Clinical Study Protocol	
Drug Substance	Durvalumab (MEDI4736) and tremelimumab
Study Code	D419MC00004
Version	6.0
Date	09 July 2021
EudraCT	2017-000920-81

A Phase III, Randomized, Multi-Center, Open-Label, Comparative Global Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for First-Line Treatment in Patients With Metastatic Non-Small-Cell Lung Cancer (NSCLC) (POSEIDON)

Sponsor:

AstraZeneca AB, S-151 85 Södertälje, Sweden

Local sponsor in Japan: AstraZeneca K.K., 3-1, Ofuka cho, Kita-ku Osaka 530-0011, Japan

Version 6.0, 09 July 2021
SYNOPSIS [Study site(s) and number of patients planned], Section 9.3 [Study timetable and end of study]: To obtain long-term follow up OS data post final analysis of OS for superiority in line with the recent positive read-out from the study, "Estimated date of last patient completed in global cohort" was changed from Q2 2021 to Q4 2023 and detailed assessments during the long-term OS follow up period was highlighted. **SYNOPSIS [international Coordintating Investigators]:** PPD has been removed from ICI list. **Section 1.3.2.1 [Durvalumab]:** This section was updated per durvalumab IB edition 16_08 Oct 2020 **Section 1.4.1 [Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis]:** This section was created to insert language describing study conduct mitigations during study disruptions due to a health crisis per Oncology Late Phase Master Clinical Study Protocol v.1_Durvalumab +- Tremelimumab-29 Jan 2021 **SYNOPSIS [Post Final Data Cut Off(DCO)], Section 4.3 [Follow-up period], Section 7.2.2.3[Post Final Data Cut Off(DCO)], Section 9.3 [Study timetable and end of study], Section 9.4 [Data Management by AstraZeneca or delegate]:** These sections were updated to add detailed assessments to proceed Long-term follow-up post final analysis of OS for superiority. **Section 5.1.2 [Survival assessments]:** This section was updated to provide clarification on how to assess patient survival post final analysis of OS for superiority. **Section 6.3.12 [Safety Data To Be Collected following the final DCO of the study]:** This section was updated to provide clarification on how to collect safety data post final DCO of OS for superiority. **Section 6.9.1 [Specific toxicity management and dose modification information – Durvalumab and durvalumab + tremelimumab]:** Removal of TMG web-portal text due to portal shutdown per Oncology Late Phase Master Clinical Study Protocol v.1_Durvalumab +-Tremelimumab-29 Jan 2021. **Section 7.2.2.2 [Treatment Arms 1 and 2: Criteria for treatment through progression and for retreatment]:** This section was updated to provide clarification on "treatment through confirmed radiological PD". **Section 7.8 [Post-study access to study treatment]:** This section was updated to provide clarification on how to supply open-label drugs to patients receiving treatment.

Appendix E [Guidelines for Evaluation of Objective Tumor Response]: This section was updated to clarify consultation is required before making a decision for patient to continue treatment through confirmed radiological PD.

Appendix G [Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak]: This section was created to insert language describing study conduct mitigations during study disruptions due to a health crisis per Oncology Late Phase Master Clinical Study Protocol v.1_Durvalumab +- Tremelimumab-29 Jan 2021.

Version 5.0, 20 April 2020

SYNOPSIS [Study site(s) and number of patients planned], Section 9.3 [Study timetable and end of study]: "Estimated date of last patient completed in global cohort" was changed from Q4 2019 to Q2 2021 according to study progress

SYNOPSIS [International Coordinating Investigators]: ICI name changed to PPD

SYNOPSIS [Safety Confirmation], Section 1.6.1 [Safety Confirmation]: Clarified language for IDMC after PFS analysis

Section 1.3.2.1[Durvalumab], 1.3.2.2[Tremelimumab]: Updates per durvalumab IB edition 14_11 Feb 2019 and tremeliumab IB edition 9_27 Nov 2018

Section 6.3.12 [Specific toxicity management and dose modification information - Durvalumab and durvalumab + tremelimumab], Section 6.5 [Treatment Arms 1 and 2 adverse events of special interest], Section 6.9 [Manage of IP-related toxicities]: Term "Appendix E" was changed to "TMG Annex"

Section 6.5[Treatment Arms 1 and 2 adverse events of special interest]: Updated AESI list from Durvalumab IB edition 14_11 Feb 2019

Section 6.9.1 [specific toxicity management and dose modification information - Durvalumab and durvalumab + tremelimumab: Updated language when applying TMGs as a separate clinical document

Appendix D [Hy's Law]: This section was updated based on "The revised CSP Appendix Hys Law v3, dated 29March2019".

Appendix E [Dose Modification and Toxicity Management Guidelines]: This section was removed to have TMG as a standalone Annex.

Appendix E [Guidelines for Evaluation of Objective Tumor Response]: This section was changed from Appendix F to Appendix E due to removal of Appendix E and a sentence was

taken out in regards to the need to consult with AZ, to add more clarity to the process. Very high recommended changed incorporated.

Appendix G [Patient Reported Outcomes]: This section was changed from Appendix G to Appendix F due to Appendix E removal.

Version 4.0, 25 September 2018

Synopsis [Study site(s) and number of patients planned, Statistical methods]: In these sections wording 'up to' was included to China patient numbers and word 'mainland' was removed to have flexibility for China patient recruitment.

Synopsis [Primary objectives]: This section was updated to be dual endpoint of overall survival (OS) (durvalumab + SoC chemotherapy).

Synopsis [Secondary objectives]: This section was updated to include patients with TMB-high and PD-L1 TC<25% as a secondary endpoint in line with PD-L1 TC<50% and TC<1%. Also additional parameters were added for combo (durvalumab + tremelimumab combination therapy + SoC chemotherapy) and monotherapy (durvalumab monotherapy + SoC chemotherapy) compared with SoC chemotherapy.

Synopsis [Statistical methods]: OS included as dual primary endpoint in this section and other statistical considerations were updated. Also wording 'up to' was included to China patient numbers and word 'mainland' was removed to have flexibility for China patient recruitment.

List of abbreviations and definition of terms: Term CCI was included.

Section 1.2.4 [Rationale for endpoints]: Rationale for endpoints have been updated based on consideration of OS as dual primary endpoint and TMB-high as secondary endpoint.

Section 1.3.1.3 (Durvalumab + tremelimumab with chemotherapy): A typo error correction was made to number of patients involved in the DCO of Phase Ib study (NCT02537418) run by the CCTG.

Section 1.4 Study design, Section 8.2 Sample size estimate, and Section 8.6 China cohort: In these sections wording 'up to' was included to China patient numbers and word 'mainland' was removed to have flexibility for China patient recruitment.

Figure 3 (overall study design): OS included as a secondary endpoint.

Section 2.1 [Primary objectives]: This section was updated to be dual endpoint of overall survival (OS) (durvalumab + SoC chemotherapy).

Section 2.2 [Secondary objectives]: This section was updated to include patients with TMB-high and PD-L1 TC<25% as a secondary endpoint in line with PD-L1 TC<50% and TC<1%. Also additional parameters were added for combo (durvalumab + tremelimumab combination

therapy + SoC chemotherapy) and monotherapy (durvalumab monotherapy + SoC chemotherapy) compared with SoC chemotherapy.

Section 3.9 [Discontinuation of IP]: The wording in this section was updated to give more clarity on IP discontinuation criteria for treatment arm 1 and 2 patients.

Section 3.9.1 [Procedures for discontinuation of patient from IP]: A sentence in this section was deleted to clarify there is no necessity to notify AZ study Physician if any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

Section 4 [Study plan and timing of procedures]: Table 2:
Footnote 'y' has been updated to provide more clarity on ePRO assessment window period.

Section 5.1 [Efficacy assessments]: The wording 'co-primary endpoint' has been changed to 'dual primary endpoint' and the wordings are updated according to changes made into objectives in this amendment

Section 5.5.1 [Collection of patient samples for stratification by PD-L1 expression]: This section was updated to include TMB and provided more rationale for the same. Also it was clarified that plasm samples will also be used for tumor markers analysis.

Section 5.5.3 [Storage, re-use, and destruction of biological samples]: A note was added in this section to clarify the sample storage requirenments for China.

Section 7.2.2.2 [Treatment Arms 1 and 2: Criteria for treatment through progression and for retreatment]: The word 'confirmed' has been removed from this section to give more clarity on criteria for treatment through progression for treatment arm 1 and 2 patients. Other relavent sections in the protocol were also updated to maintain the consistency.

Section 8.1 [Statistical considerations]: The wording 'co-primary endpoint' has been changed to 'dual primary endpoint' and the wordings are updated according to changes made into objectives in this amendment.

Section 8.2 (Sample size estimate), Section 8.3 (Definition of analysis sets), Section 8.5 (Methods for statistical analyses) and Section 8.5.9 (Interim analysis): Multiple testing procedure is updated to reflect the updated primary/secondary endpoints. One additional OS interim analysis is added at the timepoint of PFS interim analysis. The protocol updated accordingly includes: power, critical values of hazard ratio for PFS and OS analyses, projected number and percentage of PFS and OS events at interim/final analyses, projected alpha allocation at interim/final analyses and projected study duration.

Section 8.3.3 (PD-L1 TC<25% analysis set): This section was removed in the version 2 of the protocol and now this section re-inserted.

References: References 'Borghaei et al 2018', 'Gandara et al 2018', and 'Hellmann et al 2018' were added based on the update made to the main text.

Version 3.0, 16 March 2018
Synopsis [Study site(s) and number of patients planned]: Sample size increased from 801 to 1000 to adequately power OS of PDL1<50% population. **Synopsis (Secondary objectives):** This section was updated to provide clarity on key secondary objectives. **Synopsis (Survival):** To provide clarity on survival follow up, word 'randomized' was inserted in this section. **Synopsis (Safety Confirmation):** The paragraph concerning "safety confirmation for China" is included. **Synopsis (statistical methods):** Sample size was increased from 801 to 1000 to adequately power OS of PDL1<50% population. **List of abbreviations and definition of terms:** Terms DCO, SmPC and TMB were included. **Section 1.3 (Benefit/risk and ethical assessment):** A new sub-section '1.3.2.4 Standard of Care' was added to address MHRA recommendation to include warnings of ototoxicity, nephrotoxicity for chemotherapy regimens as per the SmPCs. **Section 1.4 (Study Design):** Sample size number was updated from 801 to 1000. **Figure 3 (overall study design):** Study sample size numbers are updated. **Section 1.6.1 (Safety Confirmation):** Clarity provided on patient treatment exposure requirements for first and second global IDMCs, and Japan IDMC. The paragraph concerning "Safety confirmation for China" is included. **Section 2.2 (Secondary objectives):** This section was updated to provide clarity on key secondary objectives. **Section 2.4** CCI [redacted] **Section 3.1 (Inclusion criteria):** Inclusion criterion 6 has been updated to include TMB and cross-referenced of section 5.5.2. **Section 3.2 (Exclusion criteria):** Exclusion criterion 20 has been cross-referenced of Section 3.8 as per MHRA recommendation. **Section 3.3 (Patient enrollment and randomization):** Points under this section were given in bullet format instead of numbers. **Section 3.8 (Restrictions):** this section was updated as specified below as per MHRA recommendation: • An additional note has been added to provide instruction to investigators to advise male patients to consider cryoconservation of sperm prior to treatment because of the possibility of infertility due to therapy with gemcitabine. • Contraception duration for SoC regimens has been clarified In addition to above, point number 5 was deleted under this section based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 4 (Study plan and timing of procedures): Table 2:

- Schedule of assessments for Treatment Arms 1, 2, and 3): Tuberculosis (TB) was included in the table of assessment and footnote 'i' updated to provide clarity for TB assessment.
- Typo error occurred concerning Tremelimumab PK sample time point at cycle 5 was corrected.
- Footnote 'j', 's', and 'y' have been updated to provide more clarity.

Section 4 (Study plan and timing of procedures): Table 3**:** A typo error correction was made to footnote 'n'.

Section 4.2.1 (Safety Confirmation period): The paragraph concerning "safety confirmation for China" is included.

Section 5.2.1 (Laboratory safety assessments): A paragraph concerning screening laboratory assessment was deleted to avoid confusions. Clarity for screening laboratory assessment has already been given under Table 2 footnote 'e'. Also word 'urine' was inserted to give clarity on pregnancy test.

Section 5.4.1.2 (Storage and destruction of pharmacokinetic/ADA samples): Further clarity was added to note concerning PK and ADA samples collected in China.

Section 5.5.1 (Collection of patient samples for stratification by PD-L1): Requirement of 20 unstained sections has been included in case a tissue block is not submitted for PD-L1 analysis.

Section 5.5.2 CCI [redacted]

Section 5.5.5 (Chain of custody of biological samples): Clarity provided for keeping sample shipment documentation.

Section 6.9 (Management of IP-related toxicities): few bullets under this section were removed based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program and avoid duplication.

Section 7.2.2.2 (Treatment Arms 1 and 2: Criteria for treatment through progression and for retreatment): The wording related to Criteria for treatment through progression (Treatment Arms 1 and 2) and retreatment (Treatment Arm 1) under this section was updated according to the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 7.3 (Labeling): additional paragraph related to 'Label text' was introduced under this section to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Table 9 (Supportive medications): The wording related to Herbal and natural remedies was removed according to the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 8.2 (Sample size estimate), Section 8.5 (Methods for statistical analyses) and Section 8.5.9 (Interim analysis): In these sections sample size was increased from 801 to 1000 and OS final analysis maturity increased from 75% to 80% to adequately power OS

analyses of PDL1<50% population. The protocol updated accordingly includes: power, critical values of hazard ratio for PFS and OS analyses, projected number and percentage of PFS and OS events at interim/final analyses, projected alpha allocation at interim/final analyses and projected study duration.

Section 8.6 (China cohort): Global Cohort sample size was updated from 801 to 1000.

References: Reference 'Carbone et al 2017' was added based on the update made to the main text.

Version 2.0, 12 December 2017

Synopsis (Secondary objectives): This section was updated to provide clarity on key secondary objectives.

Synopsis (Safety objectives): A minor update has been made in this section to allow more flexibility for recruitment of patients from China and do not have to be Chinese.

Synopsis (Progression during treatment and retreatment): The wording in this section was updated according to the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Synopsis (Follow-up of patients post discontinuation of study drug): A correction was made so that assessments for survival are collected every 2 months after Month 4 instead of every 2 weeks.

Synopsis (Post final Data Cut Off [DCO]): this section was introduced in synopsis to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Synopsis (Investigational product, dosage, and mode of administration): The maintenance schedule for pemetrexed has been changed to either every 3 weeks (q3w) or every 4 weeks (q4w) for Treatment Arm 3 (SoC), dependent on Investigator decision and local standards, to account for regional differences. A note was added under Figure 1 to clarify the same information and RECIST assessment schedule.

Synopsis (Safety confirmation): Clarity provided on patient treatment exposure requirements for first and second global IDMCs, and Japan IDMC.

List of abbreviations and definition of terms: Terms CFDA and SNP were included.

Section 1.1.1 (Immunotherapies): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 1.1.2 (Durvalumab): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 1.1.3 (Tremelimumab): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 1.1.4 (Durvalumab in combination with tremelimumab): The wording in this section was updated based on the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 1.2.1.2 (Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 1.2.1.3 (Durvalumab monotherapy dose rationale): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 1.3.2 (Overall risks) and sub-sections: The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Figure 3 (Overall study design): This figure is updated to reflect the schedule for pemetrexed has been changed to either every 3 weeks (q3w) or every 4 weeks (q4w) for Treatment Arm 3 (SoC), dependent on Investigator decision and local standards, to account for regional differences. Footnote 'd' deleted.

Figure 4 (Study flow chart): Footnote 'a' deleted.

Section 2.2 (Secondary objectives): This section was updated to provide clarity on key secondary objectives.

Section 2.4 CCI [redacted]

Section 3.1 (Inclusion criteria):): Inclusion criterion 2 has been updated to align with durvalumab project level CSP standard template. Inclusion criterion 6 has been updated to provide more clarity for tumor lesion used for newly acquired biopsy. A new criterion (8) regarding patient life expectancy has been introduced. Below points were clarified in the inclusion criterion 11 (now updated to number 12):

- The hemoglobin level in relation to blood transfusion prior to screening/randomization
- Total bilirubin value was updated to align to the durvalumab project level CSP standard template.

Section 3.2 (Exclusion criteria): Typo error was corrected in criterion 9. Exclusion criterion 15 has been divided into two criteria to provide more clarity on brain metastasis and spinal cord compression.

Section 3.3 (Patient enrollment and randomization): More clarity added on central and local EGFR/ALK testing. It was clarified that the 3-digit randomization number was corrected to a 4-digit number to match the IVRS.

Section 3.5 (Methods for assigning treatment arms): It was clarified that the IVRS/IWRS will provide the kit identification number to be allocated to the patient at subsequent dispensing visits also.

Section 3.8 (Restrictions): The wording in this section was updated based on durvalumab project level CSP standard template to be consistent across program. A footnote 'b' has been added under Table 1 to provide clarity on approval status of contraception methods in Japan.

Section 3.9 (Discontinuation of IP) & sub-sections: The wording in these sections were updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 3.10.2.1 (Survival status for withdrawn consent and lost to follow-up patients): This section wordings were updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 4 (Study plan and timing of procedures): Table 2**:** Clarification was added to the schedule of assessments for the treatment and retreatment periods regarding which assessments should be done during retreatment. A row for medical/surgical history was added to the schedule of assessments. The maintenance schedule for pemetrexed has been changed to either every 3 weeks (q3w) or every 4 weeks (q4w) for Treatment Arm 3 (SoC), dependent on Investigator decision and local standards, to account for regional differences. Folic acid/ Vitamin B12 pre-medication management was clarified. Footnote 'e', 'h', 'j', 'n', 's', and 't' have been updated to provide more clarity.

Table 3**:** Tumor evaluation row has been updated to provide more clarity. Footnotes 'c' and 'n' have been updated to provide more clarity on RECIST 1.1 assessments.

Section 4.1 (Screening/enrollment period): A typo error correction was made in this section.

Section 4.2 (Treatment period): This section was updated to provide clarity on RECIST assessments.

Section 4.2.1 (Safety confirmation period): Clarity provided on patient treatment exposure requirements for first and second global IDMCs, and Japan IDMC.

Section 4.3 (Follow-up period): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 5.1 (Efficacy assessments) and sub-sections: These sections wordings were updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 5.1.1 (Objective disease progression): The whole section has been deleted because this section needs to be simplified to RECIST 1.1.

Section 5.1.3 (Survival assessments): Now this is Section 5.1.2. A correction was made so that assessments for survival are collected every 2 months after Month 4 instead of every 2 weeks.

Section 5.2.1 (Laboratory safety assessments): Table 4 **(Clinical Chemistry) -** clarifications provided on creatinine clearance and TSH testing in footnote.
Table 5 **(Hematology)** - Typo error corrected for Eosinophil count, clarification provided on assessment period and a footnote inserted to explain the absolute counts or percentages.

Section 5.2.4 (Vital signs): more clarity added on vital signs collections during first and subsequent infusion. A bullet point regarding treatment observation period was deleted to eliminate the observation time gap between tremelimumab, durvalumab and SoC, under first infusion paragraph.

Section 5.2.6 (WHO/ECOG performance status): Added "5 = Dead"

Section 5.4.1.2 (Storage and destruction of pharmacokinetic/ADA samples): Sample disposition timelines has been clarified to align with Section 5.5.3 (Storage, re-use, and destruction of biological samples). A note added to clarify that PK and ADA samples collected in China will be stored and disposed according to local laws and regulations.

Section 5.5.1: (Collection of patient samples for stratification by PD-L1): Notes were added to clarify China will not take part in optional and additional biopsy samples.

Section 5.5.2: CCI [redacted]

Section 6.1 (Definition of adverse events): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 6.3 (Recording of adverse events) and sub-sections: The wording in these sections were updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 6.3.12 (Safety Data To Be Collected following the final DCO of the study): this section was introduced to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 6.5 (Treatment Arms 1 and 2 adverse events of special interest): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 6.7 (Pregnancy): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 6.9.1 (Durvalumab and durvalumab + tremelimumab): The heading and wording in this section were updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 7.1.1 (Order of administration): The wording in this section was updated to eliminate the observation time gap between tremelimumab, durvalumab and SoC infusions.

Section 7.1.2 (Durvalumab [MEDI4736]): The wording in this section was updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 7.1.3 (Tremelimumab): This section wordings were updated based on durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 7.2.1 (Treatment regimens): The maintenance schedule for pemetrexed has been changed to every 3 weeks (q3w) or every 4 weeks (q4w) for Treatment Arm 3 (SoC), dependent on Investigator decision and local standards, to account for regional differences. A note was added under 'Treatment Arm 3: SoC chemotherapy alone' and Figure 5 to clarify the same information and RECIST assessment schedule.

Section 7.2.2 (Duration of treatment and criteria for treatment through progression and retreatment): Post final Data Cut Off information was introduced in this section to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program.

Section 7.2.2.2 (Treatment Arms 1 and 2: Criteria for treatment through progression and for retreatment): Clarification was added regarding which assessments should be done during retreatment. To align to the treatment schedule, it was clarified that one of the eligibility criteria for retreatment is having completed 5 dosing cycles comprising the combination of durvalumab and tremelimumab portion of the regimen. To be consistent with the rest of the treatment regimens in the protocol, it was also clarified that a patient whose weight falls to 30 kg or below will receive weight-based dosing. **Section 7.7 (Concomitant medications and other treatments):** Table 8 (Prohibited concomitant medications) was updated to align with the durvalumab project level CSP standard template to maintain consistency across the durvalumab program. **Section 8.3.3 (PD-L1 TC<25% analysis set):** This section is now deleted. It was initially included for potential analysis but so far, no planned analysis is of interest. **Section 8.4.1** CCI [redacted] **Section 8.4.2.1 (Co-primary endpoints):** This section was updated to provide clarity on RECIST assessments. **Section 8.4.2.2 (Secondary endpoints):** A paragraph related to best objective response deleted under this section because more information has already been provided in statistical analysis plan. **Section 8.4.3.1 (Adverse events):** More clarity added to adverse events collection timelines. **Section 8.5.1.1 (Progression-free survival):** Subgroup analyses that will be conducted comparing PFS (per RECIST 1.1) between experimental arms versus SoC arm were updated. **Section 8.6 (China cohort):** Some updates were made to comply with new CFDA guidelines and allow more flexibility for recruitment of patients from China and do not have to be Chinese. **References:** Few references are added and few references were deleted, all of which are not relevant based on the update made to the main text. **Appendix E (Guidelines for Evaluation of Objective Tumor Response):** This appendix updated to align with durvalumab project level CSP standard template to maintain consistency across the durvalumab program
Version 1.0, 10 March 2017
Initial version

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, Multi-Center, Open-Label, Comparative Global Study to Determine the Efficacy of Durvalumab or Durvalumab and Tremelimumab in Combination With Platinum-Based Chemotherapy for First-Line Treatment in Patients With Metastatic Non-Small-Cell Lung Cancer (NSCLC) (POSEIDON)

International Coordinating Investigators

PPD
Sara Cannon Research Institute at Tennessee Oncology
Research Site Support
PPD
The SCRI Oncology
Tel: PPD

Study site(s) and number of patients planned

The study will randomize approximately 1000 patients in a 1:1:1 ratio to the following treatment arms: durvalumab + tremelimumab combination therapy + standard of care (SoC) chemotherapy, durvalumab monotherapy + SoC chemotherapy, or SoC chemotherapy alone (approximately 333 patients in each treatment arm), including at least approximately 250 patients in each treatment arm with programmed cell death ligand 1 (PD-L1) expression on less than 50% of tumor cells (PD-L1 TC <50%). Once global enrollment is completed, recruitment may continue in mainland China only. A total of up to 180 patients, including up to 135 patients in total with PD-L1 TC <50%, from China will be randomized.

Study period		Phase of development
Estimated date of first patient enrolled	Q2 2017	III
Estimated date of last patient completed in global cohort*	Q4 2023	III

* Estimated date of last China patient completed will be later than the estimated date of last patient completed in global cohort.

Study design

This is a randomized, open-label, multi-center, global, Phase III study to determine the efficacy and safety of durvalumab + tremelimumab combination therapy + SoC chemotherapy or durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone as first-line treatment in patients with metastatic non-small-cell lung cancer (NSCLC) with tumors that lack activating epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusions. Patients who fulfill all of the inclusion criteria and none of

the exclusion criteria will be randomized in a 1:1:1 ratio according to the following stratification scheme:

- PD-L1 tumor expression status (PD-L1 expression on at least 50% of tumor cells [PD-L1 TC ≥50%] versus PD-L1 TC <50%)
- Disease stage (Stage IVA versus Stage IVB)
- Histology (non-squamous versus squamous)

Patients will be randomized in a 1:1:1 ratio to receive treatment every 3 weeks (q3w) with durvalumab + tremelimumab combination therapy + SoC chemotherapy, durvalumab monotherapy + SoC chemotherapy, or SoC chemotherapy alone in the 'during chemotherapy' phase. During the 'post-chemotherapy' phase, patients in Treatment Arms 1 and 2 will receive durvalumab monotherapy every 4 weeks (q4w). Non-squamous patients who received pemetrexed + carboplatin/cisplatin in the 'during chemotherapy' phase will receive pemetrexed maintenance therapy, unless contraindicated per the Investigator. See Figure 1 for the dosing scheme.

