strongly encouraged. The biopsy procedure at retreatment should be omitted only if there is unacceptable clinical risk or the procedure is otherwise considered not

feasible. The Investigator must consult with the Study Physician prior to making the decision not to biopsy at retreatment.

- The collection of additional biopsies upon progression of patients in the MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy arms is strongly encouraged.

Additional tumor biopsies collected **as part** of **clinical care (eg, for mixed responses or upon PD) may be submitted f**or exploratory analyses.

Please review the Laboratory Manual for further details of requirements including sample QC and shipping.

A brief description of exploratory tumor markers likely to be explored by IHC or RNA analysis is provided in Section 5.5.1.1.

The Ventana PD-L1 IHC assay will be used to determine PD-L1 IHC status in this study for stratification. The Ventana PD-L1 IHC analysis will be performed at a Ventana approved College of American Pathologists/Clinical Laboratory Improvement Act laboratory using the Ventana assay. No other assays will be accepted in lieu of results obtained from the Ventana test using specimen submitted at screening. **Details regarding the assay and algorithm to be used for determination of the PD-L1 IHC status (positive or negative) in this study will be finalized and fully documented prior to enrollment of any patients in this study.**

To meet the requirement of Food and Drug Administration (FDA) approval of a companion diagnostic, sections of the tumor will be retained at Ventana for potential additional studies, as requested by the FDA, to support potential test approval.

[...]

Revised text:

Provision of tissue for PD-L1 IHC is as follows:

- MANDATORY – **Provision of a newly acquired tumor sample (preferred) OR formalin fixed and paraffin embedded archival tissue obtained within 3 years prior to screening. ONLY 1 sample (either newly acquired or archival tissue) will be used to determine PD-L1 status. Where multiple samples have been submitted for the same patient, the initial result will determine a patient's PD-L1 status.**

- Samples should be collected via an image-guided core needle (18 gauge or larger) or be collected as an excisional or incisional tumor biopsy sample.

Where institutional practice, in this setting, uses a smaller gauge needle, samples should be submitted in sufficient number to ensure that a valid result can be achieved.

When tissue is **acquired for this study, effort should be made to maximize material for downstream analyses.** 2 cores **using an 18 gauge or larger needle are required for establishing PD-L1 status. These** should be placed in formalin and processed to a single paraffin embedded block, **as described in the Pathology Manual.** When a smaller gauge needle is used the number of cores rises to 3 or 4. **That written, and as a guidance, it is anticipated that 4 passes of a core needle will provide sufficient tissue for establishing PD-L1 status and for delivering protocol-defined exploratory objectives. Whenever feasible, additional cores (beyond those required to establish PD-L1 status) should be obtained and immediately frozen** as described in the laboratory **manual.**

The tumor specimen submitted to establish **PD-L1 status** should be of sufficient quantity to allow for PD-L1 IHC analyses (see the Laboratory Manual. **Samples** with limited tumor content and fine needle aspirates are inadequate for defining tumor PD-L1 status.

Tumor lesions used for biopsies **acquired during screening** should not be the same lesions used as RECIST 1.1 target lesions, unless there are no other lesions suitable for biopsy. If a RECIST 1.1 target lesion is used for biopsy, the lesion must be ≥2 cm in the longest diameter and must be biopsied outside of the screening period.

- If **a newly acquired tumor sample is submitted to determine PD-L1 status during screening,** archived tumor tissue block greater (formalin-fixed paraffin-embedded) is requested**, when available and accessible,** and where such samples exist in a quantity sufficient to allow for analysis. Tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. An archived tumor tissue block or sections may be delivered at any time during the **study (when newly acquired tissue was used to establish PD-L1 status).** Please consult the Laboratory Manual for specific instructions and guidelines regarding sections.

- The collection of tumor biopsies at the time of progression and prior to retreatment is strongly encouraged. The biopsy procedure at retreatment should be omitted only if there is unacceptable clinical risk or the procedure is otherwise considered not feasible. The Investigator must consult with the Study Physician prior to making the decision not to biopsy at retreatment.

- The collection of additional biopsies upon progression of patients in the MEDI4736 + tremelimumab combination therapy and MEDI4736 monotherapy arms is strongly encouraged.

Tumor biopsies collected **after determination** of **PD-L1 status** for **stratification will** be **used only** for exploratory analyses.

Please review the Laboratory Manual for further details of requirements including sample QC and shipping.

A brief description of exploratory tumor markers likely to be explored by IHC or RNA analysis is provided in Section 5.5.1.1.

To meet the requirement of Food and Drug Administration (FDA) approval of a companion diagnostic, sections of the tumor will be retained at Ventana for potential additional studies, as requested by the FDA, to support potential test approval.

[...]

Reason for Amendment:

The text was updated to provide clarity on tumor biopsy sampling.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 19

Section of protocol affected:

1. SAFETY REPORTING AND MEDICAL MANAGEMENT, Section 6.6.Paternal exposure

Previous text:

Male patients must refrain from fathering a child or donating sperm during the study and for 180 days

[...]

Revised text:

Male patients must refrain from fathering a child or donating sperm during the study and for 180 days **after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 monotherapy. For patients receiving standard of care agents for chemotherapy, please follow the local prescribing information relating to contraception and the time limit for such precautions.**

[...]

Reason for Amendment:

The text was reviewed against other similar AstraZeneca protocols and amended to provide consistency between trials.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 20

Section of protocol affected:

1. SAFETY REPORTING AND MEDICAL MANAGEMENT, Section 6.7 Management of IP-related toxicities

Previous text:

If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted (see the Dosing Modification and Toxicity Management Guidelines).

[...]

Revised text:

If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted (see the Dosing Modification and Toxicity Management Guidelines **[MEDI4736 and MEDI4736 + tremelimumab, only; for SOC refer to Section 6.7.2])**.

[...]

Reason for Amendment:

The text was revised to provide clarity with regards to medications and applicable guidelines.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 21

Section of protocol affected:

1. SAFETY REPORTING AND MEDICAL MANAGEMENT, Section 6.7.1 MEDI4736 and MEDI4736 + tremelimumab

Previous text:

Information on MEDI4736 and MEDI4736 + tremelimumab **adverse events of special interest** and guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 and MEDI4736 + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines.

[...]

Revised text:

Adverse events of special interest (AESIs) are events of scientific and medical interest specific to the further understanding of the MEDI4736 and tremelimumab safety profile and require close monitoring and rapid communication by the Investigator to AstraZeneca. MEDI4736 and tremelimumab AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of these IPs.

Information on MEDI4736 and MEDI4736 + tremelimumab **AESIs** and guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 and MEDI4736 + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines.

[...]

Reason for Amendment:

Text was added to provide information on AESIs.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 22

Section of protocol affected:

1. SAFETY REPORTING AND MEDICAL MANAGEMENT, Section 6.8 Study governance and oversight

Previous text:

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

An IDMC will be established **and comprised of independent experts. The committee will meet approximately 6 months after the study has started or after the randomization of 30 patients, whichever happens first, then on a regular basis thereafter** to perform an interim assessment of the safety of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy in this population. Following the meeting, the IDMC will report to AstraZeneca and may recommend changes in the conduct of the study.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

[...]

Revised text:

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

An IDMC will be established to perform an interim assessment of the safety of MEDI4736 monotherapy and MEDI4736 + tremelimumab combination therapy in this population**. The IDMC will be comprised of independent experts. The committee will meet approximately 6 months after the study has started or after the randomization of 30 patients, whichever happens first. The second IDMC meeting will occur 3 months after the first IDMC meeting or when 90 patients are enrolled, whichever occurs first. A subsequent IDMC meeting will occur 3 months after 90 patients are enrolled. Further IDMC meetings will occur every 6 months, unless otherwise requested by the IDMC.**

IDMC members will be consulted to ensure appropriate frequency. Following each meeting, the IDMC will report to AstraZeneca and may recommend changes in the conduct of the study.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

[...]

Reason for Amendment:

This revision was made based on comments from the Food and Drug Administration (FDA) in its review of the protocol

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 23

Section of protocol affected:

1. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS, Section 7.7 Concomitant and other treatments

Previous text:

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study	Should not be given during the study
mAbs against CTLA-4, PD-1, or PD-L1 through 90 days after the last dose during the study (including SoC)	Should not be given during the study
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment	Should not be given during the study. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])

Prohibited medication/class of drug:	Usage:
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given during the study. (Use of immunosuppressive medications for the management of IP-related AEs, premedication for patients randomized to the SoC arm, or in patients with contrast allergies is acceptable). In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)

[...]

Revised text:

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given during the study
mAbs against CTLA-4, PD-1, or PD-L1 through 90 days after the last dose during the study (including SoC)	Should not be given during the study
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment	Should not be given during the study. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given during the study. (Use of immunosuppressive medications for the management of IP-related AEs, premedication for patients randomized to the SoC arm, or in patients with contrast allergies is acceptable). In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Sunitinib	**Should not be given to patients within 3 months of a dose of tremelimumab, as acute renal failure has been reported with combination therapy of tremelimumab and sunitinib**
Drugs with laxative properties and herbal or natural remedies for constipation	**Should be avoided through 90 days after the last dose of tremelimumab during the study, if possible. In case of strong medical need, should be used with caution.**

[...]

Reason for Amendment:

This revision was made based on comments from the Food and Drug Administration (FDA) in its review of the protocol.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

Change 24

Section of protocol affected:

1. STATISTICAL ANALYSIS BY ASTRAZENECA, Section 8.4.1.2 Primary endpoint

Previous text:

Additionally, PFS will be obtained using the algorithm described above, but following a modification whereby any objective disease progression must be confirmed by the next scheduled scan. The confirmatory scan must be no sooner than 4 weeks after the initial suspected progression. If disease progression is confirmed (or disease progression occurs and no further scans are recorded) then the date of progression will be when it was originally observed. Patients with a single disease progression and no further tumor assessment scans will be treated as PD in the analysis. In the absence of significant clinical deterioration, the investigational site is advised to continue the patient on their randomized MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy until progression has been confirmed. If progression is not confirmed, the patient should continue their randomized MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy treatment and on-treatment assessments. **Treatment through PD in the SoC group is at the Investigator's discretion; however, a** confirmatory scan is required for all patients in the SoC group, even if a subsequent treatment is started.

[...]

Revised text:

Additionally, PFS will be obtained using the algorithm described above, but following a modification whereby any objective disease progression must be confirmed by the next scheduled scan. The confirmatory scan must be no sooner than 4 weeks after the initial suspected progression. If disease progression is confirmed (or disease progression occurs and no further scans are recorded) then the date of progression will be when it was originally observed. Patients with a single disease progression and no further tumor assessment scans will be treated as PD in the analysis. In the absence of significant clinical deterioration, the investigational site is advised to continue the patient on their randomized MEDI4736 +

tremelimumab combination therapy or MEDI4736 monotherapy until progression has been confirmed. If progression is not confirmed, the patient should continue their randomized MEDI4736 + tremelimumab combination therapy or MEDI4736 monotherapy treatment and on-treatment assessments. **A** confirmatory scan is required for all patients in the SoC group, even if a subsequent treatment is started.

[...]

Reason for Amendment:

The change was made to increase the opportunity for patients to have access to alternative treatments.

Persons who initiated the Amendment:

AstraZeneca, Sponsor

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