The following are the definitions of the study treatment regimens in each treatment arm:

- **Treatment Arm 1:** durvalumab + tremelimumab combination therapy + SoC chemotherapy
- **Treatment Arm 2:** durvalumab monotherapy + SoC chemotherapy
- **Treatment Arm 3:** SoC chemotherapy alone

Tumor evaluation scans will be performed at screening (as baseline) with follow-ups at Week 6±1 week from the date of randomization, at Week 12±1 week from the date of randomization, and then every 8 weeks (q8w)±1 week until objective disease progression.

Objectives

All objectives will be evaluated for all patients, unless otherwise indicated. The multiple testing procedure is described in detail in Section 8.5.

Primary objectives

Primary objectives	Outcome measure
• To assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients	• PFS in all patients using BICR assessments according to RECIST 1.1 • OS in all patients

Note: Sensitivity analyses of PFS will be performed based on the Investigator's assessment according to RECIST 1.1.

BICR Blinded Independent Central Review; NSCLC Non-small-cell lung cancer; PFS Progression-free survival; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1; SoC Standard of care.

Secondary objectives

Secondary objectives	Outcome measures
• To assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS	• PFS in all patients using BICR assessments according to RECIST 1.1 (key secondary objective) • OS in all patients (key secondary objective)
• To further assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, BoR, DoR, APF12 and PFS2	• PFS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 <1% • ORR, DoR, BoR and APF12 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • PFS2 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using local standard clinical practice
• To further assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, DoR, BoR, APF12 and PFS2	• PFS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% • ORR, DoR, BoR and APF12 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • PFS2 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using local standard clinical practice

Secondary objectives	Outcome measures
• To assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with durvalumab monotherapy + SoC chemotherapy in terms of PFS, OS and ORR	• PFS and ORR in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients
• To assess the association of tumor mutation burden (TMB) with the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, BoR, DoR, APF12 and PFS2	• PFS, ORR, BoR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the association of TMB with the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with durvalumab monotherapy + SoC chemotherapy in terms of PFS, OS, ORR, BoR, DoR, APF12 and PFS2	• PFS, ORR, BoR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the association of TMB with the efficacy of durvalumab mono therapy + SoC chemotherapy compared with SoC chemotherapy in terms of PFS, OS, ORR, BoR, DoR, APF12 and PFS2	• PFS, ORR, BoR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the PK of durvalumab + tremelimumab combination therapy and durvalumab monotherapy	• Concentration of durvalumab and tremelimumab
• To investigate the immunogenicity of durvalumab and tremelimumab	• Presence of ADAs for durvalumab and tremelimumab
• To assess disease-related symptoms and HRQoL in patients treated with durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone using the EORTC QLQ-C30 v3, the QLQ-LC13 module, and WHO/ECOG performance status assessments	• EORTC QLQ-C30 • EORTC QLQ-LC13 • Changes in WHO/ECOG performance status will also be assessed.

ADA Anti-drug antibody; APF12 Proportion of patients alive and progression free at 12 months from randomization; BICR Blinded Independent Central Review; BoR Best objective response; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; HRQoL Health-related quality of life; NSCLC Non-small-cell lung cancer; ORR Objective response rate; OS Overall survival; PD-L1 Programmed cell death ligand 1; PFS Progression-

free survival; PFS2 Time from randomization to second progression; PK Pharmacokinetic(s); QLQ-C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1; SoC Standard of care; TC Tumor cell; Definition of TMB High in tissue and/or ctDNA to be documented in the SAP ahead of DBL with data external to Poseidon; WHO World Health Organization.

Safety objectives

Safety objective	Outcome measure
• To assess the safety and tolerability profile of durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone	• AEs, physical examinations, laboratory findings, and vital signs

AE Adverse event; SoC Standard of care.

A further objective to meet China Food and Drug Administration requirement is to evaluate consistency in efficacy and safety among patients in China for benefit-risk assessments of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone.

Target patient population

Adult patients (age ≥18 years; for those enrolled in Japan, age ≥20 years) with a histologically or cytologically documented metastatic NSCLC, with tumors that lack activating EGFR mutations and ALK fusions, are eligible for enrollment. Patients must have had no prior chemotherapy or any other systemic therapy for metastatic NSCLC. Prior to randomization, patients must have tumor PD-L1 status confirmed by a reference laboratory using the Ventana SP263 PD-L1 immunohistochemistry assay. Patients must have a World Health Organization/Eastern Cooperative Oncology Group performance status of 0 or 1 at enrollment.

Duration of treatment

Treatment with SoC chemotherapy in Treatment Arms 1 and 2 will be limited to 4 cycles on a q3w schedule subsequent to randomization. Patients in Treatment Arm 3 may receive an additional 2 doses of SoC chemotherapy at Weeks 12 and 15 (a total of 6 doses post-randomization), as clinically indicated, at the Investigator's discretion.

Treatment with immunotherapy + SoC chemotherapy in Treatment Arms 1 and 2, as well as treatment with SoC chemotherapy alone in Treatment Arm 3, will be administered beginning on Cycle 1 Day 1.

For patients randomized to Treatment Arms 1 and 2, immunotherapy treatment with durvalumab monotherapy will continue until objective disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. For

patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab will be given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose can be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses are administered in Treatment Arm 1. If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) should be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed if applicable). All non-squamous patients who received a pemetrexed doublet in the initial part of the study will receive pemetrexed maintenance in the 'post-chemotherapy' phase of the study, unless contraindicated per the Investigator.

For patients randomized to Treatment Arms 1 and 2, when SoC chemotherapy is discontinued due to treatment-related toxicity, durvalumab monotherapy or durvalumab + tremelimumab may continue at the Investigator's discretion when toxicity resolves to at least Grade 2 or less. Note: if the Investigator feels a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

Progression during treatment and retreatment

Patients in Treatment Arms 1 and 2 with objective disease progression who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for treatment in the setting of progressive disease, may continue to receive durvalumab monotherapy for as long as they are gaining clinical benefit. However, patients in the immunotherapy arms will not be permitted to continue immunotherapy if progression occurs after confirmed response (complete or partial response) (as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1]) to immunotherapy treatment in the target lesions (regardless of the appearance of new lesions), ie, the response and progression events both occurred in the target lesions while receiving immunotherapy during the same treatment period.

Patients in Treatment Arm 1 may undergo retreatment with the combination as described below:

- Patients who complete 5 dosing cycles comprising the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have clinical progression or radiological PD during the durvalumab monotherapy portion of the combination regimen, may restart treatment with the combination of durvalumab + tremelimumab.

For patients randomized to Treatment Arm 3, treatment through progression and retreatment will not be permitted.

Follow-up of patients post-discontinuation of study drug

Patients who are permanently discontinued from further receipt of investigational product, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up. Patients who have discontinued treatment due to toxicity or

symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed up until RECIST 1.1 defined radiological progression plus an additional subsequent scan and for survival. This follow-up must be performed even if the patient begins another therapy to treat their NSCLC. Assessments for survival must be made at Months 2, 3, and 4, and then every 2 months (8 weeks±2 weeks) following treatment discontinuation.

Survival

All randomized patients will be followed for survival until the end of the study.

Post Data Cut Off (DCO) for final analysis of OS for superiority

For patients continuing to receive durvalumab/tremelimumab and/or SOC chemotherapy and patients on survival follow-up following the DCO for final analysis of OS for superiority, it is recommended that patients continue the scheduled site visits according to Table 12, Table 13& Section 9.3 and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab/tremelimumab and/or SOC chemotherapy in order to manage AEs in accordance with the durvalumab/tremelimumab toxicity management guidelines or as indicated in the local prescribing information for the relevant chemotherapy agent (please see Section 6.9.1 & 6.9.2).

Post final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment (durvalumab/tremelimumab and/or SOC chemotherapy) at the final DCO and database closure may continue to receive their assigned treatment for as long as they and their physician feel they are gaining clinical benefit. Investigators will monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab/tremelimumab and/or SOC chemotherapy in order to manage AEs in accordance with the durvalumab/tremelimumab toxicity management guidelines or as indicated in the local prescribing information for the relevant chemotherapy agent (please see Section6.9.1 &6.9.2).

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patients currently receiving treatment with durvalumab and/or SOC chemotherapy may be transitioned to such a study, and the current study would reach its end. The roll-over or safety extension study would ensure treatment continuation with visits assessment per its protocol. Any patient that would be proposed to move to such study would be required to give consent to participation in the study via a new Informed Consent form.

Investigational product, dosage, and mode of administration

Patients will be randomized in a 1:1:1 ratio to receive treatment either with durvalumab + tremelimumab combination therapy + SoC chemotherapy, durvalumab monotherapy + SoC chemotherapy, or SoC chemotherapy alone.

- Durvalumab 1500 mg ± tremelimumab 75 mg will be administered via intravenous infusion concurrently with chemotherapy q3w starting on Week 0 for 4 cycles. Durvalumab monotherapy will be continued q4w post-chemotherapy. In Treatment Arm 1, up to 5 combination doses of durvalumab + tremelimumab will be administered; the detailed dose and schedule is illustrated in Figure 1.
  - Note: If a patient's weight falls to 30 kg or below, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab and 1 mg/kg tremelimumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg ± tremelimumab 75 mg.
- **Standard of care chemotherapy:** Patients will receive 1 of the following SoC regimens as part of their treatment regimen:
  - Abraxane + carboplatin (squamous and non-squamous patients): Abraxane 100 mg/m2 on Days 1, 8, and 15 of each 21-day cycle. Carboplatin AUC 5 or 6 via intravenous (IV) infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3).
  - Gemcitabine + cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m2 via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 mg/m2 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3).
  - Gemcitabine + carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m2 via IV infusion on Days 1 and 8 of each 21-day cycle + carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3).
  - Pemetrexed + carboplatin (non-squamous patients only): Pemetrexed 500 mg/m2 and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3); then continue pemetrexed 500 mg/m2 maintenance (i.e., q4w for Treatment Arms 1 and 2. For Treatment Arm 3, Pemetrexed maintenance therapy can be given either q3w or q4w dependent on Investigator decision and local standards) until objective disease progression, unless contraindicated per the Investigator.

- Pemetrexed + cisplatin (non-squamous patients only): Pemetrexed 500 mg/m2 and cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3); then continue pemetrexed 500 mg/m^2 maintenance (i.e., q4w for Treatment Arms 1 and 2. For Treatment Arm 3, Pemetrexed maintenance therapy can be given either q3w or q4w dependent on Investigator decision and local standards) until objective disease progression, unless contraindicated per the Investigator.

Figure 1 Dosing scheme

Treatment arms	During chemotherapy 1 cycle=3 weeks (21 days)				Post-chemotherapy 1 cycle=4 weeks (28 days)		
	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Week 12	Week 16	Week 20 to PD
Durva + Treme + SoC (Treatment Arm 1)	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Pemetrexed Maintenance[a]	Durva + Treme[b] Pemetrexed Maintenance[a]	Durva + Pemetrexed Maintenance[a]
Durva + SoC (Treatment Arm 2)	Durva + SoC	Durva + SoC	Durva + SoC	Durva + SoC	Durva + Pemetrexed Maintenance[a]	Durva + Pemetrexed Maintenance[a]	Durva + Pemetrexed Maintenance[a]
SoC (Treatment Arm 3)	SoC	SoC	SoC	SoC[c]	Pemetrexed Maintenance[a]	Pemetrexed Maintenance[a]	Pemetrexed Maintenance[a]

[a] Pemetrexed maintenance therapy is for non-squamous NSCLC patients who received treatment with pemetrexed and carboplatin/cisplatin during chemotherapy and did not progress after 4 to 6 cycles, unless contraindicated per the Investigator. Pemetrexed maintenance therapy can be given q4w for Treatment Arms 1 and 2. For Treatment Arm 3, Pemetrexed maintenance therapy can be given either q3w or q4w dependent on Investigator decision and local standards. **Note:** RECIST 1.1 assessment should be performed at Week 12 ±1 week from the date of randomization, and then q8w±1 week thereafter until radiological progression (regardless of whether it chosen q3w or q4w)

[b] For patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab will be given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose can be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses are administered in Treatment Arm 1. If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) should be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed if applicable).

[c] In Treatment Arm 3, SoC chemotherapy can be given for an additional 2 cycles q3w on Weeks 12 and 15 (ie, total of 6 cycles post-randomization) if clinically indicated, at the investigator's discretion before patients enter follow-up. This does not alter the planned scan schedule q8w starting at Week 12 for patients in Treatment Arm 3.

Note: Patients whose weight falls to 30 kg or below must receive weight-based dosing-equivalent to 20 mg/kg of durvalumab and 1 mg/kg of tremelimumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500 mg and tremelimumab at 75 mg. Durvalumab dose will be 1500 mg during chemotherapy and 1500 mg post-chemotherapy; tremelimumab dose will be 75 mg.

Durva Durvalumab; PD Progressive disease; q3w Every 3 weeks; q4w Every 4 weeks; SoC Standard of care; Treme Tremelimumab.

Safety Confirmation

An independent data monitoring committee (IDMC) composed of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule of durvalumab ± tremelimumab in combination with SoC chemotherapy at 2 early stages of enrollment. A step-wise approach will be adopted. The initial safety review will take place when the first 30 patients (10 in each arm) have completed the first cycle of treatment. A second review will add an additional 30 patients (10 in each arm) who have completed the first cycle of treatment, making a total of 60 patients. At the time of the second review, it is expected that the initial 30 patients would have had at least 6 weeks of follow-up, with some patients having longer follow-up. These 2 reviews will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment.

Safety confirmation for Japan: An additional safety review for Japanese patients will take place when the first 3 patients in each treatment arm in Japan have completed the first cycle of treatment. This review will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment in Japan.

Safety confirmation for China: An additional safety review for Chinese patients will take place when the first 10 patients in each treatment arm in China have completed the first cycle of treatment. This review will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment in China.

In addition, the IDMC will review the unblinded interim analysis summaries of efficacy data. The IDMC meets approximately every 6 months thereafter to continue safety monitoring up to the decision to unblind the study.

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

Statistical methods

The dual primary aims of this study are to assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients.

The study will enroll approximately 2000 patients to randomize approximately 1000 patients in a 1:1:1 ratio to durvalumab + tremelimumab combination therapy + SoC chemotherapy, durvalumab monotherapy + SoC chemotherapy, or SoC chemotherapy alone (approximately 333 patients in each treatment arm), including at least 250 patients in each treatment arm with PD-L1 TC <50%. Once global enrollment is completed, recruitment may continue in mainland China only. A total of up to 180 patients, including up to 135 patients in total with PD-L1 TC <50%, from China will be randomized (refer to Section 8.6 for more details).

The study is sized for dual primary endpoints to characterize the PFS and OS benefits of durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone in the ITT population. Sample size and power analysis for the dual primary endpoints of final analysis are described below.

The final (primary) PFS analysis for superiority will be performed when the following conditions have been met:

- Approximately 497 BICR PFS events from the global cohort have occurred across the durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone treatment arms (75% maturity)

The final OS analysis for superiority will be performed when the following conditions have been met:

- Approximately 532 OS events have occurred across the durvalumab monotherapy + SOC chemotherapy and SoC chemotherapy alone treatment arms (80% maturity)

One interim analysis of PFS will be performed when approximately 80% of the target PFS events have occurred. Three interim analyses of overall survival (OS) will be performed; the first at the time of the interim PFS analysis (approximately 45% of the target OS events), the second at the time of the primary PFS analysis (approximately 61% of the target OS events) and the third when approximately 84% of the target OS events have occurred.

Dual primary Endpoints:

Durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone

(PFS in ITT population)

Assuming the true PFS HR is 0.67 and the median PFS in SoC chemotherapy alone arm is 6 months, 497 PFS events from the global cohort (75% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha level of 0.9% (with overall alpha for PFS 1%), allowing for 1 interim analysis conducted at approximately 80% of the target events. The smallest treatment difference that is statistically significant will be an HR of 0.79. Assuming a recruitment period of 16 months, this analysis is anticipated to be 25 months from FPI.

Durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone

(OS in ITT population)

Assuming the true OS HR is 0.7 and the median OS in SoC arm is 12.9 months, 532 OS events (80% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha level of a 3.3% (with overall alpha for OS 4%), allowing for 3 interim analyses conducted at approximately 45%, 61% and 84% of the target events. The smallest treatment difference that is statistically significant will be an HR of 0.83. Assuming a recruitment period of 16 months, this analysis is anticipated to be 46 months from FPI.

PFS, based on the programmatically derived PFS from BICR, and OS will be analyzed using a stratified log-rank test. The effect of treatment will be estimated by the HR together with corresponding 2-sided appropriately sized confidence interval (adjusted for interim analyses) and p-value.

Safety data will be summarized descriptively.

TABLE OF CONTENTS PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
$AUC_{0\text{-}16wk}$	Area under the plasma drug concentration-time curve from time 0 to Week 16
AUC	Area under the plasma drug concentration-time curve
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CCTG	Canadian Cancer Trials Group
CD	Cluster of differentiation
CFDA	China Food and Drug Administration
CI	Confidence interval
CL	Calculated creatinine clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
C_{min}	Minimum plasma concentration
CR	Complete response
CRO	Clinical Research Organization
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed tomography
CTC	Common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]

Abbreviation or special term	Explanation
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CCI [redacted]	
DCO	Data Cut Off
DCR	Disease control rate
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic patient-reported outcome (device)
CCI [redacted]	
[redacted]	
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPI	First patient in
GCP	Good Clinical Practice Unless otherwise noted, 'GCP' shall mean 'the International Council for 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).
GMP	Good Manufacturing Practice
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus

Abbreviation or special term	Explanation
HIV	Human immunodeficiency virus
HL	Hy's Law
CCI	[redacted]
HR	Hazard ratio
HRCT	High-resolution computed tomography
HRQoL	Health-related quality of life
IASLC	International Association for the Study of Lung Cancer
IB	Investigator's Brochure
IC	Immune cell
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
CCI	[redacted]
IgG	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IMP	Investigational medicinal product
IP	Investigational product
IRB	Institutional Review Board, synonymous to Ethics Committee (EC) and Independent Ethics Committee (IEC)
IO	Immuno-oncology
CCI	[redacted]
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LPFV	Last patient first visit
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
NAB	Nanoparticle albumin-bound
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small-cell lung cancer

Abbreviation or special term	Explanation
NTL	Non-target lesion
OAE	Other significant adverse events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L1 TC <1%	PD-L1 expression on less than 1% of tumor cells
PD-L1 TC ≥25%	PD-L1 expression on at least 25% of tumor cells
PD-L1 TC <25%	PD-L1 expression on less than 25% of tumor cells
PD-L1 TC ≥50%	PD-L1 expression on at least 50% of tumor cells
PD-L1 TC <50%	PD-L1 expression on less than 50% of tumor cells
PD-L1 TC ≥90%	PD-L1 expression on ≥90% of tumor cells
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PFS2	Time from randomization to second progression
CCI	[redacted]
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
CCI	[redacted]
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
q12w	Every 12 weeks
QC	Quality Control
QLQ-C30 v3	30-item Core Quality of Life Questionnaire, version 3
QLQ-LC13	13-item Lung Cancer Quality of Life Questionnaire
QoL	Quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RT-QPCR	Reverse transcription quantitative polymerase chain reaction

Abbreviation or special term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
SCLC	Small-cell lung cancer
SD	Stable disease
SmPC	Summary of Product Characteristics
CCI	[redacted]
SoC	Standard of care
sPD-L1	Soluble programmed cell death ligand 1
TB	Tuberculosis
TBL	Total bilirubin
TC	Tumor cells
TL	Target lesion
TMB	Tumor Mutational Burden
TNBC	Triple-negative breast cancer
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Lung cancer has been the most common cancer in the world for several decades, with an estimated 1.8 million new cases in 2012 (12.9% of all new cancers), and was also the most common cause of death from cancer in 2012, with 1.59 million deaths (19.4% of the total cancer deaths; GLOBOCAN 2012). Non-small-cell lung cancer (NSCLC) represents approximately 80% to 85% of all lung cancers. Unfortunately, at the time of diagnosis, approximately 70% of patients with NSCLC already have advanced or metastatic disease not amenable to surgical resection. Furthermore, a significant percentage of patients with early-stage NSCLC who have undergone surgery subsequently develop distant recurrence and die as a result of their lung cancer (Pisters and LeChevalier 2005).

Despite advances in the diagnosis, imaging, staging, and treatment of NSCLC, the estimated 5-year overall survival (OS) for patients in Europe and the United States (US) continues to be low (11% and 17%, respectively; D'Addario et al 2010, Howlander et al 2014). Patients presenting with advanced NSCLC have a median OS of 10 to 12 months (Bonomi 2010). Patients without a targetable mutation (ie, epidermal growth factor receptor [EGFR] or anaplastic lymphoma kinase [ALK] mutation) demonstrate responses to systemic treatment of approximately 20% to 30% and progression-free survival (PFS) of 4 to 5 months (Sandler et al 2006, Scagliotti et al 2008, Schiller et al 2002). The duration of responses (DoRs) is also limited, and toxicities can be a major limiting factor. The 1-year survival rate is 30% to 40% for patients with a good performance status.

Common first-line treatment regimens for advanced NSCLC in major global markets are typically platinum-based doublets and include carboplatin and paclitaxel (eg, nanoparticle albumin-bound [nab] paclitaxel [Abraxane®]), carboplatin and gemcitabine (squamous only), carboplatin and pemetrexed (non-squamous only), cisplatin and gemcitabine (squamous only), and cisplatin and pemetrexed (non-squamous only). Maintenance therapy, with either continuation or switch, has also been recommended for certain histologic subtypes of NSCLC; for example, maintenance with pemetrexed has been shown to improve OS and PFS, particularly in non-squamous histologies (Ciuleanu et al 2009, Paz-Ares et al 2013). Although platinum-based doublets are interchangeable in terms of efficacy when used alone, these doublets vary to some extent with regard to convenience, associated toxicities, and cost, with the selection of a specific regimen often dictated by local practice and individualized on a case-by-case basis.

Recently, pembrolizumab, a programmed cell death 1 (PD-1) inhibitor, gained Food and Drug Administration (FDA) approval for the first-line treatment of metastatic NSCLC in patients with high programmed cell death ligand 1 (PD-L1) expression and without EGFR or ALK genomic tumor aberrations. Regulatory approval was based on safety and efficacy data from the KEYNOTE-024 study. Results from the KEYNOTE-024 study, which included patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells (TC) and with no activating EGFR mutations or ALK fusions, demonstrated that patients treated with pembrolizumab had longer PFS (10.3 versus 6.0 months) and OS (hazard ratio [HR] for death,

0.60) and higher objective response rate (ORR; 44.8% versus 27.8%) compared with patients treated with platinum-based therapy (Reck et al 2016). The KEYNOTE-021 21G cohort is an expansion cohort of a Phase I/II study that compared the efficacy and safety of pembrolizumab plus carboplatin and pemetrexed to carboplatin and pemetrexed alone as first-line therapy for patients with advanced NSCLC of non-squamous histology. Patients who were treated with first-line pembrolizumab in combination with chemotherapy had higher ORR (55%) compared with patients receiving chemotherapy alone (29%) (Langer et al 2016). Both of these studies have shown that pembrolizumab alone or in combination with chemotherapy can be an effective first-line treatment option for patients with advanced NSCLC.

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).

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

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

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

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1

pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Bonomi 2010, Brahmer et al 2012, Hirano et al 2005, Howlander et al 2014, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015a, Schiller et al 2002, Segal et al 2015). In addition, a high mutational burden (eg, in bladder carcinoma) (Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (FDA Guidance 2011, Fife and Bluestone 2008). A block of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data have now been added with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as CTLA-4 and PD-L1 has promising clinical activity. Ipilimumab was granted US FDA approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, while nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies such as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell NSCLC, squamous cell carcinoma of the head and neck (SCCHN), and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

1.1.2 Durvalumab

Durvalumab (MEDI4736) is a human mAb of the immunoglobulin G (Ig) G1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand 2 [PD-L2]) with PD-1 on T cells and CD80 (B7.1) on immune cells (ICs). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor

response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 1.2.1.3 and Section 6.5. Refer to the current durvalumab Investigator's Brochure (IB) for a complete summary of non-clinical and clinical information including safety, efficacy, and pharmacokinetics.

1.1.3 Tremelimumab

Tremelimumab (MEDI1123, formerly CP-675,206) is a human Ig G2 mAb that is directed against CTLA-4 (cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin-2 and IFN-γ) from human T cells, peripheral blood mononuclear cells, and whole blood (Tarhini and Kirkwood 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date, tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with anticancer agents other than durvalumab. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.2.2. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy, and pharmacokinetics.

1.1.4 Durvalumab in combination with tremelimumab

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

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, pharmacokinetics (PK)/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. CCI [redacted] The study is ongoing and continues to accrue. In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date, more than 3000 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in Sections 1.2.1.1 and 1.3.2.3. Refer to the current editions of the

durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK, and efficacy.

1.1.5 Rationale for the study

Current therapies for advanced NSCLC have poor outcomes (5-year survival of 17% for the US), with responses to systemic chemotherapy in the first-line setting of approximately 20% to 30% and a median OS of approximately 10 to 12 months (Bonomi 2010, D'Addario et al 2010, Sandler et al 2006, Scagliotti et al 2008, Schiller et al 2002). Systemic chemotherapy is associated with significant side effects, including neutropenia, nausea, vomiting and dehydration, and alopecia (Sandler et al 2006, Scagliotti et al 2008). Recent progress in immunotherapy for first-line NSCLC has been mixed. While previously untreated patients with PD-L1 expression on at least 50% of tumor cells (PD-L1 TC ≥50%) NSCLC receiving the PD-1 inhibitor pembrolizumab had a 44.8% response rate and median PFS of 10.3 months (Reck et al 2016), nivolumab failed to meet its primary endpoint of PFS in a similar population (Socinski et al 2016). These facts indicate that there is still a significant unmet medical need for additional treatment options for use in this patient population. In addition, patients with NSCLC may be particularly susceptible to these immunotherapies given the high mutational burden of this disease. Novel therapies are urgently needed to improve clinical outcomes, irrespective of PD-L1 status.

1.1.5.1 Rationale for the combination of durvalumab and tremelimumab with chemotherapy

Non-clinical and clinical studies have indicated that blockade of immune checkpoints (PD-1/PD-L1 and CTLA-4) can have a positive effect on antitumor immunity. One potential strategy is to combine these non-redundant and potential synergistic single-agent immune checkpoint inhibitors, thereby producing an additive improvement in tumor response (Larkin et al 2015, Pisters and LeChevalier 2005, Postow et al 2015).

The use of combination chemotherapy is a mainstay of oncology therapy. The goal of combination chemotherapy is to utilize agents that affect cancer cells by different mechanisms, thus reducing the risk of developing resistance. Current studies are now adding immunotherapeutics to chemotherapeutics to broaden antitumor responses.

Checkpoint inhibitors have been tested in NSCLC, either used alone or in combination with chemotherapy. Preliminary efficacy data from Study D4190C00006 have demonstrated that durvalumab + tremelimumab combination therapy is clinically active and well tolerated. As of 1 June 2015, in 63 patients with at least 24 weeks of follow-up, 17% achieved objective response and disease control at 24 weeks is 29%. Responses in both patients with PD-L1 TC ≥25% and those with PD-L1 TC <25% demonstrated evidence of clinical activity. Investigator-reported confirmed objective responses were achieved by 23% of patients in the combined tremelimumab 1 mg/kg cohort, including 22% of patients with PD-L1 TC ≥25% and 29% of patients with PD-L1 TC <25% (Antonia et al 2016a).

Nivolumab (PD-1 inhibitor) in combination with platinum-based doublet chemotherapy (Rizvi et al 2016) and nivolumab in combination with ipilimumab (anti-CTLA-4 mAb)

(Hellmann et al 2017) as first-line treatment for advanced NSCLC have been studied in CheckMate 012. The antitumor activity of first-line nivolumab in combination with platinum doublets appeared highly promising, and the safety profile of nivolumab in combination with either ipilimumab or with chemotherapy was tolerable (Sections 1.3.1.2 and 1.3.1.3, respectively).

The safety and efficacy of checkpoint inhibitors combined with chemotherapy have also been demonstrated across multiple tumor types. Data for durvalumab ± tremelimumab with standard platinum-based chemotherapy in advanced cancers are being generated from 2 ongoing Phase I studies: the internal Study D419SC00001 (n=6) and a Phase Ib study (NCT02537418) run by the Canadian Cancer Trials Group (CCTG; n=111 as of an October 2016 cut-off). The combinations tested are tolerable and toxicities manageable; details on the safety profile found in these studies are summarized in Sections 1.2.2 and 1.3.2.5. Preliminary results from the CCTG study were presented for the NSCLC cohorts at the International Association for the Study of Lung Cancer (IASLC) 2016 meeting; the overall ORR in NSCLC cohort (n=26) was 61.5%.

In addition, KEYNOTE-021 is a multi-cohort Phase I/II study comparing pembrolizumab in combination with various chemotherapy regimens to chemotherapy alone as first-line treatment for NSCLC. In the cohort of patients receiving pembrolizumab in combination with chemotherapy (carboplatin and pemetrexed), the objective response was 55% (95% confidence interval [CI]: 42 to 68) compared with 29% (95% CI: 18 to 41) in patients receiving chemotherapy (carboplatin and pemetrexed) alone. Objective response was significantly improved in patients receiving pembrolizumab with chemotherapy compared with those receiving chemotherapy alone (estimated treatment difference 26% [95% CI: 9% to 42%]; p=0.0016). In patients receiving pembrolizumab with chemotherapy, the response rate was 57% (95% CI: 34 to 79) in patients who had a PD-L1 tumor proportion score of less than 1% and was 54% (95% CI: 37 to 70) in patients with a PD-L1 tumor proportion score of ≥1%. In patients receiving pembrolizumab with chemotherapy, median time to response was 1.5 months compared with 2.7 months in patients receiving chemotherapy alone. Kaplan-Meier estimates of response duration of at least 6 months were 92% (95% CI: 73 to 98) in the pembrolizumab with chemotherapy group and 81% (95% CI: 51 to 93) in the chemotherapy alone group. In patients receiving pembrolizumab with chemotherapy, the most common Grade 3 or worse treatment-related adverse events (AEs) were anemia (12%); decreased neutrophil count (5%); and acute kidney injury, decreased lymphocyte count, fatigue, neutropenia, sepsis, and thrombocytopenia (3% each). Additional results on tolerability of pembrolizumab in combination with chemotherapy are discussed in Section 1.3.2.5 (Langer et al 2016).

In addition to these completed studies, a number of studies of immunotherapies in combination with chemotherapy in first-line NSCLC are ongoing. These include CheckMate 227 (nivolumab plus platinum doublet in PD-L1-negative NSCLC; NCT02477826); KEYNOTE-189 (pembrolizumab plus pemetrexed in non-squamous NSCLC; NCT02578680); KEYNOTE-407 (carboplatin and paclitaxel or nab-paclitaxel with or without pembrolizumab in first-line metastatic NSCLC; NCT02775435); and IMpower 130, IMpower 131, and IMpower 150 (atezolizumab plus carboplatin,

nab-paclitaxel, or paclitaxel with or without bevacizumab in squamous and non-squamous NSCLC; NCT02367781, NCT02367794, and NCT02366143, respectively) (reviewed in Gainor 2016 and Langer et al 2016).

In summary, the preliminary efficacy, safety, and tolerability data of durvalumab ± tremelimumab generated to date, together with early positive signals with other immunotherapies in combination with chemotherapy, support the continued development of these treatments in combination with standard of care (SoC) chemotherapy in NSCLC.

1.2 Rationale for study design, doses, and control groups

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

1.2.1 Durvalumab and tremelimumab dose and treatment regimen justification

1.2.1.1 Durvalumab+ tremelimumab combination therapy dose rationale

The durvalumab + tremelimumab combination therapy doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (PD-L1 and CTLA-4, respectively), demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetics/Pharmacodynamics data

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

Monotonic increases in pharmacodynamic activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented pharmacodynamic activity relative to durvalumab monotherapy with combination doses containing CCI tremelimumab, including both the CCI durvalumab + CCI tremelimumab combinations.

Clinical data

In Study D4190C00006, various dose combinations have been explored, with doses of tremelimumab ranging from CCI and doses of durvalumab ranging from CCI Tremelimumab was given on a CCI schedule, while durvalumab was explored in both a CCI 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 AEs, including discontinuations due to AEs, serious adverse events (SAEs), and severe AEs. Between the CCI durvalumab + CCI tremelimumab and CCI durvalumab + CCI tremelimumab cohorts treated at the CCI schedule, the number of patients reporting any AE, Grade ≥3 AEs, SAEs, and treatment-related AEs was higher in the CCI durvalumab + CCI tremelimumab cohort than the CCI durvalumab + CCI tremelimumab cohort. A similar pattern was noted in the CCI regimens, suggesting that, as the dose of tremelimumab increased above CCI a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis, colitis, and other immune mediated events, were more commonly seen in cohorts using either CCI of tremelimumab compared to the CCI dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of CCI appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the CCI doses of tremelimumab were eliminated in the final dose selection.

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

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

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The CCI durvalumab CCI 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 CCI durvalumab + CCI tremelimumab dose cohort may demonstrate equivalent clinical activity to those of other dose combinations.

Altogether, the data suggested that a CCI durvalumab + CCI tremelimumab dose combination should be selected for further development.

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

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

Long-term follow-up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed CCI 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 (Sandler et al 2006, Schadendorf et al 2013).

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

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

The durvalumab + tremelimumab combination regimen will be administered for 4 doses q3w in combination with chemotherapy followed by durvalumab monotherapy q4w until disease progression or unless other specific discontinuation criteria are met. One additional combination dose will be administered post-chemotherapy (see Section 1.2.2). This is to account for the possibility that the ability of T cells to respond to tremelimumab may be dampened in the presence of cytotoxic chemotherapy.

1.2.1.3 Durvalumab monotherapy dose rationale

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

PK/pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from CCI durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at CCI suggesting near-complete target saturation (membrane-bound and soluble programmed cell death ligand 1 [sPD-L1]), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than CCI The expected half-life with doses CCI is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with the engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease

following exposure to durvalumab. (For further information on immunogenicity, please see the current IB.)

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

Given the similar area under the serum 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 CCI [redacted] regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of CCI [redacted]

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and pharmacokinetics at the CCI [redacted] regimen.

1.2.1.4 Rationale for fixed dosing

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

Similarly, a population PK model was developed for tremelimumab using data from Phase I through Phase III (N=654; doses CCI [redacted] metastatic melanoma) (Wang et al 2014). Population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of ≤0.5). The weight-based CCI [redacted] and fixed dosing CCI [redacted] based on median body weight of ~75 kg) regimens were compared using predicted PK concentrations (5th, median, and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to

120 kg. Similar to durvalumab, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady-state PK concentrations with slightly less between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (NCCN 2014, Ng et al 2006, Wang et al 2009, Zhang et al 2012, Narwal et al 2013). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamic parameters (Zhang et al 2012).

CCI

1.2.2 Rationale for proposed Phase III dose and schedule

The proposed dosing schedule is aligned with the standard fixed dosing of CCI durvalumab + CCI tremelimumab for CCI followed by durvalumab monotherapy CCI which is supported by efficacy and safety as well as tolerability data across multiple studies in multiple tumor types. To conform to the chemotherapy schedule in the study, we propose to use standard durvalumab + tremelimumab combination therapy dose and ratio at a CCI dosing interval for the CCI rather than the standard CCI schedule.

The safety of a CCI dosing schedule in combination with chemotherapy has been explored in the ongoing Study D419SC00001 (described below), where tremelimumab is administered at CCI in combination with CCI durvalumab CCI followed by CCI durvalumab CCI The combination has been declared tolerable and manageable (see below for more detail). The CCI dose of durvalumab is the CCI equivalent of the standard CCI dose. The tremelimumab dose was not lowered proportionally to CCI because CCI is the lowest tested biologically effective dose.

In this study, AstraZeneca proposes to use the Phase III fixed dose of durvalumab, so this study will combine 75 mg tremelimumab with 1500 mg durvalumab q3w in combination with chemotherapy. The relative increase in dose density of durvalumab (ie, 1500 mg q3w instead of CCI is supported by the fact that toxicities attributable to durvalumab do not appear dose dependent, and PK modeling reveals no meaningful differences in drug levels between CCI CCI dosing. After chemotherapy, the dose will be 1500 mg durvalumab q4w.

Study BR.34 is a Phase II randomized trial of durvalumab and tremelimumab ± platinum-based chemotherapy in patients with metastatic (Stage IV) squamous or non-squamous NSCLC. Both Study BR.34 and the CCTG (NCT02537418) described below are assessing CCI tremelimumab with CCI durvalumab CCI in combination with platinum-based chemotherapy.

Supportive clinical data

The safety and tolerability data that support the proposed combination and schedule are based on 2 ongoing Phase I/IB studies investigating the safety and tolerability of durvalumab + tremelimumab in combination with various chemotherapy regimens in solid tumors, an AstraZeneca internal study (D419SC00001) and a CCTG study (NCT02537418).

AstraZeneca Phase I study (D419SC00001)

This Phase I open-label study is evaluating the safety and tolerability of durvalumab + tremelimumab combination therapy in combination with first-line chemotherapy regimens in patients with locally advanced or metastatic solid tumors. The tumor types originally included ovarian/peritoneal/fallopian tube cancer, SCCHN, triple-negative breast cancer (TNBC), small cell lung carcinoma (SCLC), and gastric/gastroesophageal junction cancer.

As of 6 December 2016, 6 patients with SCLC had completed CCI of treatment with durvalumab CCI + tremelimumab CCI given concurrently with carboplatin AUC CCI and etoposide CCI followed by durvalumab CCI monotherapy CCI No DLT was reported during the first cycle of treatment (a 21-day period). One patient developed Grade 4 hepatitis with elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase at Cycle 5 Day 1. Although the onset of this event was 1 day after the protocol-defined DLT period of 4 cycles, it was considered as a DLT following discussion with the Investigator. The liver enzymes were normalized within 16 days after steroid use and was confirmed as not a Hy's law case. As there was only 1 DLT reported in 6 patients, the safety profile of this combination with chemotherapy at the q3w schedule is declared tolerable and manageable.

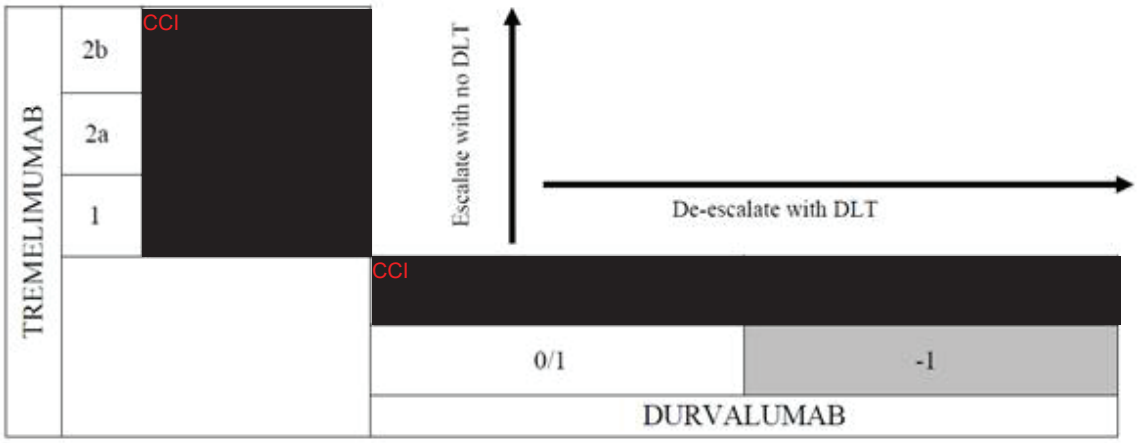
Additional details on safety are provided in Section 1.3.2.5.

CCTG study (NCT02537418)

This is an ongoing multi-center, Phase I study of single or double immunotherapy (durvalumab ± tremelimumab) in combination with multiple standard platinum-based chemotherapy regimens in patients with incurable advanced or metastatic cancer and is sponsored and conducted by the CCTG. Chemotherapy regimens assessed in the study include cisplatin + pemetrexed, cisplatin + gemcitabine, cisplatin + etoposide, carboplatin + pemetrexed, carboplatin + gemcitabine, nab-paclitaxel + carboplatin, and etoposide + carboplatin at standard doses for each regimen.

The dose escalation and dose regimen are outlined below (Figure 2). Another dose level (DL3, durvalumab CCI + tremelimumab CCI [maximum 6 doses of tremelimumab] CCI with chemotherapy) was added after the protocol was initiated. A total of 4 dose levels of durvalumab ± tremelimumab are being assessed.

Figure 2 Study schematic for the CCTG study



As of an October 2016 data cut-off, a total of 111 patients have been dosed with 7 chemotherapy regimens across multiple tumor types; the majority of patients enrolled have metastatic/advanced NSCLC (44%), followed by SCLC (16%) and then bladder cancer (7%), and most have had no prior chemotherapy (71%). SCLC patients enrolled into the etoposide-carboplatin cohorts started immuno-oncology (IO) treatment in Cycle 3 of chemotherapy; all other chemotherapy regimens assessed the IO combination starting at Cycle 1.

Overall, toxicities related to the chemotherapy core regimen appeared as expected in severity and frequency (see Section 1.3.2.5 for more detail on the safety profile from this study). Overall, across all dose levels, there was no clear dose dependency in any of the reported AEs, and there was no DLT reported per protocol-defined criteria (DLT period of 21 days). Toxicities related to durvalumab and tremelimumab were also those expected for these agents, although a number of potential IO-related toxicities such as diarrhea, skin rash, hepatic function changes, or pneumonitis were difficult to differentiate from those reported from cytotoxic agents. As expected, there were more IO-related toxicities reported for dose levels containing tremelimumab. In general, all regimens were tolerable and toxicities were manageable at all dose levels. There was no discernible difference in the tolerability profile when IO treatment was administered in Cycle 1 (including SCLC patients) versus Cycle 3 of chemotherapy for SCLC patients only.

In general, the overall safety profile from these 2 studies with regard to the IO+IO treatment appears to be consistent with available safety and tolerability data for durvalumab in combination with tremelimumab.

PK modeling

PK modeling and simulation have been conducted to evaluate the switch from q4w dosing to q3w dosing for both durvalumab and tremelimumab. Simulated PK profiles of both drug components based on the study design (CCI dosing regimen of CCI durvalumab in combination with CCI tremelimumab given at CCI durvalumab as a single agent in CCI a combination dose given at CCI followed by durvalumab

monotherapy [CCI] were compared with simulated PK profiles of the [CCI] dosing regimen [CCI] dosing regimen of [CCI] durvalumab in combination of [CCI] tremelimumab given at [CCI] followed by durvalumab monotherapy [CCI]

Results suggest that tremelimumab exposure is similar between the [CCI] dosing regimen of the study (tremelimumab given at [CCI] and the [CCI] dosing regimen (tremelimumab given at [CCI] For the [CCI] dosing regimen versus the [CCI] dosing regimen, median maximum serum concentration (C_{max}) following 4th dose were 26.2 µg/mL versus 24.5 µg/mL, median trough concentration following 4th dose at Week 16 was 3.56 µg/mL versus 5.62 µg/mL, and area under the plasma drug concentration-time curve from time 0 to Week 16 ($AUC_{0\text{-}16wk}$) was 1045 µg*day/mL versus 982 µg*day/mL for the q3w and q4w schedules, respectively.

For durvalumab, median C_{max} following the 5th dose of the [CCI] regimen and the 4th dose of the [CCI] regimen was 689 and 624 µg/mL, median trough concentration at Week 16 was 125 and 94.5 µg/mL, and $AUC_{0\text{-}16wk}$ was 28726 and 22772 µg*day/mL for the [CCI] schedule, respectively.

Therefore, PK modeling suggests that a [CCI] schedule does not impose a significant increased safety risk based on expected durvalumab and tremelimumab exposures.

Taken together, the totality of data provides sufficient safety data to support the combination of [CCI] durvalumab + [CCI] tremelimumab with chemotherapy. There is supportive safety data for the combination of [CCI] durvalumab + [CCI] tremelimumab [CCI] followed by [CCI] durvalumab [CCI] from Study D419SC00001. The safety of the combination of [CCI] durvalumab [CCI] plus tremelimumab [CCI] with chemotherapy has been assessed in more than 100 patients in the CCTG Phase I study. Clinical data from NSCLC patients in Study 006 suggest that increasing the dose of durvalumab has no significant impact on the safety and tolerability of the durvalumab and tremelimumab combination. In addition, PK modeling data suggest that there will be a minimal impact on investigational product (IP) exposure if the standard doses [CCI] are given on a [CCI] regimen.

Additional dose of tremelimumab

Patients in Treatment Arm 1 will receive an additional dose of durvalumab + tremelimumab after chemotherapy at Week 16 if they tolerate the combination and complete all 4 doses of durvalumab + tremelimumab combination therapy during chemotherapy. The rationale to have an additional dose of tremelimumab after chemotherapy is based on the possibility that chemotherapy may limit the responsiveness of T cells to tremelimumab and that tremelimumab given after chemotherapy will help control rapid progression that is inherent to the clinical course of NSCLC, thereby sustaining the responses that may have been achieved during induction.

1.2.2.1 Safety confirmation of proposed doses

To better support the use of the 1500 mg durvalumab ± 75 mg tremelimumab q3w in this study and to ensure safety and tolerability in this larger Phase III study, an evaluation and confirmation of safety of the combination using the proposed dose and schedule will be conducted by an independent data monitoring committee (IDMC) (see Section 1.6).

1.2.3 Rationale for control treatment arm: standard care therapy

The choice of SoC chemotherapy options provided in this study includes abraxane + carboplatin, gemcitabine + cisplatin (squamous patients only), gemcitabine + carboplatin (squamous patients only), pemetrexed + carboplatin (non-squamous patients only), and pemetrexed + cisplatin (non-squamous patients only). Patients in the SoC treatment arm will receive treatment determined by the Investigator, from the SoC agents approved for use in NSCLC in their local market, until progression per standard practice. The SoC options provided in this study include agents that are commonly used in advanced or metastatic NSCLC and allow sufficient flexibility for Investigators and patients to select the agents that reflect their normal clinical practice and national guidelines (NCCN 2014, Reck et al 2014).

1.2.4 Rationale for endpoints

The dual primary aims of this study are to assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients. The key secondary aims of the study are to assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients. PFS may serve as a surrogate endpoint for OS when differences between treatment arms are of sufficient magnitude and clinical importance (FDA Guidance 2011, Paz-Ares et al 2013, Pazdur 2008). In certain settings, the utility of survival as an endpoint may potentially be confounded by subsequent therapies. Specifically, there are a number of molecules that target the PD-1/PD-L1 pathway, including pembrolizumab, nivolumab, and atezolizumab that are now available for the treatment of NSCLC. Access to these agents creates challenges in being able to fully characterize the effects of study treatment on OS if patients subsequently receive these immunotherapeutic agents.

Secondary aims of the study also include evaluation of the efficacy endpoints OS, PFS and ORR in biomarker defined populations, to further evaluate the antitumor effect and survival benefit of durvalumab + tremelimumab + SoC chemotherapy compared with SoC chemotherapy alone in such biomarker selected patient population. The biomarker defined populations are those patients with high tumor mutational burden (TMB high detected in tumor tissue and/or ctDNA, cut-offs to be detailed in the SAP), those patients with PD-L1 expression on less than 50% of tumor cells (PD-L1 TC <50%), patients with PD L1 expression on less than 25% of tumor cells (PD L1 TC <25%) and patients with PD-L1 expression on less than 1% of tumor cells (PD-L1 TC <1%).

In addition to the comparisons of durvalumab ± tremelimumab + SoC chemotherapy treatment arms to the SoC chemotherapy alone treatment arm, the comparison of the

durvalumab + tremelimumab combination therapy + SoC chemotherapy and the durvalumab monotherapy + SoC chemotherapy treatment arms will provide information as to the relative contribution of adding tremelimumab to the established benefit-risk profile of durvalumab monotherapy+ SoC chemotherapy. This comparison is not currently included in the multiplicity-controlled statistical testing procedure because the proposed study is not powered for the comparison. However, the treatment difference will be summarized descriptively to evaluate the relative benefit-risk difference between the 2 experimental treatment arms.

Antitumor activity will be assessed according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) guidelines. The interim and primary analysis of PFS will be based on programmatically derived PFS calculated from the tumor scan assessments according to RECIST 1.1 by Blinded Independent Central Review (BICR). CCI [redacted]

Secondary efficacy endpoints of proportion of patients alive and progression free at 12 months from randomization (APF12), ORR, DoR, best objective response (BoR), and time from randomization to second progression (PFS2) will be examined to further evaluate the antitumor effect and survival benefit of durvalumab ± tremelimumab + SoC chemotherapy compared with SoC chemotherapy alone in all patients.

The secondary endpoints of health-related quality-of-life (HRQoL), patient-reported outcome (PRO) assessments, the European Organisation for Research and Treatment of Cancer [EORTC] 30-item Core Quality of Life Questionnaire, version 3 [QLQ-C30 v3], and the 13-item Lung Cancer Quality of Life Questionnaire [QLQ-LC13]) will show the overall influence of the benefits and toxicity of the treatment from the patient's perspective and will aid in assessing of the benefit-risk evaluation. These PRO questionnaires are well-established instruments that have been previously included in lung cancer clinical studies.

The PK and immunogenicity of durvalumab and tremelimumab are being examined to assess any potential impact on PK, pharmacodynamics, safety, and efficacy parameters. CCI [redacted]

1.3 Benefit/risk and ethical assessment

The following sections include summaries of the potential benefits and risks associated with durvalumab and tremelimumab prior to the overall benefit-risk assessment.

1.3.1 Potential benefits

1.3.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first-in-human, single-agent study (Study 1108) in patients with advanced solid tumors and the study of durvalumab monotherapy in NSCLC (Study D4191C00003 [ATLANTIC]). In Study 1108, as of 7 May 2015, 456 of 694 patients treated with durvalumab 10 mg/kg q2w

were evaluable for response (defined as having ≥24 week follow-up, measurable disease at baseline, and ≥1 follow-up scan or discontinued because of disease progression or death without any follow-up scan). Data from treatment-naïve patients with NSCLC in this study (n=59) showed a favorable disease control rate (DCR) at ≥12 weeks of 56% when durvalumab was given 10 mg/kg q2w (Antonia et al 2016b).

In PD-L1 unselected patients, the ORR, based on Investigator's assessment per RECIST 1.1, ranged from 0% in uveal melanoma to 20.0% in bladder cancer, and DCR at 24 weeks ranged from 4.2% in triple-negative breast cancer to 39.1% in advanced cutaneous melanoma. PD-L1 status was known for 383 of the 456 response evaluable patients. Across the PD-L1-positive tumors (defined as PD-L1 TC ≥25%), ORR was highest (>10%) for bladder cancer, advanced cutaneous melanoma, and hepatocellular carcinoma (33.3% each); NSCLC (26.7%); and SCCHN (18.2%). Moreover, in the PD-L1-positive subset, DCR at 24 weeks was highest (>10%) in advanced cutaneous melanoma (66.7%), NSCLC (36.0%), hepatocellular carcinoma and bladder cancer (33.3% each), and SCCHN (18.2%).

A total of 444 patients with locally advanced or metastatic NSCLC were treated in ATLANTIC. As of the data cut-off of 03 June 2016, in Cohort 2 (EGFR/ALK wild type/unknown, PD-L1 expression on ≥25% of TCs), durvalumab monotherapy showed clinically meaningful activity based on ORR in patients with locally advanced or metastatic NSCLC who had received at least 2 prior systemic treatment regimens. The responses were numerically greater in the PD-L1 TC ≥25% group (16.4%) compared with the PD-L1 expression on less than 25% of tumor cells (PD-L1 TC <25%) group (7.5%). The DCR at 6 months was 28.8% in the PD-L1 TC ≥25% group and 20.4% in the PD-L1 TC <25% group. The median OS was 10.9 months in the PD-L1 TC ≥25% patients and 9.3 months in the PD-L1 TC <25% patients. For the PD-L1 TC ≥25% patients, the OS rate at 6 and 12 months was 67.4% and 47.7%, respectively. For the PD-L1 TC <25% patients, the OS rate at 6 and 12 months was 60.3% and 34.5%, respectively. Observed PFS was numerically longer in the PD-L1 TC ≥25% group compared with the PD-L1 TC <25% group. In Cohort 3 (EGFR/ALK wild type/unknown, PD-L1 expression on ≥90% of TCs [PD-L1 TC ≥90%]), the ORR was 30.9%. The DCR at 6 months was 38.2%. Observed PFS and OS were similar to PD-L1 TC ≥25% patients in Cohort 2. For patients with PD-L1 ≥90% in the combined Cohorts 2 and 3, the ORR was 23.2%. The DCR at 6 months was 34.1%. Observed PFS and OS were similar to PD-L1 TC ≥25% patients in Cohort 2. For patients who responded, the response was durable across various subgroups (median DoR of 12.3 months in the PD-L1 TC ≥25% group in Cohort 2). In Cohort 2, 66.7% of responders in the PD-L1 TC ≥25% group had their first response at the time of the first on-treatment tumor assessment (Week 8). The median time to response was 1.9 months. In Cohort 1 (EGFR/ALK positive), the ORR was numerically lower than in the EGFR/ALK wild type/unknown cohorts. The responses were numerically greater in the PD-L1 TC ≥25% group (12.2%) compared with the PD-L1 TC <25% group (3.6%). The DCR at ≥6 months was 28.8% in the PD-L1 TC ≥25% group, 20.4% in the PD-L1 TC <25% group, and 38.2% in the PD-L1 TC ≥90% group. Observed PFS and OS were numerically longer in the PD-L1 TC ≥25% group compared with the PD-L1 TC <25% group (Garassino et al 2016; AstraZeneca internal data).

1.3.1.2 Durvalumab + tremelimumab

Preliminary efficacy data from Study 006 have demonstrated that this combination is clinically active and well tolerated in NSCLC. As of 1 June 2015, 63 patients with at least 24 weeks of follow-up were evaluable for response across various durvalumab + tremelimumab combination therapy dose regimens. Of these, 11 patients (17%) had achieved an objective response, and 18 patients (29%) had achieved disease control at 24 weeks (Antonia et al 2016a).

Nivolumab as monotherapy or in combination with ipilimumab (anti-CTLA-4 mAb) has also been investigated as first-line treatment for NSCLC in the CheckMate 012 study. The ORRs reported were similar, 47% in nivolumab 3 mg/kg q2w plus ipilimumab 1 mg/kg q12w and 38% nivolumab 3 mg/kg q2w plus ipilimumab 1 mg/kg q6w. Median DoR was not reached in either cohort. The safety profile of the combination was tolerable (Hellmann et al 2017).

1.3.1.3 Durvalumab + tremelimumab with chemotherapy

Studies evaluating agents targeting PD-L1 or CTLA-4 in combination with chemotherapy have yielded encouraging results (see Section 1.1.5.1).

Durvalumab ± tremelimumab with standard platinum-based chemotherapy in advanced cancers are being generated from an ongoing Phase Ib study (NCT02537418) run by the CCTG. Preliminary results were presented in IASLC 2016. Up to the October 2016 cut-off, a total of 111 patients have been dosed with various chemotherapy regimens and different tumor type. The overall ORR in the NSCLC cohort (n=26) was 61.5% (NSCLC data based on a data cut-off of July 2016) (Juergens et al 2016).

CheckMate 012 (NCT01454102) is a multi-arm Phase I study of nivolumab in combination with various anticancer agents or as monotherapy in chemotherapy-naïve patients with NSCLC. The results published in the Journal of Clinical Oncology showed that the ORRs for nivolumab 10 mg/kg plus gemcitabine-cisplatin, nivolumab 10 mg/kg plus pemetrexed-cisplatin, nivolumab 10 mg/kg plus paclitaxel-carboplatin, and nivolumab 5 mg/kg plus paclitaxel-carboplatin were 33%, 47%, 47%, and 43%, respectively; 24-week PFS rates were 51%, 71%, 38%, and 51%, respectively. On the basis of these results, the antitumor activity of first-line nivolumab in combination with platinum-based doublets is highly promising (Rizvi et al 2016).

In addition, the Phase II KEYNOTE-021 study showed that the addition of pembrolizumab to SoC carboplatin and pemetrexed followed by pembrolizumab for 2 years and indefinite pemetrexed maintenance therapy significantly improved the proportion of patients who achieved an objective response compared with carboplatin and pemetrexed alone in patients with chemotherapy-naïve, advanced non-squamous NSCLC. In the study, 123 patients with Stage IIIB/IV, chemotherapy-naïve, non-squamous NSCLC were randomized to receive 4 cycles of carboplatin and pemetrexed (500 mg/m^2 q3w), with or without 24 months of treatment with pembrolizumab (200 mg q3w). Of 60 patients, 33 (55%; 95% CI: 42 to 68) in the pembrolizumab plus chemotherapy group achieved an objective response compared with 18 of 63 patients (29%; 95% CI: 18 to 41) in the chemotherapy alone group (estimated

treatment difference 26% [95% CI: 9% to 42%]; p=0.0016) (Langer et al 2016). PFS was significantly longer in patients treated with pembrolizumab plus chemotherapy compared with chemotherapy alone (HR 0.53 [95% CI: 0.31 to 0.91]; p=0.010). Median PFS was 13.0 months (95% CI: 8.3 to not reached) for pembrolizumab plus chemotherapy and 8.9 months (95% CI: 4.4 to 10.3 months) for chemotherapy alone. No difference in survival was noted between treatment arms (22% of patients died in both treatment arms). On the basis of these clinical data, the antitumor activity of PD-L1/CTLA-4 in combination with first-line platinum-based doublets is highly promising. Given the synergistic potential of durvalumab and tremelimumab, the combination of both these drugs with chemotherapy has the potential to further improve the response rates and response durability.

1.3.2 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or CTLA-4, aim to boost endogenous immune responses directed against TC. By stimulating the immune system, however, there is the potential for adverse effects on other tissues.

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

1.3.2.1 Durvalumab

Risks with durvalumab include, but are not limited to diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency), hyper- and hypo-thyroidism, type I diabetes mellitus and diabetes insipidus), hepatitis/ increases in transaminases, nephritis/increases in creatinine, rash/ dermatitis(including pemphigoid), myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities(e.g. Guillain barre syndrome, myasthenia gravis).

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

In monotherapy clinical studies, AEs at an incidence of $\geq$ 20% include events such as fatigue, cough, decreased appetite, dyspnea and nausea. Approximately 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs, and CTC Grade 3 to 5 events reported across the durvalumab program.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (please see Section 6.9.1).

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

1.3.2.2 Tremelimumab

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

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

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

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

1.3.2.3 Durvalumab + tremelimumab combination therapy

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

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20m/kg and a tremelimumab dose of 1mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from Study 006, other studies evaluating the combination and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

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

In durvalumab + tremelimumab combination studies at the dose of durvalumab 20 mg/kg and tremelimumab 1 mg/kg AEs (all grades) reported very commonly (≥10% of patients) are fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, edema peripheral, weight, decreased hyponatremia and rash.

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

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

1.3.2.4 Standard of Care

Risks associated with SoC are described in the local prescribing information (i.e., SmPC, etc). In addition to the local prescribing information and associated risks with SoC, the investigator should be cognizant that ototoxicity and nephrotoxicity have been observed with carboplatin and cisplatin.

1.3.2.5 Durvalumab ± tremelimumab with chemotherapy

Two ongoing studies are evaluating the safety and tolerability of combining durvalumab and tremelimumab with different chemotherapy regimens in patients with solid tumors. One study is an AstraZeneca internal study (D419SC00001) and the other is CCTG Study NCT02537418 (see Section 1.2.2 for details on the designs of these studies).

In the AstraZeneca internal study (D419SC00001), 6 patients with SCLC were evaluable for safety as of 6 December 2016. Common adverse events reported were neutropenia (6 patients), nausea (4 patients), decreased appetite (4 patients), rash (3 patients), diarrhea (2 patients) and pyrexia (2 patients). Diarrhea, skin rash were generally low grade, with the exception of 1 Grade 3 erythroderma that responded to topical steroids. One patient with intermittent Grade 1 diarrhea required steroid treatment and resolved. Cycle 4 was modified in this patient where immunotherapy was held and chemotherapy was dose reduced to 75% due to Grade 4 neutropenia. Grade 3 and above events were febrile neutropenia (2 patients), platelet decrease (1 patient), and lung infection (1 patient) which were considered to be chemotherapy related, hepatitis (1 patient), and erythroderma (1 patient) which were considered to be immune related. Febrile neutropenia, lung infection, hepatitis were reported as SAE. Two patients had Grade 3/4 lipase/amylase elevation at baseline and were considered not drug related; these were due to pancreatic metastasis at baseline confirmed by imaging. One patient died due to disease progression as primary cause and a secondary cause of lung infection. Two patients discontinued treatment due to immune-related hepatitis and persistent skin rash. Two patients continue on active study treatment and are being followed up for long term safety.

In the CCTG study (NCT02537418), a total of 488 cycles have been administered up to the data cut-off of October 2016, with 103 patients evaluable for non-hematologic AEs. Overall, all patients experienced at least 1 AE; 96% were considered by the Investigator as causally related to chemotherapy, 75% were considered as causally related to durvalumab, and 55% were considered as causally related to tremelimumab. A total of 69 events (26% of all events) were Grade ≥3, regardless of causality. Of these, 20 events were considered by the Investigators as causally related to durvalumab treatment, and 15 events were considered as causally related to tremelimumab treatment. SAEs were reported in 38% of patients (39/103) regardless of causality; 19% was related to chemotherapy, 15% was considered by the Investigator as related to durvalumab, while 11% was related to tremelimumab treatment. Note that some events considered related to durvalumab and tremelimumab treatment may be reported in the same patient(s).

Overall, the common AEs reported were Grade 1 to 2 with the most commonly reported being fatigue (93%), nausea (72%), dyspnea (63%), constipation (59%), and cough (52%) regardless of causality. The most common chemotherapy-related AEs were fatigue (62%), nausea (58%), vomiting (32%), anorexia (28%), alopecia (27%), and peripheral sensory neuropathy (24%). The most common durvalumab-related AEs were fatigue (42%), rash maculo-papular (17%), nausea (16%), and diarrhea (12%). The most common tremelimumab-related AEs were fatigue (26%), rash maculo-papular (13%), and diarrhea (11%). The most common CTC Grade >3 events were fatigue (11 events), thrombotic events (9), dyspnea (7), lung infection (7), and diarrhea (7). Transient elevations in amylase and lipase were seen, but no patient had clinical or radiological evidence of pancreatitis. Thyroid-stimulating hormone (TSH) elevations of ≥5× upper limit of normal (ULN) were documented in 10 patients (10%), and 6 patients required initiation of thyroid replacement therapy on study. Three of these patients with elevated TSH had a previous history of hypothyroidism.

In all dose levels, dose delays of durvalumab were mostly for administrative reasons/patient request and neutropenia related to chemotherapy, while those for durvalumab ± tremelimumab were interrupted in 4 patients because of pneumonitis, colitis, or rash.

Seven patients (6.7%) discontinued durvalumab ± tremelimumab due to the following AEs: pneumonitis (3 patients), hepatitis (1 patient), myocarditis (1 patient), hyperthyroidism (1 patient), and limbic encephalitis (1 patient).

There were 7 deaths within 30 days of the last dose of protocol therapy. Two of these were considered to be at least possibly related to durvalumab or tremelimumab; 1 patient (Case No. PPD had diarrhea, hyperthyroidism, and myocarditis, which was steroid responsive but later declined active therapy. The cause of death has not yet been determined. The final post-mortem examination has not been reported. One patient (Case No. PPD had confusion and possible encephalitis.

The 2 possibly related fatal cases are briefly described as follows:

Case Report No. PPD - An event of myocarditis (Grade 5) occurred in a PPD with metastatic SCLC who on Cycle 1 Day 12 presented with s/s of fever,

nausea, vomiting, and decreased neutrophil count of 0.68 for which patient was eventually admitted. PPD developed diarrhea. Computed tomography (CT) abdomen showed liver metastasis, with inflammatory changes of duodenum suggestive of uncomplicated duodenitis or ulcer. The patient also developed acute renal failure and pulmonary edema. On Cycle 1 Day 16, the patient presented with s/s of Grade 4 heart failure and myocarditis as well as Grade 3 thyroiditis that initially responded to steroid administration. PPD was sent home only to be readmitted with weakness, fever, dizziness, and dehydration. The patient's condition deteriorated despite steroids and supportive treatment (inotropic support, use of ace inhibitors) and eventually died. Preliminary autopsy report showed multiple metastases in the involved lungs (effusions), liver, and lymph nodes. Except for atherosclerosis, there was no evidence of myocardial infarction or pulmonary emboli.

Case Report No. PPD – An event of limbic encephalitis (Grade 5) occurred in a PPD with metastatic SCLC who on Cycle 2 Day 27 presented with s/s of limbic encephalitis (eg, cognitive decline, restlessness, agitation, electroencephalogram findings suggestive of encephalopathy, CSF findings of increased white blood cells and protein, magnetic resonance imaging [MRI] finding of no intra-cranial mass), and despite treatment with antibiotics and steroids, the patient eventually died. Confounding factors that may likely also provide alternative cause/explanation for this event include the following: 1) a possible paraneoplastic effect of underlying SCLC, 2) concomitant medications that included treatment with phenobarbitone and midazolam, 3) underlying diabetes mellitus for which the patient had insulin/oral hypoglycemic treatment, and 4) possible central nervous system infection.

Overall, toxicities related to the chemotherapy core regimen and to durvalumab and tremelimumab were as expected for these agents. In general, the combination of durvalumab + tremelimumab with chemotherapy appears tolerable and manageable.

External clinical data also support these findings. In a randomized Phase III study in patients with extensive-stage SCLC treated with etoposide-platinum ± ipilimumab, the overall incidence of treatment-related Grade 3/4 AEs was 48% for chemotherapy plus ipilimumab and 44% for chemotherapy plus placebo. The most common irAEs in patients treated with chemotherapy plus ipilimumab involved skin (rash and pruritus) and gastrointestinal tract (diarrhea) (Reck et al 2014). In the CheckMate 012 study, in patients with NSCLC treated with nivolumab 10 mg/kg or 5 mg/kg plus platinum-based doublet chemotherapy concurrently q3w for 4 cycles, the overall incidences of treatment-related Grade 3/4 AEs were 50% and 29%, respectively. Overall, the most common (≥5% of patients) treatment-related Grade 3/4 AEs were pneumonitis (7%), fatigue (5%), and acute renal failure (5%) (Rizvi et al 2016). In KEYNOTE-021, in patients with NSCLC treated with pembrolizumab and chemotherapy or chemotherapy alone, the incidence of treatment-related Grade 3 or worse AEs was 39% and 26%, respectively. In the pembrolizumab plus chemotherapy group, the most common treatment-related Grade 3 or worse AEs were anemia (12%); decreased neutrophil count (5%); and acute kidney injury, decreased lymphocyte count, fatigue, neutropenia, sepsis, and thrombocytopenia (3% each). In the chemotherapy alone group, the most common treatment-related Grade 3 or worse AEs were anemia (15%) and decreased neutrophil count, pancytopenia, and thrombocytopenia (3% each). There were 3 treatment-related deaths,

2 deaths due to sepsis (1 patient in each treatment arm) and 1 death due to pancytopenia in a patient in the chemotherapy alone group (Langer et al 2016).

1.3.3 Overall benefit-risk assessment

Platinum-based chemotherapies have been considered the standard treatment regimens for NSCLC for the past 2 decades; however, OS remains poor with a 5-year survival rate between 11% and 17% (D'Addario et al 2010, Howlander et al 2014). Patients presenting with advanced NSCLC have a median OS of 10 to 12 months (Bonomi 2010), and patients without targetable mutations (EGFR and ALK) show responses to treatment of approximately 20% to 30% and PFS of 4 to 5 months (Sandler et al 2006, Scagliotti et al 2008, Schiller et al 2002). The poor prognosis reflects the limited treatment options available, highlighting the need for the development of newer therapeutic options.

There remains a significant unmet medical need for additional treatment options for patients with metastatic NSCLC, irrespective of PD-L1 status, whose tumors lack activating EGFR mutations and ALK fusions and who have not received prior chemotherapy or any systemic therapy for metastatic NSCLC.

Treatment with durvalumab and/or tremelimumab has shown activity in several tumor types in a subset of patients deriving meaningful and durable benefit. Efficacy data for patients treated with durvalumab monotherapy have shown clinical activity across several tumor types. Preliminary data generated from patients with NSCLC treated with durvalumab + tremelimumab combination therapy have also shown early signs of clinical activity, and data from the literature indicate that the combination may act synergistically (Wolchok et al 2013). Thus, these agents may potentially offer benefit to this patient population. Also as presented in Section 1.1.5.1, the studies evaluating agents targeting PD-L1 or CTLA-4 in combination with chemotherapy have yielded encouraging efficacy data, with a seemingly tolerable toxicity profile.

The study design also aims to minimize potential risks. For example, intensive monitoring, including early safety assessment, is in place for those risks deemed to be most likely based on prior experience with the IPs (ie, durvalumab + tremelimumab combination therapy, durvalumab monotherapy) and SoC.

Therefore, the rationale for this study is supported by the available non-clinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, the activity seen with durvalumab alone and in combination with tremelimumab in a number of tumor types, the preliminary data on the efficacy and tolerability of the combination of PD-L1 or CTLA-4 with chemotherapy, and the strength of the scientific hypotheses evaluating the safety and tolerability of adding durvalumab and tremelimumab to first-line standard platinum-based chemotherapy for the treatment of NSCLC.

Based on these considerations, the proposed treatments may have the potential to provide meaningful clinical benefit by generating durable clinical responses, thereby potentially extending survival. Therefore, the overall benefit-risk assessment supports the proposed study

to evaluate the safety and tolerability of the combination of durvalumab and tremelimumab with standard platinum-based chemotherapy regimens.

1.4 Study design

This is a randomized, open-label, multi-center, global, Phase III study to determine the efficacy and safety of durvalumab + tremelimumab combination therapy + SoC chemotherapy or durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone as first-line treatment in patients with metastatic NSCLC with tumors that lack activating EGFR mutations and ALK fusions. A schematic diagram of the overall study design is presented in Figure 3, and a detailed study flow chart is presented in Figure 4. SoC chemotherapy will be one of the following regimens: abraxane + carboplatin, pemetrexed + cisplatin or carboplatin, or gemcitabine + cisplatin or carboplatin.

This study will randomize approximately 1000 eligible patients at sites worldwide. Once global enrollment is complete, enrollment may continue in mainland China only. A total of up to 180 patients, including up to 135 patients in total with PD-L1 TC <50%, from China will be randomized.

Patients who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1:1 ratio in a stratified manner according to the following:

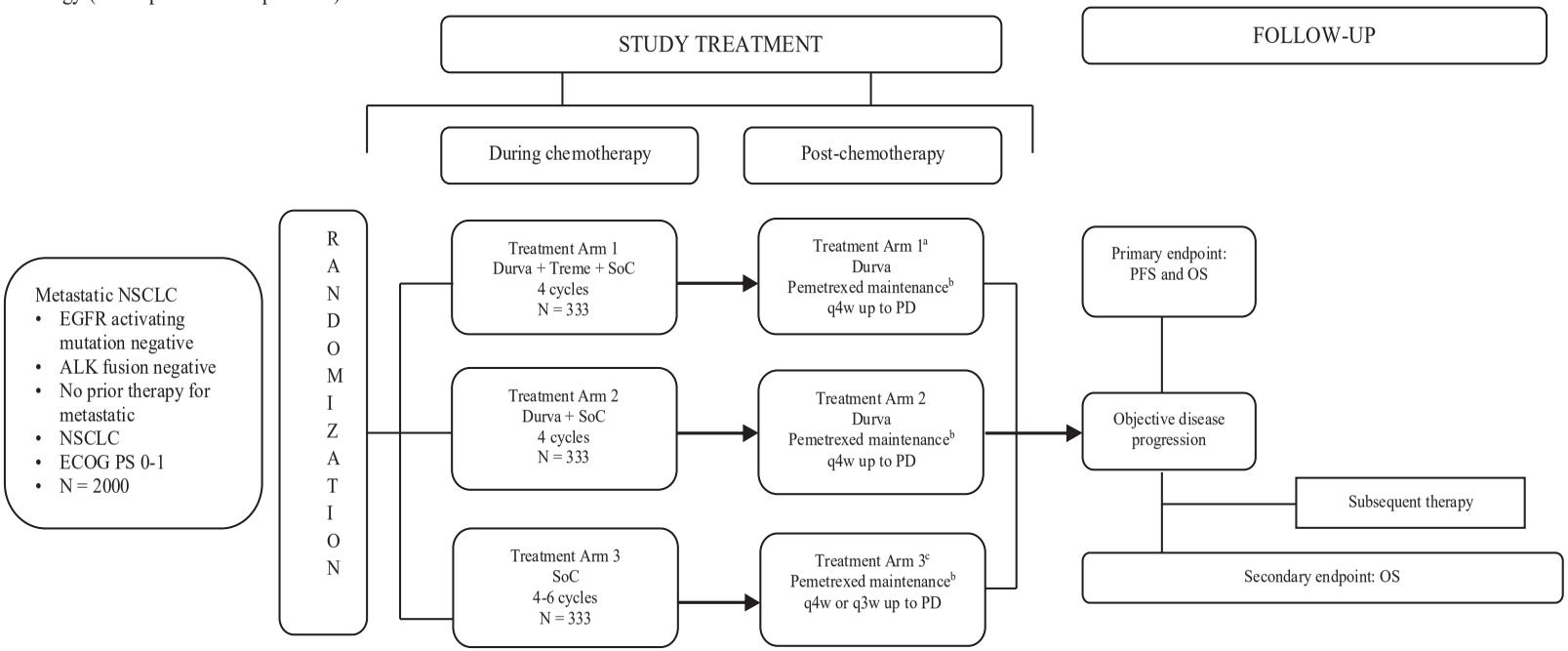
- PD-L1 tumor expression status (PD-L1 expression on at least 50% of tumor cells [PD-L1 TC ≥50%] versus PD-L1 TC <50%)
- Disease stage (Stage IVA versus Stage IVB)
- Histology (non-squamous versus squamous)

Crossover will not be permitted as part of this study. Study treatment doses and regimens are described in Section 7.2. Assessments will be conducted as indicated in Table 2 and Table 3.

Tumor evaluation scans will be performed at screening (as baseline) with follow-ups at Week 6±1 week from the date of randomization, at Week 12±1 week from the date of randomization, and then every 8 weeks (q8w)±1 week until radiological progression. The management of patients will be based solely upon the results of the tumor evaluation scans conducted by the Investigator. The BICR of all radiologic scans will be performed to derive the PFS, ORR, DoR, BoR, and APF12 endpoints according to RECIST 1.1.

Figure 3 Overall study design

Stratified randomization factors:
1. PD-L1 tumor expression status (TC ≥50% versus <50%)
2. Disease stage (Stage IVA versus Stage IVB)
3. Histology (non-squamous or squamous)



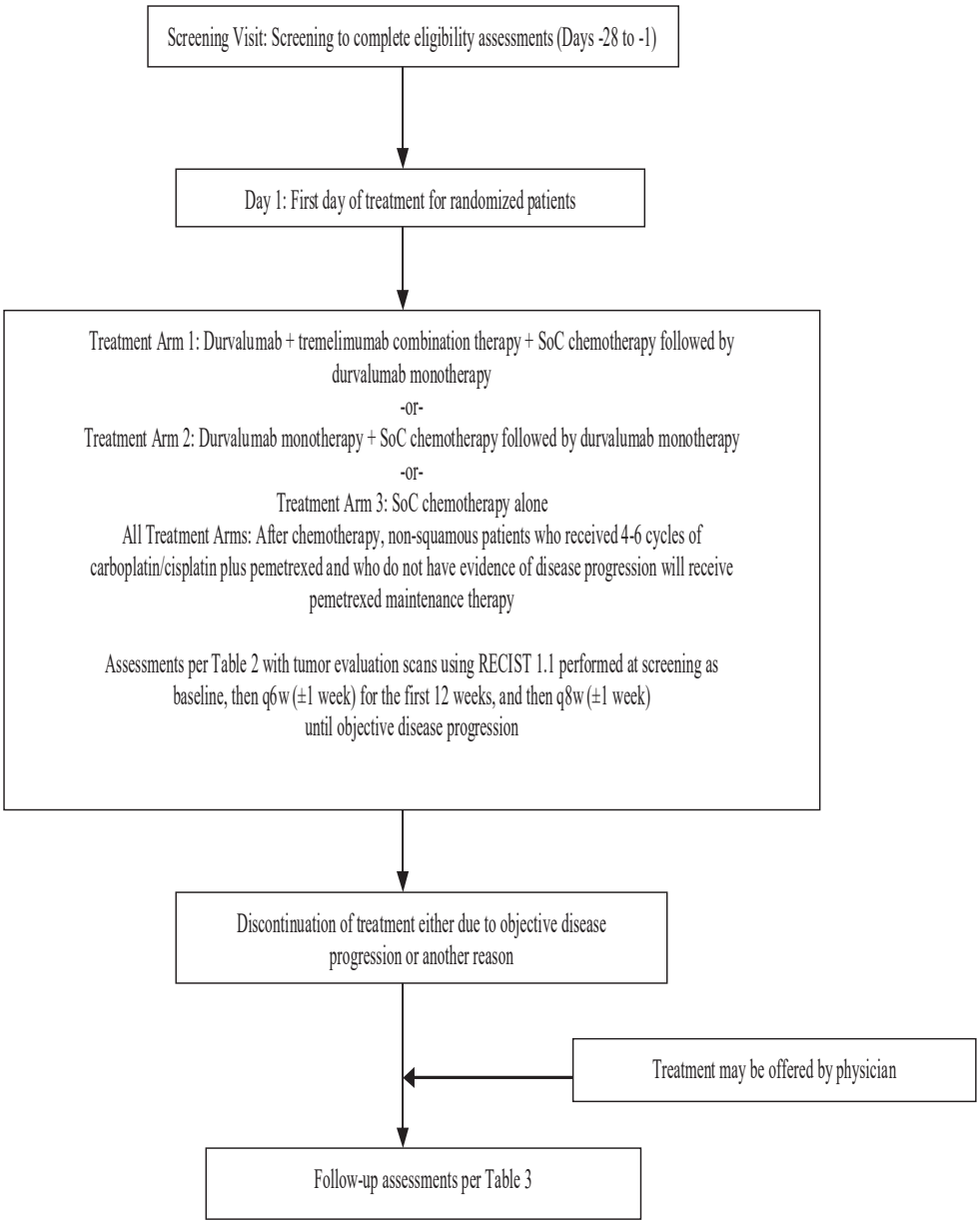
[a] One additional durvalumab + tremelimumab combination therapy dose will be given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose can be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses are administered in Treatment Arm 1. If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) should be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed, if applicable) (see Section 7.2).

[b] Pemetrexed maintenance therapy from Week 12 to clinical progression or radiological progression for non-squamous NSCLC patients who initially received treatment with pemetrexed and carboplatin/cisplatin, unless contraindicated per the Investigator.

[c] SoC chemotherapy will be given q3w up to 4 doses; extension into Weeks 12 and 15 is as clinically indicated, at the Investigator's discretion.

Durva Durvalumab; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; NSCLC Non-small-cell lung cancer; OS Overall survival; PD Progressive disease; PFS Progression-free survival; q4w Every 4 weeks; q3w - Every 3 weeks; SoC Standard of care; TC Tumor cell; Treme Tremelimumab.

Figure 4 Study flow chart



q6w - Every 6 weeks; q8w - Every 8 weeks; RECIST 1.1 - Response Evaluation Criteria in Solid Tumors, Version 1.1; SoC -Standard of care.

1.4.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with GCP, and minimise risks to study integrity. Where allowable by local health authorities, ethics committees, health care provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the informed consent form [ICF] should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study clinical lead.
- Home or Remote visit: Performed by a site qualified health care professional (HCP) or HCP provided by a third-party vendor (TPV).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix G.

1.5 Study aim

This is a Phase III, randomized, open-label, comparative, multi-center, global study that aims to determine the efficacy and safety of durvalumab + tremelimumab combination therapy + SoC chemotherapy versus SoC chemotherapy alone and to assess the efficacy of durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone as first-line treatment in patients with metastatic NSCLC with tumors that lack activating EGFR mutations or ALK fusions.

1.6 Study governance and oversight

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

1.6.1 Safety confirmation

An IDMC composed of independent experts will be convened to confirm the safety and tolerability of the proposed dose and schedule of durvalumab ± tremelimumab in combination with SoC chemotherapy at 2 early stages of enrollment. A step-wise approach will be adopted. The initial safety review will take place when the first 30 patients (10 in each arm) have completed the first cycle of treatment. A second review will add an additional 30 patients (10 in each arm) who have completed the first cycle of treatment, making a total of 60 patients. At the time of the second review, it is expected that the initial 30 patients would have had at least 6 weeks of follow-up, with some patients having longer follow-up. These 2 reviews will be carried out by the IDMC in an unblinded manner. After a review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment.

Safety confirmation for Japan: An additional safety review for Japanese patients will take place when the first 3 patients in each treatment arm in Japan have completed the first cycle of treatment. This review will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment in Japan.

Safety confirmation for China: An additional safety review for Chinese patients will take place when the first 10 patients in each treatment arm in China have completed the first cycle of treatment. This review will be carried out by the IDMC in an unblinded manner. After review of the unblinded data, the IDMC will make a recommendation on whether the study should continue recruitment as planned or hold recruitment in China.

In addition, the IDMC will review the unblinded interim analysis summaries of efficacy data. The IDMC meets approximately every 6 months thereafter to continue safety monitoring up to the decision to unblind the study.

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

2. STUDY OBJECTIVES

All objectives will be evaluated for all patients, unless otherwise indicated.

2.1 Primary objectives

Primary objectives	Outcome measure
• To assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients	• PFS in all patients using BICR assessments according to RECIST 1.1 • OS in all patients

Note: Sensitivity analyses of PFS will be performed based on the Investigator's assessment according to RECIST 1.1.

BICR Blinded Independent Central Review; NSCLC Non-small-cell lung cancer; PFS Progression-free survival; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1; SoC Standard of care.

2.2 Secondary objectives

Secondary objectives	Outcome measures
• To assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS	• PFS in all patients using BICR assessments according to RECIST 1.1 (key secondary objective) • OS in all patients (key secondary objective)
• To further assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, BoR, DoR, APF12 and PFS2	• PFS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% • ORR, DoR, BoR and APF12 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • PFS2 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using local standard clinical practice

Secondary objectives	Outcome measures
• To further assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, DoR, BoR, APF12 and PFS2	• PFS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25% and patients with PD-L1 TC <1% • ORR, DoR, BoR and APF12 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • PFS2 in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using local standard clinical practice
• To assess the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with durvalumab monotherapy + SoC chemotherapy in terms of PFS, OS and ORR	• PFS and ORR in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients using BICR assessments according to RECIST 1.1 • OS in patients with PD-L1 TC <50%, patients with PD-L1 TC <25%, patients with PD-L1 TC <1% and all patients
• To assess the association of tumor mutation burden (TMB) with the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS, OS, ORR, BoR, DoR, APF12 and PFS2	• PFS, ORR, BoR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the association of TMB with the efficacy of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with durvalumab monotherapy + SoC chemotherapy in terms of PFS, OS, ORR, BoR, DoR, APF12 and PFS2	• PFS, ORR, BoR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high
• To assess the association of TMB with the efficacy of durvalumab mono therapy + SoC chemotherapy compared with SoC chemotherapy in terms of PFS, OS, ORR, BoR, DoR, APF12 and PFS2	• PFS, ORR, BOR, DoR, APF12 in patients with TMB high using BICR assessments according to RECIST 1.1 • PFS2 in patients with TMB high using local standard clinical practice • OS in patients with TMB high

Secondary objectives	Outcome measures
• To assess the PK of durvalumab + tremelimumab combination therapy and durvalumab monotherapy	• Concentration of durvalumab and tremelimumab
• To investigate the immunogenicity of durvalumab and tremelimumab	• Presence of ADAs for durvalumab and tremelimumab
• To assess disease-related symptoms and HRQoL in patients treated with durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone using the EORTC QLQ-C30 v3, the QLQ-LC13 module, and WHO/ECOG performance status assessments	• EORTC QLQ-C30 • EORTC QLQ-LC13 • Changes in WHO/ECOG performance status will also be assessed.

ADA Anti-drug antibody; APF12 Proportion of patients alive and progression free at 12 months from randomization; BICR Blinded Independent Central Review; BoR Best objective response; DoR Duration of response; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; HRQoL Health-related quality of life; NSCLC Non-small-cell lung cancer; ORR Objective response rate; OS Overall survival; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PFS2 Time from randomization to second progression; PK Pharmacokinetic(s); QLQ-C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, Version 1.1; SoC Standard of care; TC Tumor cell; Definition of TMB High in tissue and/or ctDNA to be documented in the SAP ahead of DBL with data external to Poseidon; WHO World Health Organization.

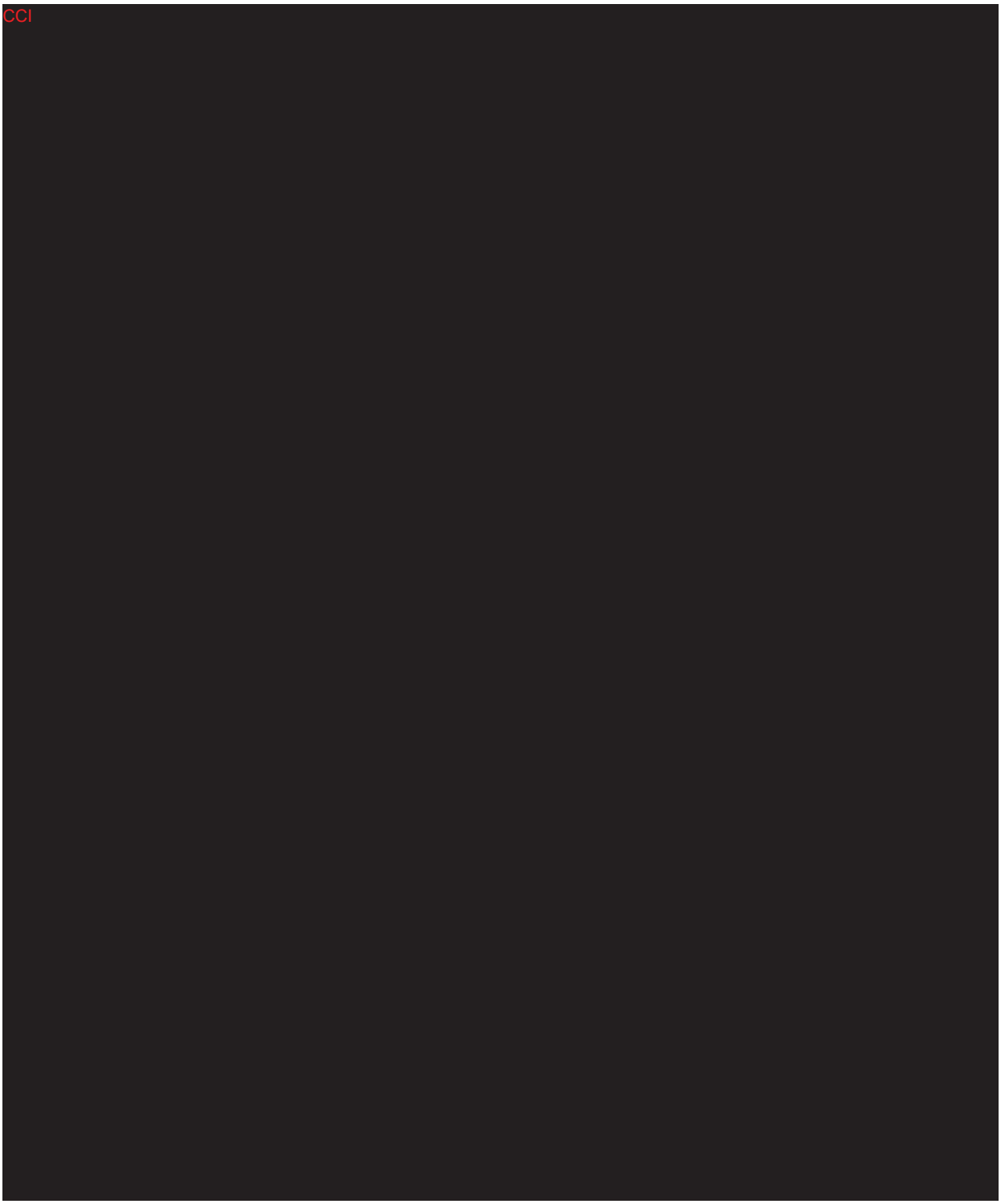
2.3 Safety objectives

Safety objective	Outcome measure
• To assess the safety and tolerability profile of durvalumab + tremelimumab combination therapy + SoC chemotherapy and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone	• AEs, physical examinations, laboratory findings, and vital signs

AE Adverse event; SoC Standard of care.

2.4 Exploratory objectives

CCI


CCI

CCI

A further objective to meet China FDA (CFDA) requirement is to evaluate consistency in efficacy and safety among patients in China for benefit-risk assessments of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy alone and durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone.

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 will 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. In Japan, patients must be ≥20 years at the time of screening.
2. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations. For patients aged <20 years and enrolling in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.
3. Histologically or cytologically documented Stage IV NSCLC not amenable to curative surgery or radiation (according to Version 8 of the IASLC Staging Manual in Thoracic Oncology 2016).
4. Patients must have tumors that lack activating EGFR mutations (eg, exon 19 deletion or exon 21 L858R, exon 21 L861Q, exon 18 G719X, or exon 20 S768I mutation) and ALK fusions. If a patient has squamous histology or is known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required.
5. No prior chemotherapy or any other systemic therapy for metastatic NSCLC. Patients who have received prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation for advanced disease are eligible, provided that progression has occurred >12 months from end of last therapy (see exclusion criterion 7).
6. Tumor PD-L1 status, confirmed by a reference laboratory using the Ventana SP263 PD-L1 immunohistochemistry (IHC) assay, 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 enrollment. Tumor lesions used for newly acquired biopsies during screening period should not be the same lesions used as RECIST 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 biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2

weeks before imaging scans are acquired. 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 eligibility should be of sufficient quantity to allow for PD-L1 IHC, TMB and other CCI analyses (also see Section 5.5.2) and is preferred in formalin-fixed paraffin-embedded blocks.

7. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at enrollment and randomization.

8. Life expectancy ≥12 weeks at randomization (Day 1).

9. Body weight >30 kg

10. 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 CT or MRI and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.

11. No prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines.

12. Adequate organ and marrow function as defined below:

- Hemoglobin ≥9.0 g/dL without transfusion 4 weeks prior to the screening and randomization
- Absolute neutrophil count ≥1.5 × 109/L
- Platelet count ≥100 × 109/L
- Serum bilirubin ≤1.5 × ULN. This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician
- ALT and AST ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN
- Calculated creatinine clearance (CL) ≥40 mL/min as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine collection
- For patients **receiving cisplatin**: CL **≥50** mL/min as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine collection

Males:

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

Females:

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

13. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

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

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 staff and/or staff at the study site).
2. Previous IP assignment in the present study.
3. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.
4. Participation in another clinical study with an IP during the last 12 months.
5. Mixed small-cell lung cancer and NSCLC histology, sarcomatoid variant.
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.
7. No radiation therapy is allowed, unless it is 1) definitive radiation that had been administered at least 12 months prior, 2) palliative radiation to brain, with associated criteria for stability or lack of symptoms (see also exclusion criterion 16), or 3) palliative radiation to painful bony lesions (this must comprise less than 30% of the bone marrow).
8. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of the IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
9. History of allogeneic organ transplantation.

10. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with celiac disease controlled by diet alone
11. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, ILD, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, that substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
12. Medical contraindication to platinum-based doublet chemotherapy.
13. History of another primary malignancy except for
    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of the IP and of low potential risk for recurrence
    - Adequately treated nonmelanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)
14. History of leptomeningeal carcinomatosis.
15. Spinal cord compression.
16. Brain metastases. Patients with suspected brain metastases at screening should have an intravenous (IV) contrast-enhanced MRI (preferred) or IV contrast-enhanced CT of the brain prior to study entry. If brain metastases are detected patients must be treated before randomization. Randomization is only permitted if patients with brain metastases have:

- Confirmed stable condition 4 weeks after the intervention using imaging
- Returned neurologically to baseline
- Completed associated steroids at least 5 days prior to randomization

Brain metastases will not be recorded as RECIST Target Lesions at baseline.

17. History of active primary immunodeficiency.
18. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
19. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
    - Intra-nasal, 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, cytotoxic chemotherapy premedication)
20. Receipt of live, attenuated vaccine within 30 days prior to the first dose of the IP. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of the IP.
21. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. Also see Section 3.8.
22. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
23. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.
24. Judgment by the Investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions, and requirements.

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 (Days -28 to -1), the Investigators or the suitably trained delegate will do the following:

- Obtain signed informed consent from the potential patient before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all imaging results must have been obtained within 28 days of randomization (Appendix E). For patients with a single TL, if screening biopsy is collected prior to the screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired. (Informed consent of study procedures may be obtained prior to the 28-day screening window to permit tumor biopsy sample acquisition, which must be analyzed prior to randomization.)
- Obtain a unique PPD enrollment number (E-code) through the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) in the following format: PPD This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).
- Obtain tumor sample and send for centralized PD-L1 testing. Obtaining the tumor biopsy sample should be given the highest priority, and as such, the sample may be obtained and sent for PD-L1 expression status evaluation prior to the 28-day screening window (after obtaining signed informed consent) to permit analysis prior to randomization. See Section 5.5.1 for details on tumor samples.

  The sample for centralized PD-L1 testing should be sent only for patients with known EGFR and ALK status. **If a patient has squamous histology or is known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required.** If EGFR and ALK status is unknown, then the tumor sample (archive or fresh, primary or metastatic) should be used first for local EGFR mutation and ALK fusion testing or, if not feasible, be sent directly to be EGFR/ALK tested centrally concomitantly with PD-L1, in accordance with inclusion criterion 4.

  Tumor samples will be used to determine PD-L1 expression status (defined by the Ventana SP263 PD-L1 IHC assay) in which:

  – ≥50% of TC with membrane staining for PD-L1 at any intensity (PD-L1 TC ≥50%)

  – <50% of TC with membrane staining for PD-L1 at any intensity (PD-L1 TC <50%)

- Determine patient eligibility (see Sections 3.1 and 3.2).
- CCI [redacted]

At randomization, eligibility criteria will be confirmed on Cycle 1 Day 1, prior to the first dose of IP. At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will do the following:

1. Define the SoC treatment (based on the most appropriate option for the patient) that the patient will receive. This must be completed for all patients. The information will be recorded in the IVRS/IWRS system.

   Note: For all patients with non-squamous tumor histology scheduled to receive pemetrexed, folic acid and vitamin B12 should commence prior to randomization for up to 7 days, in line with local practice. This is to ensure treatment can begin on Day 1.

2. Obtain a unique randomization number via the IVRS/IWRS. Numbers will start at 001 and 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 (PD-L1 expression status results must be received from the central laboratory by the IVRS/IWRS prior to randomization).

Patients will be randomized in a 1:1:1 ratio in a stratified manner according to the following:

- PD-L1 tumor expression status (PD-L1 TC ≥50% versus PD-L1 TC <50%)
- Disease stage (Stage IVA versus Stage IVB)
- Histology (non-squamous versus squamous)

If the patient is ineligible and not randomized, the IVRS/IWRS status should be changed to screen failure.

Patients will begin treatment on Cycle 1 Day 1. Treatment should start no more than 3 working days after being randomized. Patients must not be randomized and treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrollment/randomization code 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 randomized or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but found to not meet all the eligibility criteria must not be randomized and must not be initiated on treatment and must be withdrawn from the study as a screen failure.

When a patient does not meet all the eligibility criteria but is randomized in error or incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and the Study Physician and the Investigator should discuss whether to continue or discontinue the patient from treatment. The Study Physician must ensure that all decisions are appropriately documented. In situations where an agreement cannot be reached, the patient should have their study therapy stopped and be withdrawn from the study.

3.5 Methods for assigning treatment arms

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 stratum. A blocked randomization will be generated, and all centers will use the same list to minimize any imbalance in the number of patients assigned to each treatment arm.

Patients will be identified to the IVRS/IWRS per country regulations. Randomization codes will be assigned strictly sequentially, within each stratum, as patients become eligible for randomization. The IVRS/IWRS will provide the kit identification number to be allocated to the patient at the randomization visit and subsequent treatment dispensing visits.

3.6 Methods for ensuring blinding (Not applicable)

Not applicable; this study is not blinded.

3.7 Methods for unblinding (Not applicable)

Not applicable; this study is not blinded.

3.8 Restrictions

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

1. Female patient of childbearing potential
   - Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 1) from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). Nonsterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods

of birth control. Female patients should also refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

   – Nonsterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

   – Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1).

Note 1: Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Note 2: For male patients receving gemcitabine SoC chemotherapy, in addition to referring to the current local prescribing information, cryopreservation of male sperm should be considered due to the risk of infertility.

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

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

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

All patients: Follow the local prescribing information relating to contraception, the time limits for such precautions (6 months following discontinuation of SoC treatment), and any additional restrictions for agents in the SoC group.

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

Barrier/Intra-uterine methods	Hormonal methods
• Copper T intra-uterine device • Levonorgesterel-releasing intra-uterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplan®) [b] • Intra-vaginal devices: Ethinylestradiol/etonogestrel-releasing intra-vaginal devices (eg, NuvaRing®) [b] • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) [b] • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) [b] • Minipill: Progesterone-based oral contraceptive pill using desogestrel (Cerazette® is currently the only highly effective progesterone-based pill) [b]

[a] This is also considered a hormonal method.
[b] Not approved in Japan.

3. **All patients:** Patients should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.
4. Restrictions relating to concomitant medications are described in Section 7.7.

3.9 Discontinuation of IP

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

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

- An AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (please see Section 6.9.1) or as defined in the local prescribing information for the SoC agent.
- Pregnancy or intent to become pregnant.
- Noncompliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy including another investigational agent.
- Treatment Arms 1 and 2: Clinical progression, i.e. Investigator determination that the patient is no longer benefiting from treatment with IP, or radiological progressive disease (PD) based on RECIST 1.1 criteria and Investigator determination that the patient is no longer benefiting from treatment with the IP.
- Treatment Arm 3: Clinical progression, i.e. Investigator determination that the patient is no longer benefiting from treatment with IP, or RECIST 1.1 defined radiological progression.

For patients in Treatment Arms 1 and 2, when SoC chemotherapy is discontinued due to treatment-related toxicity, durvalumab monotherapy or durvalumab + tremelimumab may continue at the Investigator's discretion when toxicity resolves to at least Grade 2 or less. Note: if the Investigator feels that a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

3.9.1 Procedures for discontinuation of patient from IP

At any time, patients are free to discontinue IP without prejudice to further treatment. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, they will be seen and assessed by an Investigator(s). AEs will be followed up (see Section 6).

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 the follow-up period (see Table 3).

Patients who permanently discontinue drug for reasons other than objective disease progression should continue to have RECIST scans performed at Week 6±1 week from the date of randomization, Week 12±1 week from the date of randomization, and then q8w±1 week thereafter until RECIST 1.1 defined radiological progression plus an additional subsequent scan or death (whichever comes first) as defined in Table 3.

All patients will be followed for survival until the end of the study. This follow-up must be performed even if the patient begins another therapy to treat their NSCLC.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in Table 3 as an alternative.

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

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

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/meets exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients may be rescreened a single time, but they cannot be re-randomized. Patients may **not** be rescreened after enrollment to the study has closed.

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 their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow-up AEs outside of the clinical study.

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

- All further participation in the study including any further follow-up (eg, survival contact telephone calls).
- Withdrawal to the use of any samples (see Section 5.5.6).

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

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 9.3), such that there is insufficient information to determine the patients' status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key endpoints 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. (The applicable eCRF modules will be updated.)
- Withdrawal of consent: 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 resources where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable eCRF 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 1.6).

Regardless of the reason for termination, all data available for the patients at the time of discontinuation of 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 durvalumab 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 study treatment periods in this study are presented in Table 2, and the procedures for the follow-up period are presented in Table 3.

The following are the definitions of the study treatment regimens in each treatment arm:

- Treatment Arm 1: durvalumab + tremelimumab combination therapy + SoC chemotherapy
- Treatment Arm 2: durvalumab monotherapy + SoC chemotherapy

- Treatment Arm 3: SoC chemotherapy alone

The study treatment period of this study includes the following 2 phases (Table 2):

- 'During chemotherapy': during which patients receive durvalumab ± tremelimumab + SoC chemotherapy or SoC chemotherapy alone
- 'Post-chemotherapy': during which patients in Treatment Arms 1 and 2 receive durvalumab monotherapy, and non-squamous patients in all treatment arms who received pemetrexed + carboplatin/cisplatin in the 'during chemotherapy' phase and who have not progressed after 4 to 6 cycles will receive pemetrexed maintenance therapy, unless contraindicated per the Investigator.

Patients who continue study treatment beyond Week 20 will continue with all Week 20 assessments defined in Table 2 until discontinuation of study treatment. Patients who discontinue study treatment will follow assessments as defined in Table 3. All patients must follow the tumor evaluation scan schedule, which is at screening (as baseline), Week 6±1 week from the date of randomization, Week 12±1 week from the date of randomization, and q8w±1 week, thereafter, until RECIST 1.1 defined radiological progression plus an additional subsequent scan or until death, for those patients who discontinue study treatment for reasons other than objective disease progression. Follow-up visits for tumor evaluation scans should be planned to align to this schedule where possible.

For all treatment arms

PRO and tumor efficacy (RECIST) assessment dates will not be affected by dose delays since they will be based on the date of randomization (not the date of therapy); hence, the assessment dates will remain as originally scheduled.

All other scheduled assessments must be performed relative to the start of the dosing cycle, such that all laboratory procedures required for dosing should be performed within 3 days prior to dosing.

For durvalumab + tremelimumab combination arms or durvalumab monotherapy (Treatment Arms 1 and 2)

- 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 (during chemotherapy, the interval is 21 days and during post-chemotherapy, the interval is 28 days) may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) and PRO assessments. For subsequent cycles the time between 2 consecutive doses cannot be less than

21 days, based on the half-lives of durvalumab and tremelimumab (see current Investigator's Brochures for durvalumab and tremelimumab). If there is a dosing delay while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days.

For standard of care therapy arm (Treatment Arm 3)

- 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 2 Study treatment and retreatment periods: Schedule of assessments for Treatment Arms 1, 2, and 3

	Screening	During chemotherapy 1 cycle = 3 weeks (21 days)								Post-chemotherapy 1 cycle = 4 weeks (28 days)			For details, see Section
		C1/ D1	C1/ D8	C2/ D1	C2/ D8	C3/ D1	C3/ D8	C4/ D1	C4/ D8	C5	C6	C7 to PD (q4w)	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20 to PD**	
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days)*	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±3**	**±3**	
Informed consent	X												3.3, 4.1, 10.4
CCI	X												Appendix C
Study procedures													
Full physical examination	X												5.2.2
Targeted physical examination		X	X	X	X	X	X	X	X	X	X	X	5.2.2
Vital signs[b]	X	X	X	X	X	X	X	X	X	X	X	X	5.2.4
12-lead ECG[c]	X	As clinically indicated											5.2.3
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	7.7
Demography	X												4.1
Eligibility criteria	X	X											3.1, 3.2
Medical/ surgical history	X												
Laboratory assessments													
Clinical chemistry[d]	X	X[e]	X	X	X	X	X	X	X	X	X	X	5.2.1
Hematology[d]	X	X[e]	X	X	X	X	X	X	X	X	X	X	5.2.1
APTT and INR[d]	X	As clinically indicated											5.2.1
TSH, free T_3, and free T_4[d,f]	X	X[e]		X		X		X		X	X	X	5.2.1
Urinalysis	X	X[e]	X	X	X	X	X	X	X	X	X	X	5.2.1
TB (in line with local standards), Hepatitis B, Hepatitis C, and HIV	X												5.2.1
Pregnancy test[g]	X	X[e]		X		X		X		X	X	X	5.2.1

Table 2 Study treatment and retreatment periods: Schedule of assessments for Treatment Arms 1, 2, and 3

	Screening	During chemotherapy 1 cycle = 3 weeks (21 days)								Post-chemotherapy 1 cycle = 4 weeks (28 days)			For details, see Section
		C1/ D1	C1/ D8	C2/ D1	C2/ D8	C3/ D1	C3/ D8	C4/ D1	C4/ D8	C5	C6	C7 to PD (q4w)	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20 to PD**	
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days)*	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±3**	**±3**	
Efficacy assessments													
Tumor evaluation (CT or MRI) (RECIST 1.1)[h]	X[i]					X				X		X[j]	5.1
PK assessments													
Durvalumab PK sample (serum; Treatment Arms 1 and 2 only)		X[k]		X[l]						X[l]			5.4.1
Tremelimumab PK sample (serum; Treatment Arm 1 only)		X[k]		X[l]						X[l]		X (3 months after tremelimumab discontinuation)[m]	5.4.1
Abraxane PK sample (plasma; selected sites only)		X[n]											5.4.1
Gemcitabine PK sample (plasma; selected sites only)		X[n]											5.4.1
Safety monitoring													
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	5.2.6
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	6.3.1
Drug accountability		X		X		X		X		X	X	X	7.6
Pre-randomization medication													
Folic acid/ Vitamin B12[o]	X	Continue in line with local practice											3.3

Table 2 Study treatment and retreatment periods: Schedule of assessments for Treatment Arms 1, 2, and 3

	Screening	During chemotherapy 1 cycle = 3 weeks (21 days)								Post-chemotherapy 1 cycle = 4 weeks (28 days)			For details, see Section
		C1/ D1	C1/ D8	C2/ D1	C2/ D8	C3/ D1	C3/ D8	C4/ D1	C4/ D8	C5	C6	C7 to PD (q4w)	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20 to PD**	
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days)*	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±3**	**±3**	
IP administration (Interval between 2 consecutive doses must be at least 21 days)													
Treatment Arm 1: durvalumab + tremelimumab combination therapy + SoC chemotherapy													
Durvalumab[d,p]		X		X		X		X		X	X	X[q]	7.2.1
Tremelimumab[d,p]		X		X		X		X			X[dd]		7.2.1
Abraxane[r,s]		X	X	X	X	X	X	X	X				7.2.1
Gemcitabine[r]		X	X	X	X	X	X	X	X				7.2.1
Pemetrexed[r,t]		X		X		X		X		X[t]	X[t]	X[t]	7.2.1
Carboplatin or cisplatin[r,u]		X		X		X		X					7.2.1
Treatment Arm 2: durvalumab monotherapy + SoC chemotherapy													
Durvalumab[d,p]		X		X		X		X		X	X	X[q]	7.2.1
Abraxane[r,s]		X	X	X	X	X	X	X	X				7.2.1
Gemcitabine[r]		X	X	X	X	X	X	X	X				7.2.1
Pemetrexed[r,t]		X		X		X		X		X[t]	X[t]	X[t]	7.2.1
Carboplatin or cisplatin[r,u]		X		X		X		X					7.2.1
Treatment Arm 3: SoC chemotherapy alone													
Abraxane[r,s,v]		X	X	X	X	X	X	X	X				7.2.1
Gemcitabine[r,v]		X	X	X	X	X	X	X	X				7.2.1
Pemetrexed[r,t,v]		X		X		X		X		X[t]	X[t]	X[t]	7.2.1
Carboplatin or cisplatin[r,u,v]		X		X		X		X					7.2.1

Table 2 Study treatment and retreatment periods: Schedule of assessments for Treatment Arms 1, 2, and 3

	Screening	During chemotherapy 1 cycle = 3 weeks (21 days)								Post-chemotherapy 1 cycle = 4 weeks (28 days)			For details, see Section
		C1/ D1	C1/ D8	C2/ D1	C2/ D8	C3/ D1	C3/ D8	C4/ D1	C4/ D8	C5	C6	C7 to PD (q4w)	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20 to PD**	
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				
Window (days)*	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±3**	**±3**	
PRO assessments													
EORTC QLQ-C30 v3, EORTC QLQ-LC13, CCI , and CCI	X	X		X		X		X		X	X	X	5.3.1.1, 5.3.1.2, 5.3.1.3, 5.3.1.5
CCI				X		X		X		X	X	X	5.3.1.4
Other laboratory assessments and assays													
Immunogenicity assessment (ADA sampling)[z]		X[l]		X[l]						X[l]		X (3 months after tremelimumab discontinuation)[l,aa]	5.4.1.1
Tumor biopsy (newly acquired or archived <3 months old)	X												5.5.1
Archival tumor sample ≥3 months old, where available	X												5.5.1
CCI		X											Appendix C
CCI		X[l]		X		X							5.5.2
EGFR and ALK test[cc]	X[cc]												3.3
PD-L1 test	X												5.5.1
CCI		X											5.5.2
		X		X									5.5.2

Table 2 Study treatment and retreatment periods: Schedule of assessments for Treatment Arms 1, 2, and 3

	Screening	During chemotherapy 1 cycle = 3 weeks (21 days)								Post-chemotherapy 1 cycle = 4 weeks (28 days)			
		C1/ D1	C1/ D8	C2/ D1	C2/ D8	C3/ D1	C3/ D8	C4/ D1	C4/ D8	C5	C6	C7 to PD (q4w)	
Week		**0**	**1**	**3**	**4**	**6**	**7**	**9**	**10**	**12**	**16**	**20 to PD**	
Day	**-28 to -1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**				**For details, see Section**
Window (days)*	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±3**	**±3**	
CCI [redacted]													
CCI [redacted]	X		X	X		X		X		X	X	X	5.3.3

Note: **All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated. Every effort should be made to minimize the time between randomization and starting treatment. (i.e. within one day after randomization)**

Note: **For retreatment, the same assessments should be done as in the first treatment period, with the exception of the hepatitis B, hepatitis C and HIV tests. In addition, PK, ADA, CCI [redacted] EGFR/ALK, PD-L1, and CCI [redacted] which do not need to be collected a second time.**

* **Visit windows:** For durvalumab and tremelimumab treatment schedules: If there is a dosing delay while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days. For SoC: Dosing delays should be managed as per local prescribing guidelines.

a CCI [redacted]

b Body weight will be recorded along with vital signs.

c Any clinically significant cardiovascular findings require confirmation by ECG.

d Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion).

e If screening laboratory assessments are performed within 3 days prior to Day 1 (first infusion day), they 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. If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 1.

f Free T_3 and free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

g Pregnancy test will be performed in women of childbearing potential only. A urine or serum pregnancy test is acceptable.

h Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to and prior to the date of randomization. RECIST 1.1 assessments will be performed on images from CT scans (preferred) or MRI scans, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands). Additional anatomy (e.g., pelvis, brain) should be scanned based on signs and symptoms of individual patients at baseline and during follow-up period. Scheduled on-study scans should be collected within ±1 week of the scheduled imaging visit. For patients who reach a RECIST 1.1-defined PD, a subsequent scan should be performed preferably at the next scheduled imaging visit and no earlier than 4 weeks after the prior assessment of radiological PD and Confirmation of Radiological Progression criteria should be used to evaluate this subsequent scan (please refer to Appendix E). If an unscheduled assessment has been performed and the patient has not reached PD, every attempt should be made to perform the subsequent assessments at his or her next scheduled visit.

i Patients' diagnostic scan may be used as a baseline scan if taken within 28 days of randomization and provides assessment of any radiologic findings that would indicate active infectious processes includinge TB status and, if it is in accordance with the requirements outlined in Appendix E.

j Patients will have tumor evaluation scans performed at Week 6±1 week from the date of randomization, Week 12 ±1 week from the date of randomization, and then q8w±1 week thereafter until radiological progression

k PK sampling should be performed within 10 minutes of the end of infusion.

l Pre-dose samples; should collected within 60 minutes pre-dose (same day of infusion).

m For patients in Treatment Arm 1 only, a sample for tremelimumab PK will be collected 3 months after the last tremelimumab dose. This will be Week 28, assuming the last dose of tremelimumab was at Week 16. If there are dose delays and the last tremelimumab dose was after Week 16, the tremelimumab PK should be collected 3 months after the last tremelimumab dose.

n Abraxane PK sample- collect at end of infusion, 8 hours post-infusion, and 48 hours post-infusion; gemcitabine PK sample- collect at end of infusion, 1 hour post-infusion, 3 hours post-infusion, and 8 hours post-infusion. Window period for PK samples collection is ±5 minutes.

o To be administered in line with local practice for patients with non-squamous tumors who will receive pemetrexed.

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

q In Treatment Arms 1 and 2, durvalumab treatment will be continued until clinical progression or radiological progression. Scenarios for treatment through progression, including with the combination for Treatment Arm 1, are discussed in Section 7.2.2.2.

r The immunotherapy agents will be infused first followed by the SoC chemotherapy regimen.

s Abraxane will be dosed at Days 1 (±3), 8 (±2), and 15 (±2). The Day 15 assessements are similar to Day 8.

t Non-squamous patients who received carboplatin/cisplatin + pemetrexed and who have not progressed after 4 to 6 cycles of carboplatin/cisplatin + pemetrexed will receive pemetrexed maintenance therapy, unless contraindicated per the Investigator. Pemetrexed maintenance therapy can be given q4w for Treatment Arms 1 and 2. For Treatment Arm 3, Pemetrexed maintenance therapy can be given either q3w or q4w dependent on Investigator decision and local standards. **Note:** RECIST 1.1 assessment should be performed at Week 12 ±1 week from the date of randomization, and then q8w±1 week thereafter until radiological progression (regardless of whether it chosen q3w or q4w).

u If cisplatin: infuse over 1 to 2 hours. If carboplatin: infuse over 0.5 to 1 hour.

v For Treatment Arm 3, SoC chemotherapy will be given q3w up to 4 doses; extension into Weeks 12 and 15 is as clinically indicated, at the Investigator's discretion. Note: tumor evaluation at Week 12±1 week and q8w thereafter and PRO collection q4w until objective disease progression are required irrespective of the number of cycles of SoC given.

w For the PRO collection, the research nurse or study coordinator should ensure that the patient completes the questionnaire prior to any other study procedures and before discussion of PD to avoid introducing bias to the patient's responses to the questions. The EORTC QLQ-C30 should always be completed prior to the EORTC QLQ-LC13 module.

x CCI [redacted]

y CCI [redacted]

z ADA for tremelimumab will be assessed for Treatment Arm 1 patients only; ADA for durvalumab will be assessed for Treatment Arms 1 and 2 patients only.

aa A sample to look for antibodies to tremelimumab will be taken 90 days±7 days after last dose of tremelimumab for Treatment Arm 1.

bb CCI [redacted]

cc For patients with unknown status of ALK and/or EGFR NSCLC. If EGFR and ALK status is unknown, then the tumor sample (archive or fresh, primary or metastatic) should be used first for (local or central) EGFR mutation and ALK fusion testing in accordance to inclusion criterion 4. (If patients have squamous histology or are known to have a tumor with a KRAS mutation, then EGFR and ALK testing is not required.)

dd For patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab will be given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose can be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses are administered

in Treatment Arm 1. If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) should be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed, if applicable).

ADA Anti-drug antibody; AE Adverse event; ALK Anaplastic lymphoma kinase; APTT Activated partial thromboplastin time; C Cycle; CT Computed tomography; CCI D Day; CCI ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EGFR Epidermal growth factor receptor; EORTC European Organisation for Research and Treatment of Cancer; CCI HIV Human immunodeficiency virus; CCI INR International normalized ratio; IP Investigational product; CCI IV Intravenous; MRI Magnetic resonance imaging; NA Not available; PD Progressive disease; PD-L1 Programmed cell death ligand 1; CCI PK Pharmacokinetic(s); CCI q3w Every 3 weeks; q4w Every 4 weeks; QLQ-C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; RNA SAE Serious adverse event; SoC Standard of care; CCI T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 3 Follow-up period: Schedule of assessments for patients in Treatment Arms 1, 2, and 3 who have completed/discontinued treatment

	Time since last dose of IP									For details, see Section
	Day (±3)	Months (±1 week)							Every 2 months (±2 weeks)	
Evaluation	**28**	**2**	**3**	**4**	**6**	**8**	**10**	**12**		
Full physical examination[a]	X									5.2.2
Vital signs	X									5.2.4
Weight	X	X	X		X					5.2.4
Pregnancy test[b]	X	As clinically indicated								5.2.1
AE/SAE assessment[c]	X	X	X	Follow-up of ongoing AEs						6.3.1
Concomitant medications	X	X	X							7.7
WHO/ECOG performance status[d]	At timepoints consistent with tumor assessments, at 30, 60, and 90 days and at initiation of subsequent anticancer therapy									5.2.6
Subsequent anticancer therapy[e]	X									5.1
Survival status[f]		X	X	X	X	X	X	X	X	5.1.2
Hematology	X	X	X							5.2.1
Clinical chemistry	X	X	X							5.2.1

Table 3 Follow-up period: Schedule of assessments for patients in Treatment Arms 1, 2, and 3 who have completed/discontinued treatment

	Time since last dose of IP									For details, see Section
	Day (±3)	Months (±1 week)							Every 2 months (±2 weeks)	
Evaluation	**28**	**2**	**3**	**4**	**6**	**8**	**10**	**12**		
TSH, free T_3, and free T_4[g]	X	X	X							5.2.1
Durvalumab PK sample (serum; Treatment Arms 1 and 2 only)			X (3 months after durvalumab discontinuation)[h]							5.4.1
Tremelimumab PK sample (serum; Treatment Arm 1 only)			X (3 months after tremelimumab discontinuation)[h]							5.4.1
Immunogenicity assessment (ADA sampling)[i]			X (3 months after durvalumab discontinuation for Treatment Arms 1 and 2; 3 months after tremelimumab discontinuation for Arm 1)[j]							5.4.1.1
EORTC QLQ-C30 v3,[k] CCI CCI EORTC QLQ-LC13,[k] CCI	X	q4w until PD and then q8w until second progression/death (whichever comes first)								5.3.1.1, 5.3.1.2, 5.3.1.3, 5.3.1.4, 5.3.1.5
CCI	X									5.3.3
Tumor evaluation (CT or MRI)[n] (RECIST 1.1)	RECIST 1.1 tumor assessments should be performed at Week 6±1 week, at Week 12±1 week, and then q8w±1 week until RECIST 1.1 defined radiological progression plus an additional subsequent scan or death.									5.1
Second progression assessment[o]	Assessment will be performed by the Investigator and defined according to local standard clinical practice and may involve any of the following: objective radiologic imaging, symptomatic progression, or death (using the patient's status at first progression as the reference for assessment of second progression).									

[a] Physical examinations are described in Section 5.2.2.
[b] Pregnancy test will be performed in women of childbearing potential only. A urine or serum pregnancy test is acceptable.

[c] AEs and SAEs will be collected until 90 days following discontinuation of study treatment (ie, the last dose of durvalumab, durvalumab + tremelimumab, or SoC chemotherapy)

[d] WHO/ECOG performance status should also be collected at other site visits that the patient attends; if appropriate, site staff are available to collect such information. In addition, WHO performance status should be provided when information on subsequent anticancer therapy is provided, where possible.

[e] Details of any treatment for NSCLC (including surgery) after the last dose of study treatment must be recorded in the eCRF.

[f] Patients may be contacted in the week following the data cut-off to confirm survival status. Details of any treatment for NSCLC (including surgery) after the last dose of study treatment must be recorded in the eCRF. Every effort should be made to contact patients by telephone to follow and record survival status.

[g] Free T_3 and free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[h] The 3-month follow-up samples for each molecule are relative to the respective last dose: the tremelimumab sample will be collected 3 months after the last tremelimumab dose (Treatment Arm 1). The durvalumab sample will be collected 3 months after the last durvalumab dose (Treatment Arms 1 and 2).

[i] ADA for tremelimumab will be assessed for Treatment Arm 1 patients only; ADA for durvalumab will be assessed for Treatment Arms 1 and 2 patients only.

[j] A sample to look for antibodies to tremelimumab will be taken 90 days±7 days after last dose of tremelimumab. A sample to look for antibodies to durvalumab will be taken 90 days±7 days after last dose of durvalumab.

[k] For the PRO data collection, the research nurse or study coordinator should ensure that the patient completes the questionnaire prior to any other study procedures and before discussion of PD to avoid introducing bias to the patient's responses. The EORTC QLQ-C30 should always be completed prior to the EORTC QLQ-LC13 module.

[l] CCI [redacted]

[m] CCI [redacted]

[n] Only for patients yet to progress, RECIST 1.1 assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients. For Treatment Arms 1 and 2 scans subsequent to a prior radiological PD should be performed preferably at the next scheduled imaging visit and no earlier than 4 weeks after the immediate prior assessment of radiological PD. If an unscheduled assessment has been 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).

[o] For patients who discontinue durvalumab + tremelimumab combination therapy + SoC chemotherapy, durvalumab monotherapy + SoC chemotherapy, or SoC chemotherapy alone following objective disease progression, available readings of CT/MRI from local practice will be collected from the patients' medical charts while information on subsequent anticancer treatment and/or PFS2 is collected.

ADA Anti-drug antibody; AE Adverse event; CT Computed tomography; CCI [redacted] eCRF electronic case report form; ECOG Eastern Cooperative Oncology Group; EORTC European Organisation for Research and Treatment of Cancer; CCI [redacted] IP Investigational product; IV Intravenous; MRI Magnetic resonance imaging; NSCLC Non-small cell lung cancer; PD Progressive disease; PFS2 Time from randomization to second progression; CCI [redacted] PK Pharmacokinetic(s); CCI [redacted] q4w Every 4 weeks; q8w every 8 weeks; QLQ-C30 v3 30-item Core Quality of Life Questionnaire, version 3; QLQ-LC13 13-item Lung Cancer Quality of Life Questionnaire; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; SoC Standard of care; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

4.1 Screening/enrollment period

All screening and enrollment procedures will be performed according to the assessment schedules in Table 2. Demographic data and other characteristics will be recorded including date of birth or age, sex, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. If imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening imaging results must have been obtained within 28 days of randomization (Appendix E). All patients will be required to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent will be included in the main patient informed consent form (ICF).

Screening/baseline evaluations may be performed over more than 1 visit. If the screening/baseline evaluations are spread across more than 1 visit, the screening visit date will be the date that screening started.

The timing of vital signs assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Table 2.

4.2 Treatment period

All procedures to be conducted during the study treatment period will be performed according to the assessment schedule (see Table 2).

Treatment with immunotherapy + SoC chemotherapy in Treatment Arms 1 and 2, as well as treatment with SoC chemotherapy alone in Treatment Arm 3, will be administered beginning on Cycle 1 Day 1.

All patients will receive study treatment until clinical progression or radiological progression (Arm 1 and Arm 2) or RECIST 1.1 defined radiological progression (Arm 3).

Patients in Treatment Arms 1 and 2 who are treated beyond progression (see Section 7.2.2) will be expected to follow the assessment schedule in Table 2.

Whenever vital signs, electrocardiograms (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 vital signs assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Table 2.

Patients in Treatment Arm 3 only:

Patients who receive additional cycles of SoC chemotherapy at Weeks 12 and 15 will be expected to follow the assessment schedule in Table 2 after 4 to 6 cycles of SoC

chemotherapy; additional visits or scans due to the optional extension of SoC chemotherapy will be recorded in applicable eCRF modules.

4.2.1 Safety confirmation period

This applies to the first 60 patients randomized to the study and will be split into 2 parts; an unblinded safety review carried out by the IDMC will be conducted after the initial 30 patients have completed the first cycle of treatment and again after an additional 30 patients have been randomized and have completed the first cycle of treatment. More details on the IDMC are provided in Section 1.6.1.

Safety confirmation for Japan: An additional unblinded safety review for Japanese patients will take place when the first 3 patients in each treatment arm in Japan have completed the first cycle of treatment (see Section 1.6.1 for details).

Safety confirmation for China: An additional unblinded safety review for Chinese patients will take place when the first 10 patients in each treatment arm in China have completed the first cycle of treatment (see Section 1.6.1 for details).

4.3 Follow-up period

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued study treatment and will enter follow-up (see Table 3).

Patients in Treatment Arms 1, 2, and 3 who permanently discontinue study treatment for reasons other than objective RECIST 1.1 disease progression should continue to have tumor evaluation scans performed q6w±1 week for the first 12 weeks (relative to the date of randomization), and then q8w±1 week thereafter until RECIST 1.1 defined radiological progression plus an additional subsequent scan or death (whichever comes first) as defined Table 3. All scans will be read centrally (Section 5.1.1).

Patients in Treatment Arms 1 and 2 who discontinue study treatment for unconfirmed progression should also continue to have tumor evaluation scans performed q6w±1 week for the first 12 weeks (relative to the date of randomization), and then q8w±1 week thereafter until confirmed objective disease progression or death (whichever comes first) as defined in Table 3. All scans will be read centrally (Section 5.1.1).

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule (see Table 3).

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 timepoints indicated in Table 3.

All patients will be followed for survival until the end of the study. The schedule of study procedures for patients in long-term follow up is presented in Table 12, Table 13 in Section 9.3 Study timetable and end of study.

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 eCRFs as specified in this study protocol and in accordance with the instructions provided.

The Investigator will ensure the accuracy, completeness, and timeliness of the data recorded and 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.

5.1 Efficacy assessments

The dual primary aims of this study are to assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients. Efficacy assessments of PFS, APF12, DoR, BoR, and ORR will be derived (by AstraZeneca) using BICR assessments according to RECIST 1.1. A sensitivity analysis of PFS and OS will be performed using Investigator assessments. Secondary objectives will include OS and PFS of durvalumab + tremelimumab combination therapy + SoC chemotherapy compared with SoC chemotherapy as well as APF12, DoR, BoR, ORR and PFS2.

Tumor evaluations utilize images from CT [preferred] or MRI, each preferably with IV contrast, of the chest and abdomen (including the entire liver and both adrenal glands), collected during screening/baseline and at selected timepoints during the study treatment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

The RECIST 1.1 guidelines (Appendix E) provide a method of assessment of change in tumor burden in response to treatment. Screening/baseline imaging should be performed no more than 28 days before the date of randomization and ideally should be performed as close as possible to and prior to the date of randomization. The RECIST 1.1 assessments of baseline images identify target lesions (TLs [defined as measurable]) and non-target lesions (NTLs), and each lesion (and any new lesion) is evaluated in subsequent, on-treatment follow-up images. This allows the determination of follow-up TL response, NTL response, New Lesions, and overall timepoint tumor responses (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], or not evaluable [NE]).

5.1.1 Central reading of scans

All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization for quality control (QC) and storage. A BICR of images will be performed at the direction of

AstraZeneca. 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 RECIST 1.1 assessment conducted by the Investigator. The BICR of all radiological scans will be performed to derive the ORR, PFS, DoR, BoR, and APF12 endpoints according to RECIST 1.1. The BICR will include assessment by RECIST 1.1 and CCI Only Investigator assessments will be captured in the RAVE system in RECIST folders.

5.1.2 Survival assessments

Assessments for survival must be made at Months 2, 3, and 4, and then every 2 months (8 weeks±2 weeks) 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. These assessments must be performed even if the patient begins another therapy to treat their NSCLC. 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 cut-off 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 cut-off. Survival assessments may continue as per protocol (every 2 months) post the final analysis of OS for superiority.

5.2 Safety assessments

5.2.1 Laboratory safety assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 2 and Table 3).

Clinical laboratory safety tests, including serum/urine pregnancy tests (on women of childbearing potential), thyroid-stimulating hormone, free triiodothyronine, and free thyroxine, according to Table 2 and Table 3, 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. Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Pregnancy tests, on either urine (human chorionic gonadotropin [hCG]) or blood (serum β-hCG) samples, will be performed for pre-menopausal women of childbearing potential at screening and subsequent visits as specified in the assessment schedule (Table 2 and Table 3). Tests will be performed by the hospital's local laboratory. If results are positive, the patient must not start or continue treatment. In the event of a suspected pregnancy during the study, the test should be repeated.

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

The laboratory variables to be measured are presented in Table 4 (clinical chemistry), Table 5 (hematology), and Table 6 (urinalysis).

Other safety tests to be performed at screening will include assessment for HbsAg, HCV antibodies, and HIV antibodies.

The following laboratory variables will be measured:

Table 4 Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH[e]
Chloride[c]	T_3 free[f] (reflex)
Creatinine[d]	T_4 free[f] (reflex)
Gamma-glutamyl transferase[c]	Urea or blood urea nitrogen, depending on local practice
Glucose	
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome), then the fractions of direct and indirect bilirubin should be determined.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured, then either lipase or amylase is acceptable.

c Bicarbonate (where available), chloride, creatinine clearance, gamma-glutamyl transferase, and magnesium testing are to be performed at baseline and on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.

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

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

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

ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; T_3 - Triiodothyronine; T_4 - Thyroxine; TSH - Thyroid-stimulating hormone.

Table 5 Hematology

Absolute lymphocyte count[a]	Hemoglobin
Absolute neutrophil count[a]	Platelet count
Absolute eosinophil count[a]	Total white blood cell count

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.
a Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by data management if entered as percentage. Total white cell count therefore has to be provided.

Table 6 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

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

All patients should have further hematology and clinical chemistry profiles performed at 28 days (±3 days), 2 months (±1 week), and 3 months (±1 week) after permanent discontinuation of IP (see Table 3).

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 6.3.7.

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 (Table 2 and Table 3). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat, and the respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the

Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 6.3.6.

5.2.3 Electrocardiogram

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study (see Table 2). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, including a QT interval corrected for heart rate using Fridericia's formula (QTcF) value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 6.3.7.

5.2.4 Vital signs

Vital signs (blood pressure [BP], pulse rate, temperature, and respiration rate) will be evaluated according to the assessment schedules (Table 2 and Table 3). Body weight is also recorded at each visit along with vital signs.

First infusion

On the first infusion day, patients in Treatment Arms 1 and 2 will be monitored and vital signs will be collected/recorded in the eCRF prior to, during, and after infusion of IP as presented in the bulleted list below. Patients in Treatment Arm 3 will be monitored pre-dose and as clinically indicated before every infusion or administration.

BP, pulse rate, temperature and respiratory rate will be collected from patients in Treatment Arms 1 and 2 prior to, during, and after each infusion at the following times (based on a 60-minute infusion):

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

If the infusion takes longer than 60 minutes, then BP and pulse rate measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab. Additional monitoring with assessment of vital signs will be at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Subsequent infusions

BP, pulse rate, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of the every subsequent infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and after infusion as per institution

standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF.

Situations in which vital signs results should be reported as AEs are described in Section 6.3.7. For any AEs of infusion reactions, please enter the vital signs values into the eCRF.

5.2.5 Early patient review for safety

Patients will be evaluated 7 days after the first dose of each cycle of chemotherapy across all treatment arms to ensure early identification and management of toxicities. It is strongly recommended for any patient experiencing Grade 3 or 4 neutropenia that granulocyte colony-stimulating factor is administered according to local practice.

5.2.6 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see Table 2 and Table 3) based on the following:

- 0 = Fully active; able to carry out all usual activities without restrictions
- 1 = Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)
- 2 = Ambulatory and capable of 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; unable to carry out any self-care and totally confined to bed or chair
- 5 = Dead

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

5.2.7 Other safety assessments

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 (please see Section 6.9.1), will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT) scans, blood and sputum culture, hematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis/ILD investigation

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

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc.), including auscultation for lung field will be assessed.
- SpO_2
  - Saturation of peripheral oxygen (SpO_2)
- Other items
  - When pneumonitis/ILD is suspected during study treatment, the following markers should be measured, where possible:
    (i) ILD markers (KL-6, SP-D) and β-D-glucan
    (ii) Tumor markers: particular tumor markers which are related to disease progression
    (iii) Additional clinical chemistry: C-reactive protein, lactate dehydrogenase

5.3 Other assessments

5.3.1 Clinical outcome assessments/patient-reported outcomes

Patient-reported outcomes (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: EORTC QLQ-C30 v3 (core questionnaire), EORTC QLQ-LC13 (lung cancer module), CCI [redacted] (see Appendix F).

The PRO instruments will be completed by the patients using a handheld electronic patient-reported outcome (ePRO) device. All assessments should be completed without assistance from anyone according to the assessment schedules (see Table 2 and Table 3). It will take approximately 30 minutes for patients to complete the questionnaires; therefore, the burden to the patient should be moderate.

5.3.1.1 EORTC QLQ-C30

The EORTC QLQ-C30 v3 questionnaire is included for the purpose of assessing HRQoL and is a well-established measure of HRQoL/health status and is commonly used as an endpoint in cancer clinical studies. It assesses HRQoL/health status through 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality of life (QoL) scale.

It also includes 6 single-item symptom measures: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties (see Appendix F). For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms (Aaronson et al 1993).

5.3.1.2 EORTC QLQ-LC13

For patients with NSCLC, a disease-specific 13-item self-administered questionnaire for lung cancer was developed (EORTC QLQ-LC13; Appendix F) to be used in conjunction with the EORTC QLQ-C30 (Bergman et al 1994). It comprises both multi-item and single-item measures of lung cancer-associated symptoms (ie, coughing, hemoptysis, dyspnea, and pain) and treatment-related symptoms from conventional chemotherapy and radiotherapy (ie, hair loss, neuropathy, sore mouth, and dysphagia). Similar to the EORTC QLQ-C30, all questions except 1 have a 4-point scale: "not at all," "a little," "quite a bit," and "very much". One question (no. 43: "Did you take any medicine for pain?") has a response option of "yes" or "no." The scoring approach for the EORTC QLQ-LC13 is similar to the EORTC QLQ-C30.

5.3.1.3 CCI

CCI

5.3.1.4 CCI

CCI

5.3.1.5 CCI

CCI

CCI

[redacted]

5.3.2 Administration of the patient-reported outcome questionnaires

Patients will complete the PRO assessments by using an electronic tablet (ePRO) during clinic visits.

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. The PRO questionnaires must be administered and completed at the clinic as per the schedule of assessments. The PRO questionnaires will be administered on the days specified in the schedules of assessments (see Table 2 and Table 3). The EORTC QLQ-C30 should always be completed prior to the EORTC QLQ-LC13 module.

It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection. The following best practice guidelines should be followed when collecting PRO data via an electronic device:

- It is preferred that PRO questionnaires are completed prior to any other study procedures (following informed consent) and before discussion of disease progression to avoid biasing the patient's responses to the questions.
- PRO questionnaires must be completed in private by the patient.
- Patients should be given sufficient time to complete the PRO questionnaires at their own speed.
- The research nurse or appointed site staff should stress that the information is confidential. Therefore, if the patient has any medical problems, he or she 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 in the ePRO device. 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.

5.3.3 CCI

CCI

5.4 Pharmacokinetics

5.4.1 Collection of samples

Blood samples for determination of gemcitabine, abraxane, durvalumab, and tremelimumab concentrations in serum or plasma will be obtained according to the assessment schedules (see Table 2 and Table 3). Samples for gemcitabine and abraxane PK determination will be collected from selected sites only and will include approximately 12 patients per treatment arm dosed with abraxane and carboplatin and approximately 12 patients per treatment arm dosed with either gemcitabine regimen (approximately 6 patients per gemcitabine + cisplatin and approximately 6 patients per gemcitabine + carboplatin). AstraZeneca will inform the selected sites once this requirement has been fulfilled.

Blood samples for determination of durvalumab and tremelimumab concentrations in serum will be obtained according to the assessment schedules (see Table 2 and Table 3). Note that

for patients in Treatment Arms 1 and 2, the 3-month (90-day) follow-up samples for each molecule are relative to the respective last dose:

- Treatment Arm 1: The tremelimumab PK sample will be collected 3 months after the last tremelimumab dose.
- Treatment Arms 1 and 2: The durvalumab PK sample will be collected 3 months after the last durvalumab dose.

Samples for determination of durvalumab and tremelimumab concentrations 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.

5.4.1.1 Collection of samples to measure for the presence of ADAs

The presence of ADA will be assessed in serum samples taken according to the assessment schedules (see Table 2 and Table 3).

Samples will be measured for the presence of ADAs and ADA neutralizing antibodies for both IPs (durvalumab and tremelimumab) using validated assays.

ADA for tremelimumab will be assessed for Treatment Arm 1 patients only; ADA for durvalumab will be assessed for Treatment Arms 1 and 2 patients only.

Note that for patients in Treatment Arms 1 and 2, the 3-month (90-day) follow-up samples for each molecule are relative to the respective last dose:

- A sample to look for antibodies to tremelimumab will be taken 90 days±7 days after the last dose of tremelimumab.
- A sample to look for antibodies to durvalumab will be taken 90 days±7 days after the last dose of durvalumab.

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 employed.

5.4.1.2 Storage and destruction of pharmacokinetic/ADA samples

Durvalumab and tremelimumab PK and ADA samples will be disposed after a maximum of 15 years after the IPs are approved for marketing. SoC PK samples will be disposed after a maximum of 15 years from the end of study.

PK and ADA samples may be disposed of or destroyed or 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 be reported separately in a Bioanalytical Validation Report and not in the CSR.

CCI [redacted]

For China: PK and ADA samples collected in China will be stored and disposed according to local laws and regulations. PK and ADA samples collected in China will be destroyed after finalization of bioanalytical report or completion of CSR.

5.5 Biomarkers Analysis

By participating in this study, the patient is mandatorily consenting to the collection and use of donated biological samples as described here. Tumor tissue samples will be obtained from all screened patients. CCI [redacted] Samples will be obtained according to the assessment schedules provided in Table 2 and Table 3.

Details for collection, volumes, storage, and shipment of biologic samples are presented separately in the Laboratory Manual.

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy.

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

5.5.1 Collection of patient samples for stratification by PD-L1 and for expression of PD-L1 and Tumor Mutation Burden (TMB)

At screening, there are 2 mandatory provisions of tissue to be used for determination of eligibility. There is 1 subsequent mandatory provision of tissue at progression if retreatment is planned (Treatment Arm 1).

- MANDATORY: Provision of a tumor biopsy that is formalin fixed and embedded in paraffin. A freshly collected tumor biopsy is strongly preferred; however, if not clinically feasible, an archival sample taken less than 3 months prior to screening may be submitted.
  - Samples should be collected via a 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 this study, 3 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 and TMB analyses (see the Laboratory Manual). Tumor tissue block is preferred. If a tissue block is unavailable, 20 unstained sections from the tissue block may be submitted. Please consult the Laboratory Manual for specific instructions and guidelines regarding sample collection and handling. Newly acquired or archived specimens with limited tumor content and fine-needle aspirates are inadequate for defining tumor PD-L1 status and TMB determination.
  - Tumor lesions used for fresh biopsies should not be the same lesions used as RECIST 1.1 TLs, unless there are no other lesions suitable for biopsy. If a RECIST 1.1 TL is used for biopsy (preferably core needle biopsy), the lesion must be imaged after biopsy prior to randomization (see inclusion criterion 6).

- MANDATORY: The collection of additional archived tumor tissue block (formalin-fixed and paraffin-embedded) is mandated, 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. Please consult the Laboratory Manual for specific instructions and guidelines regarding sections. **Note:** These samples will not be collected in China.
- MANDATORY: For patients in Treatment Arm 1, the collection of tumor biopsies at the time of progression prior to retreatment is mandated. The Investigator can consult with the Study Physician if such sampling is not feasible. **Note:** These samples will not be collected in China.
- CCI [redacted]
- Additional tumor biopsies collected as part of clinical care (eg, for mixed responses or upon PD) can be submitted for further analysis. **Note:** These samples will not be collected in China.

See the Laboratory Manual for further details of requirements including sample QC and shipping.

CCI [redacted]

To meet the requirement of 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.

5.5.2 CCI

CCI

CCI

[redacted]

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

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab or tremelimumab to generate hypotheses to be tested in future research.

Note: Tumor samples collected in China will be destroyed or repatriated maximally 5 years after study drug is approved for marketing in China.

5.5.4 Labeling and shipment of biological samples

The Principal Investigator will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria; see Appendix B [IATA 6.2 Guidance Document]).

Any samples identified as Infectious Category A materials are not shipped, and no further samples will be taken from the patient unless agreed 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 Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of sample shipments.

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 sample shipments.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers. Samples retained for further use will be stored in the AZ-assigned biobank and 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 or destroyed and the action is documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator will perform the following:

- 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 the action is documented.
- Ensure that the organization(s) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented, and a copy is returned to the clinical study team for communication to the study site.
- Ensure that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca will ensure that the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and a copy is returned to clinical study team for communication to the study site.

5.6 CCI

CCI

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

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

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

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

6.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), which fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

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 will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab ± tremelimumab or SoC). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug (for all arms) then it should be reported as an AE or SAE as applicable.

6.3.2 Follow-up of unresolved adverse events

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution

for all events, even if the events continue after the patient has discontinued study drug or the study completed.

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

6.3.3 Variables

The following variables will be collected for each AE:

- AE (verbatim)
- Date when the AE started and stopped
- Maximum CTCAE grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- 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 SAE
- Seriousness of criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 6.3.4
- Description of SAE

The grading scales found in the revised NCI CTCAE Version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE Version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

It is important to distinguish between SAEs 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 need not necessarily 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.

6.3.4 Causality collection

The Investigator will assess the 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 medications 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.

6.3.5 Relationship to protocol procedures

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

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

6.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel, "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the 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.

6.3.7 Adverse events based on examinations and tests

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

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

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

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

6.3.8 Hy's law

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

6.3.9 Disease progression

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

6.3.10 New cancers

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

6.3.11 Deaths

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

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

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

6.3.12 Safety Data To Be Collected following the final DCO of the study

For patients continuing to receive durvalumab/tremelimumab treatment and/or SOC chemotherapy after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab/tremelimumab in order to manage AEs in accordance with the durvalumab/tremelimumab toxicity management guidelines (TMG Annex) and per label information of chemotherapy. All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of Serious Adverse Events, will not otherwise be reported for the purposes of this study.

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

6.4 Reporting of serious adverse events

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

If any SAE occurs during the course of the study, then the Investigator 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 will work 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 in which important or relevant information is missing, active follow-up is undertaken immediately. The Investigator or other site personnel will inform AstraZeneca representatives 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 Investigator or other site personnel indicates that an AE is serious in the WBDC system, an automated e-mail alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study site personnel will report the SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator or study site personnel how to proceed.

The reference documents for the definition of expectedness or listedness are the IBs for durvalumab and tremelimumab and the EU Summary of Product Characteristics for the active comparator product (including any AstraZeneca comparator).

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

6.5 Treatment Arms 1 and 2 adverse events of special interest

An adverse event of special interest (AESI) is one of the scientific and medical interests specific to understanding 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.

AESIs for durvalumab ± tremelimumab include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism and which may require more frequent

monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

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.

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological, rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Section 6.9.1 and TMG Annex. 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. In the event of an AESI or suspected AESI, the AstraZeneca study team may request relevant clinical information (including images) for those patients who demonstrate the event and may request the independent review.

6.6 Overdose

6.6.1 Durvalumab or tremelimumab

Use of durvalumab or tremelimumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of

overdose of durvalumab or tremelimumab, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

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

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

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

6.6.2 Standard of care

For patients randomized to the SoC (Treatment Arm 3) group, refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE, record the AE/SAE diagnosis or symptoms only in the relevant AE modules of the eCRF.

6.7 Pregnancy

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

- Pregnancy discovered before the study patient has received any study drugs.

6.7.1 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs during the course of the study, then the Investigator 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 will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.7.2 Paternal exposure

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

Please follow the local prescribing information relating to contraception and the time limit for such precautions for SoC agents.

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

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

6.8 Medication Error

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

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

Medication error includes situations where an error:

- Occurred;
- Was identified and intercepted before the patient received the drug;
- Did not occur, but circumstances were recognized that could have led to an error.

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

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

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

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

6.9 Management of IP-related toxicities

The following general guidance should be followed for the management of toxicities (see TMG Annex):

- 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.
- In the event that durvalumab ± tremelimumab is discontinued or delayed as part of the toxicity management guidance SoC may still be administered as scheduled.

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

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

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

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE

diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 3.9 of this protocol and the Dosing Modification and Toxicity Management Guidelines in TMG Annex).

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in TMG Annex. 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 durvalumab monotherapy and the durvalumab + tremelimumab combination therapy regimen by the reporting Investigator.

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

6.9.2 Standard of care agents

Chemotherapies are associated with a number of unwanted effects. SoC-related toxicity management and dose adjustment, including dose delays and reductions, should be performed as indicated in the local prescribing information for the relevant agent. In the event of unfavorable tolerability, patients can switch between cisplatin and carboplatin therapy at any point on study (assuming eligibility for the switched therapy is met).

In the event that an AE can reasonably be attributed to SoC, dose adjustment of SoC should be attempted before modifying the administration of durvalumab ± tremelimumab.

In the event that SoC is delayed, durvalumab ± tremelimumab should also be delayed. Every effort should be made to ensure patients receive at least 4 cycles of SoC across all treatment arms in the study, if conditions allow.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational products

AstraZeneca will supply durvalumab (MEDI4736) and tremelimumab, while the SoC chemotherapies will be supplied locally (Table 7). Under certain circumstances when local sourcing is not feasible, SoC treatment may be supplied centrally through AstraZeneca.

Table 7 List of investigational products for this study

Investigational product	Dosage form and strength
Durvalumab (MEDI4736)	50 mg/mL, solution for infusion after dilution
Tremelimumab	20 mg/mL, solution for infusion after dilution
Standard of care	

Abraxane[a]	IV (as sourced locally)
Carboplatin[a]	IV (as sourced locally)
Cisplatin[a]	IV (as sourced locally)
Gemcitabine[a]	IV (as sourced locally)
Pemetrexed[a]	IV (as sourced locally)

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

7.1.1 Order of administration

Treatment Arm 1:

Patients will receive 1 dose of tremelimumab (75 mg) via IV infusion over 1 hour, which will be followed by durvalumab (MEDI4736; 1500 mg) via IV infusion over 1 hour, starting approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion.

SoC chemotherapy will start approximately 1 hour (maximum 2 hours) after the end of the Durvalumab infusion.

If there is no clinically significant concerns after the first cycle, then at the Investigator's discretion, durvalumab (MEDI4736) can be given immediately after tremelimumab in subsequent cycles.

If there is no clinically significant concerns after the first cycle, reducing the observation period after durvalumab (MEDI4736) administration to 30 minutes is recommended, at the Investigator's discretion.

Immunotherapy administration will then be followed by SoC chemotherapy via IV infusion as indicated in Section 7.2.2.

Treatment Arm 2:

Patients will receive durvalumab (MEDI4736; 1500 mg) via IV infusion over 1 hour.

SoC chemotherapy will start approximately 1 hour (maximum 2 hours) after the end of the Durvalumab infusion.

If there is no clinically significany concerns after the first cycle, reducing the observation period after durvalumab (MEDI4736) administration to 30 minutes is recommended, at the Investigator's discretion.

Immunotherapy administration will then be followed by SoC chemotherapy via IV infusion as indicated in Section 7.2.2.

Treatment Arm 3:

Patients will receive SoC chemotherapy via IV infusion as indicated in Section 7.2.2.

7.1.2 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Preparation of durvalumab (MEDI4736) doses for administration with an IV bag

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

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

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

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500 mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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

Standard infusion time is 60 minutes (±5 minutes). In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

If either preparation time or infusion time exceeds the time limit, a new dose must be prepared from new vials. Durvalumab (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.

7.1.3 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial concentrate 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 20.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary container until use to prevent excessive light exposure.

Preparation of tremelimumab doses for administration with an IV bag

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

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

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

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

If weight falls to $\leq$ 30 kg during the study, weight-based dosing will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Standard infusion time is 60 minutes (±5 minutes). Less than 55 minutes is considered a protocol deviation. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

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

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

7.1.4 Standard of care

SoC chemotherapy will be locally sourced 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, AstraZeneca will centrally source the drug, which will be labeled with text translated to local language in accordance with regulatory guidelines.

7.2 Dose and treatment regimens

Patients will be randomized in a 1:1:1 ratio to receive treatment q3w with durvalumab (MEDI4736) + tremelimumab combination therapy+ SoC chemotherapy, durvalumab (MEDI4736) monotherapy + SoC chemotherapy, or SoC chemotherapy alone in the 'during chemotherapy' phase. During the 'post-chemotherapy' phase, patients in Treatment Arms 1 and 2 receive durvalumab (MEDI4736) monotherapy q4w. Non-squamous patients who received pemetrexed + carboplatin/cisplatin in the 'during chemotherapy' phase will receive pemetrexed maintenance therapy, unless contraindicated per the Investigator. See Figure 5 for the dosing scheme.

The following are the definitions of the study treatment regimens in each treatment arm:

Treatment Arm 1: durvalumab (MEDI4736) + tremelimumab combination therapy + SoC chemotherapy

Treatment Arm 2: durvalumab (MEDI4736) monotherapy + SoC chemotherapy

Treatment Arm 3: SoC chemotherapy alone

During the 'post-chemotherapy' phase of the study, patients in Treatment Arms 1 and 2 will receive durvalumab (MEDI4736) monotherapy until disease progression. See Section 7.2.2 for the duration of treatments and criteria for treatment through progression and retreatment.

7.2.1 Treatment regimens

Standard of care chemotherapy: Patients will receive 1 of the following SoC regimens as part of their treatment regimen:

- Abraxane + carboplatin (squamous and non-squamous patients): Abraxane 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle. Carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3).
- Gemcitabine + cisplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 21-day cycle + cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3).
- Gemcitabine + carboplatin (squamous patients only): Gemcitabine 1000 or 1250 mg/m^2 via IV infusion on Days 1 and 8 of each 21-day cycle + carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3).
- Pemetrexed + carboplatin (non-squamous patients only): Pemetrexed 500 mg/m^2 and carboplatin AUC 5 or 6 via IV infusion on Day 1 of each 21-day cycle for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3); then continue pemetrexed 500 mg/m^2 maintenance (i.e., q4w for Treatment Arms 1 and 2. For Treatment Arm 3, Pemetrexed maintenance therapy can be given either q3w or q4w dependent on Investigator decision and local standards) until objective disease progression, unless contraindicated per the Investigator.
- Pemetrexed + cisplatin (non-squamous patients only): Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 via IV infusion on Day 1 of each 21-day cycle, for 4 to 6 cycles (ie, 4 cycles for Treatment Arms 1 and 2 and 4 to 6 cycles for Treatment Arm 3); then continue pemetrexed 500 mg/m^2 maintenance (i.e., q4w for Treatment Arms 1 and 2. For Treatment Arm 3, Pemetrexed maintenance therapy can be given either q3w or q4w dependent on Investigator decision and local standards) until objective disease progression, unless contraindicated per the Investigator.

Treatment Arm 1: Durvalumab (MEDI4736) + tremelimumab combination therapy + SoC chemotherapy

During chemotherapy

NSCLC type	Agent and dose	Route	Duration	Schedule
Squamous and non-squamous patients	Durvalumab (MEDI4736; 1500 mg)	IV	60 min	4 doses q3w Weeks 0, 3, 6, and 9
Squamous and non-squamous patients	Tremelimumab (75 mg)	IV	60 min	4 doses q3w Weeks 0, 3, 6, and 9
Squamous and non-squamous patients	SoC (abraxane [100 mg/m^2] with carboplatin [AUC 5 or 6])	IV		Days 1, 8, and 15 of each 21-day cycle (abraxane) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles

NSCLC type	Agent and dose	Route	Duration	Schedule
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with cisplatin [75 mg/m^2])	IV		Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (cisplatin) for 4 cycles
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with carboplatin [AUC 5 or 6])	IV		Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] with carboplatin [AUC 5 or 6])	IV		Day 1 of each 21-day cycle for 4 cycles
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] and cisplatin [75 mg/m^2])	IV		Day 1 of each 21-day cycle for 4 cycles

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing—equivalent to 20 mg/kg of durvalumab and 1 mg/kg of tremelimumab q3w until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500 mg and tremelimumab at 75 mg.

Note: If there is a dosing delay during chemotherapy while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days.

AUC Area under the curve; IV Intravenous; q3w Every 3 weeks; SoC Standard of care.

Post-chemotherapy

Agent	Dose	Route	Duration	Schedule
Durvalumab (MEDI4736)	1500 mg	IV	60 min	q4w Week 12 to PD[a]
Tremelimumab	75 mg	IV	60 min	1 dose at Week 16[b]
Pemetrexed[c]	500 mg/m^2	IV		q4w Week 12 to PD[d]

[a] Patients are treated until clinical progression or radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. For criteria for treatment through progression and for retreatment with the combination, see Section 7.2.2.2.

[b] For patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab will be given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose can be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses are administered in Treatment Arm 1. If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a

total of 5) should be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed, if applicable).

[c] Non-squamous patients who received carboplatin/cisplatin + pemetrexed and who have not progressed after 4 cycles of carboplatin/cisplatin + pemetrexed will receive pemetrexed maintenance therapy, unless contraindicated per the Investigator.

[d] Patients are treated until clinical progression or RECIST1.1 defined radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing-equivalent to 20 mg/kg of durvalumab and 1 mg/kg of tremelimumab q4w until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500 mg and tremelimumab at 75 mg.

IV Intravenous; NSCLC Non-small-cell lung cancer; PD Progressive disease; q4w Every 4 weeks.

Note: Dose reductions of durvalumab (MEDI4736) and tremelimumab are not permitted.

Treatment Arm 2: Durvalumab (MEDI4736) monotherapy + SoC chemotherapy

During chemotherapy

NSCLC type	Agent and dose	Route	Duration	Schedule
Squamous and non-squamous patients	Durvalumab (MEDI4736; 1500 mg)	IV	60 min	4 doses q3w Weeks 0, 3, 6, and 9
Squamous and non-squamous patients	SoC (abraxane [100 mg/m^2] with carboplatin [AUC 5 or 6])	IV		Days 1, 8, and 15 of each 21-day cycle (abraxane) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with cisplatin [75 mg/m^2])	IV		Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (cisplatin) for 4 cycles
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with carboplatin [AUC 5 or 6])	IV		Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] with carboplatin [AUC 5 or 6])	IV		Day 1 of each 21-day cycle for 4 cycles
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] and cisplatin [75 mg/m^2])	IV		Day 1 of each 21-day cycle for 4 cycles

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing-equivalent to 20 mg/kg of durvalumab q3w until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500 mg.

Note: If there is a dosing delay during chemotherapy while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days.

IV Intravenous; NSCLC Non-small-cell lung cancer; q3w Every 3 weeks; SoC Standard of care.

Post-chemotherapy

Agent	Dose	Route	Duration	Schedule
Durvalumab (MEDI4736)	1500 mg	IV	60 min	q4w Week 12 to PD[a]
Pemetrexed[b]	500 mg/m^2	IV		q4w Week 12 to PD[c]

[a] Patients are treated until clinical progression or radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. For criteria for treatment through progression, see Section 7.2.2.2.

[b] Non-squamous patients who received carboplatin/cisplatin + pemetrexed and who have not progressed after 4 cycles of carboplatin/cisplatin + pemetrexed will receive pemetrexed maintenance therapy, unless contraindicated per the Investigator.

[c] Patients are treated until clinical progression or RECIST1.1 defined radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Note: Patients whose weight falls to 30 kg or below should receive weight-based dosing—equivalent to 20 mg/kg of durvalumab q4w until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500 mg.

IV Intravenous; PD Progressive disease; q4w Every 4 weeks.

Note: Dose reductions of durvalumab (MEDI4736) are not permitted.

Treatment Arm 3: SoC chemotherapy alone

NSCLC type	Agent and dose	Route	Duration	Schedule
Squamous and non-squamous patients	SoC (abraxane [100 mg/m^2] with carboplatin [AUC 5 or 6])	IV		Days 1, 8, and 15 of each 21-day cycle (abraxane) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles[a]
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with cisplatin [75 mg/m^2])	IV		Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (cisplatin) for 4 cycles[a]
Squamous patients only	SoC (gemcitabine [1000 mg/m^2 or 1250 mg/m^2] with carboplatin [AUC 5 or 6])	IV		Days 1 and 8 of each 21-day cycle (gemcitabine) and on Day 1 of each 21-day cycle (carboplatin) for 4 cycles[a]
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] with carboplatin [AUC 5 or 6])[b]	IV		Day 1 of each 21-day cycle for 4 cycles[a]
Non-squamous patients only	SoC (pemetrexed [500 mg/m^2] and cisplatin [75 mg/m^2])[b]	IV		Day 1 of each 21-day cycle for 4 cycles[a]

[a] An additional 2 doses of SoC (Weeks 12 and 15) can be given at the Investigator's discretion, if clinically indicated.

[b] Non-squamous patients who received carboplatin/cisplatin + pemetrexed and who have not progressed after 4 to 6 cycles of carboplatin/cisplatin + pemetrexed will receive pemetrexed maintenance therapy can be given q3w or q4w, dependent on Investigator decision and local standards, unless contraindicated per the Investigator. **Note:** RECIST 1.1 assessment should be performed at Week 12 ±1 week from the date of randomization, and then q8w±1 week thereafter until radiological progression (regardless of whether it chosen q3w or q4w).

Note: Patients who receive extra cycles of SoC will still be expected to follow the planned scan schedule visits as detailed in Table 2 and Table 3.

Note: If there is a dosing delay during chemotherapy while on the q3w schedule, all future dosing days should be delayed to ensure that the intervals between dosing study treatment are always at least 21 days.

IV Intravenous; NSCLC Non-small-cell lung cancer; q3w Every 3 weeks; q4w Every 4 weeks; SoC Standard of care.

The full dosing scheme is provided below in Figure 5.

Figure 5 Dosing scheme

Treatment arms	During chemotherapy 1 cycle=3 weeks (21 days)				Post-chemotherapy 1 cycle=4 weeks (28 days)		
	Cycle 1 Week 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Week 12	Week 16	Week 20 to PD
Durva + Treme + SoC (Treatment Arm 1)	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Treme + SoC	Durva + Pemetrexed Maintenance[a]	Durva + Treme[b] Pemetrexed Maintenance[a]	Durva + Pemetrexed Maintenance[a]
Durva + SoC (Treatment Arm 2)	Durva + SoC	Durva + SoC	Durva + SoC	Durva + SoC	Durva + Pemetrexed Maintenance[a]	Durva + Pemetrexed Maintenance[a]	Durva + Pemetrexed Maintenance[a]
SoC (Treatment Arm 3)	SoC	SoC	SoC	SoC[c]	Pemetrexed Maintenance[a]	Pemetrexed Maintenance[a]	Pemetrexed Maintenance[a]

[a] Pemetrexed maintenance therapy is for non-squamous NSCLC patients who received treatment with pemetrexed and carboplatin/cisplatin during chemotherapy and did not progress after 4 to 6 cycles, unless contraindicated per the Investigator. Pemetrexed maintenance therapy can be given q3w or q4w (i.e., q4w for Treatment Arms 1 and 2. For Treatment Arm 3, Pemetrexed maintenance therapy can be given either q3w or q4w dependent on Investigator decision and local standards). **Note:** RECIST 1.1 assessment should be performed at Week 12 ±1 week from the date of randomization, and then q8w±1 week thereafter until radiological progression (regardless of whether it chosen q3w or q4w).

[b] For patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab will be given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose can be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses are administered in Treatment Arm 1. If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) should be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed, if applicable).

[c] In Treatment Arm 3, SoC chemotherapy can be given for an additional 2 cycles q3w on Weeks 12 and 15 (ie, total of 6 cycles post-randomization) if clinically indicated, at the Investigator's discretion before patients enter follow-up. This does not alter the planned scan schedule q8w starting at Week 12 for patients in Treatment Arm 3.

Note: Patients whose weight falls to 30 kg or below must receive weight-based dosing—equivalent to 20 mg/kg of durvalumab and 1 mg/kg of tremelimumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab at 1500 mg and tremelimumab at 75 mg. Durvalumab dose will be 1500 mg during chemotherapy and 1500 mg post-chemotherapy; tremelimumab dose will be 75 mg.

Durva Durvalumab (MEDI4736); PD Progressive disease; q3w Every 3 weeks; q4w Every 4 weeks; SoC Standard of care; Treme Tremelimumab.

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

7.2.2.1 Duration of treatment

Treatment with SoC chemotherapy in Treatment Arms 1 and 2 will be limited to 4 cycles on a q3w schedule subsequent to randomization. Patients in Treatment Arm 3 may receive an additional 2 doses of SoC chemotherapy at Weeks 12 and 15 (a total of 6 doses post-randomization), as clinically indicated, at the Investigator's discretion.

Treatment with immunotherapy + SoC chemotherapy in Treatment Arms 1 and 2, as well as treatment with SoC chemotherapy alone in Treatment Arm 3, will be administered beginning on Cycle 1 Day 1.

For patients randomized to Treatment Arms 1 and 2, immunotherapy treatment with durvalumab monotherapy will continue until clinical progression or radiological progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. For patients in Treatment Arm 1, an additional dose of durvalumab + tremelimumab will be given at Week 16 post-chemotherapy. In the case of dose delay(s), more than 1 durvalumab + tremelimumab combination dose can be given at and after Week 16 post-chemotherapy to ensure that up to 5 combination doses are administered in Treatment Arm 1. If patients receive fewer than 4 cycles of platinum doublet chemotherapy, the remaining cycles of combined durvalumab/tremelimumab (up to a total of 5) should be given after combination of platinum doublet chemotherapy (with maintenance pemetrexed if applicable). All non-squamous patients who received a pemetrexed doublet in the initial part of the study will receive pemetrexed maintenance in the 'post-chemotherapy' phase of the study, unless contraindicated per the Investigator.

For patients randomized to Treatment Arms 1 and 2, when SoC chemotherapy is discontinued due to treatment-related toxicity, durvalumab monotherapy or durvalumab + tremelimumab may continue at the Investigator's discretion when toxicity resolves to at least Grade 2 or less. Note: if the Investigator feels a patient is ready to restart treatment prior to the toxicity resolving to Grade 2 or less, AstraZeneca should be consulted for an exception to this rule.

For patients randomized to Treatment Arm 3, treatment through progression and retreatment will not be permitted.

7.2.2.2 Treatment Arms 1 and 2: Criteria for treatment through progression and for retreatment

Treatment through progression (Treatment Arms 1 and 2)

During the treatment period, patients in Treatment Arms 1 and 2 may continue receiving their assigned therapy in the setting of unconfirmed radiological progressive disease (PD) according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1), at the Investigator's discretion, until progressive disease is confirmed (Appendix E). A confirmatory scan is required following a RECIST 1.1 overall timepoint assessment of progression (PD),

preferably at the next scheduled imaging visit and no earlier than 4 weeks after the prior assessment of PD.

For patients in Treatment Arms 1 and 2 with confirmed objective radiological progression who, in the Investigator's opinion continue to receive benefit from their assigned treatment and following consultation with AstraZeneca, may continue to receive durvalumab monotherapy for as long as they are gaining clinical benefit providing they meet the criteria for treatment in the setting of PD (see section on Criteria for treatment through progression (Treatment Arms 1 and 2) and retreatment (Treatment Arm 1).

Retreatment (Treatment Arm 1)

Patients in Treatment Arm 1 with radiological progression who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and who meet the criteria for retreatment in the setting of PD (below), may start retreatment with durvalumab + tremelimumab combination therapy. For retreatment, the same assessments should be done as in the first treatment period, with the exception of the hepatitis B, hepatitis C and HIV tests. In addition, PK, ADA, CCI EGFR/ALK, PD-L1, and whole blood for gene expression, which do not need to be collected a second time.

Patients with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible for starting retreatment with durvalumab + tremelimumab combination therapy.

For all patients in Treatment Arm 1 who begin retreatment, the Investigator should ensure the patients do not have any significant, unacceptable, or irreversible toxicities that indicate restarting treatment would not further benefit the patient.

Patients in Treatment Arm 1 meeting the retreatment criteria below will follow the same treatment guidelines followed during the original 'post-chemotherapy' q4w treatment period (Table 2):

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

Crossover within the study will not be permitted.

Patients randomized to the durvalumab + tremelimumab combination therapy arm (Treatment Arm 1) may undergo retreatment with the combination as described below:

- Patients who complete the 5 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of clinical progression or radiological PD during the durvalumab monotherapy portion of the combination regimen (see Appendix E), may restart treatment with the combination.

- During the retreatment period, patients in the durvalumab + tremelimumab combination therapy group (Treatment Arm 1) will continue durvalumab dosing at 1500 mg q4w with 75 mg of tremelimumab q4w for 4 doses/cycles each. Patients will then continue with durvalumab monotherapy at 1500 mg q4w.

Note: If a patient's weight falls to 30 kg or below, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab and 1 mg/kg tremelimumab until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg ± tremelimumab 75 mg.

Criteria for treatment through progression (Treatment Arms 1 and 2) and retreatment (Treatment Arm 1)

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

- The patient does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient.
- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG performance status to >1.
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention.
- The patient still fulfills the eligibility criteria for this study (see Sections 3.1 and 3.2) with the exception of inclusion criteria 5, 9, and 11 and exclusion criteria 2, 19, and 23.

Patients in Treatment Arms 1 and 2 will not be permitted to continue immunotherapy if progression occurs after confirmed response (CR or PR as defined by RECIST 1.1) to immunotherapy treatment in the target lesions (regardless of the appearance of new lesions), ie, the response and progression events both occurred in the target lesions while receiving immunotherapy during the same treatment period.

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

The investigator may offer other therapies to patients who AstraZeneca and the Investigator determine may not continue treatment following objective disease progression.

7.2.2.3 Treatment Arm 3: No treatment through progression

For patients randomized to Treatment Arm 3, treatment through progression will not be permitted, and crossover to durvalumab + tremelimumab combination therapy + SoC chemotherapy or durvalumab monotherapy + SoC chemotherapy following objective disease progression will not be permitted.

Following objective disease progression, the Investigator may offer other therapies to the patient.

Following objective disease progression, patients in Treatment Arm 3 will continue to be followed for survival, even if another therapy to treat NSCLC is started.

Post Data Cut Off (DCO) for final analysis of OS for superiority

For patients continuing to receive durvalumab/tremelimumab treatment and/or SOC chemotherapy and patients on survival follow-up following the DCO for final analysis of OS for superiority, it is recommended that the patients continue the scheduled site visits according to Table 12, Table 13 & Section 9.3 and investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab/tremelimumab and/or SOC chemotherapy in order to manage AEs in accordance with the durvalumab/tremelimumab toxicity management guidelines or as indicated in the local prescribing information for the relevant chemotherapy agent(please see Section6.9.1 & 6.9.2).

Post final Data Cut Off (DCO)

Patients who continue to receive benefit from their assigned treatment (durvalumab and/or SOC chemotherapy) at the final DCO and database closure may continue to receive their assigned treatment as long as they and their physician feel they are gaining clinical benefit(See section 7.8). Investigators will monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab/tremelimumab and/or SOC chemotherapy in order to manage AEs in accordance with the durvalumab/tremelimumab toxicity management guidelines or as indicated in the local prescribing information for the relevant chemotherapy agent (please see Section 6.9.1 & 6.9.2).

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

7.3 Labeling

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

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

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

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.

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.

The IP label on the pack/bottle/carton for SoC specifies the appropriate storage for these agents.

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 reconciliation of site drug accountability logs.

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 dispensed to and returned from the patient.

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the study site until the return of all unused study

drug to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements. The Investigator(s) is responsible for ensuring that the patient has returned all unused study drug.

7.7 Concomitant medications and other treatments

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

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 Table 8 and Table 9. Refer also to the Dosing Modification and Toxicity Management Guidelines (please see Section 6.9.1.

For chemotherapy agents, please refer to the local prescribing information with regard to warnings, precautions, and contraindications.

Table 8 Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
For all treatment arms	
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 other than those under investigation in this study	Should not be given concomitantly 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])
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP
For the durvalumab (MEDI4736) ± tremelimumab treatment arms only	
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or	Should not be given concomitantly, or used for premedication prior to the immuno-oncology infusions. The following are allowed exceptions:

Prohibited medication/class of drug:	Usage:
equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	• Use of immunosuppressive medications for the management of IP-related AEs. • Short-term premedication for patients receiving combination agents SoC, in which the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions. • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intra-nasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post-last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concurrently unless agreed by the Sponsor

AE Adverse event; CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4; EGFR Epidermal growth factor receptor; IP Investigational product; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1; SoC Standard of care; TKI Tyrosine kinase inhibitor.

Table 9 Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

7.7.1 Other concomitant treatment

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

7.7.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either pre-clinically or in patients. As durvalumab is a mAb and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected pharmacokinetic drug-drug interactions. The mechanism of action of durvalumab involves binding to PD-L1, and 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.

7.8 Post-study access to study treatment

Patients receiving study treatment at the time of study completion (ie, after final data cut-off date) may continue to receive study treatment up to meeting discontinuation criteria(see section 3.9) if, in the opinion of the Investigator, they are continuing to receive benefit from treatment.

The provision of durvalumab/tremelimumab treatment at study completion may include, but is not limited to, transition to a roll-over study, continuous supply within this trial (for example in countries where regulatory approval is not obtained for a roll-over study) or switching to commercial drug as permitted by local regulations. SOC chemotherapy will not be provided unless it is not locally available as standard of care.

After discontinuation of study treatment, the Investigator will be at liberty to define further the most appropriate anticancer treatment.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

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

A comprehensive statistical analysis plan (SAP) will be prepared and finalized within 3 months of the first randomized patient, and any subsequent amendments will be documented, with final amendments completed prior to the reporting of the data. The dual primary aims of this study are to assess the efficacy of durvalumab monotherapy + SoC chemotherapy compared with SoC chemotherapy alone in terms of PFS and OS in all patients.

8.2 Sample size estimate

The study will enroll approximately 2000 patients to randomize approximately 1000 patients in a 1:1:1 ratio to durvalumab + tremelimumab combination therapy + SoC chemotherapy, durvalumab monotherapy + SoC chemotherapy, or SoC chemotherapy alone (approximately 333 patients in each treatment arm), including at least 250 patients in each treatment arm with PD-L1 TC <50%. Once global enrollment is completed, the recruitment may continue in mainland China only. A total of up to 180 patients, including up to 135 patients in total with PD-L1 TC <50%, from China will be randomized (refer to Section 8.6 for more details).

The study is sized for dual primary endpoints to characterize the PFS and OS benefits of durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone in the intent-to-treat (ITT) population. Sample size and power analysis for the dual primary endpoints are described below. Refer to Section 8.5 for the multiple testing procedure and Section 8.5.9 for alpha allocation and alpha spending.

One interim analysis of PFS will be performed when approximately 80% of the target PFS events have occurred. Three interim analyses of overall survival (OS) will be performed; the first at the time of the interim PFS analysis (approximately 45% of the target OS events), the second at the time of the primary PFS analysis (approximately 61% of the target OS events) and the third when approximately 84% of the target OS events have occurred. The alpha will be split between the interim and final analyses using the Lan and DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, with the boundaries for the treatment comparison derived based upon the exact number of events at the time of analysis.

The final (primary) PFS analysis for superiority will be performed when the following conditions have been met:

- Approximately 497 BICR PFS events from the global cohort have occurred across the durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone treatment arms (75% maturity)

The final OS analysis for superiority will be performed when the following conditions have been met:

- Approximately 532 OS events have occurred across the durvalumab monotherapy + SOC chemotherapy and SoC chemotherapy alone treatment arms (80% maturity)

Dual primary Endpoints:

Durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone

(PFS in ITT population)

Assuming the true PFS HR is 0.67 and the median PFS in SoC chemotherapy alone arm is 6 months, 497 PFS events from the global cohort (75% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha level of 0.9% (with overall alpha for PFS 1%), allowing for 1 interim analysis conducted at approximately 80% of the target events. The smallest treatment difference that is statistically significant will be an HR of 0.79. Assuming a recruitment period of 16 months, this analysis is anticipated to be 25 months from FPI.

Durvalumab monotherapy + SoC chemotherapy versus SoC chemotherapy alone

(OS in ITT population)

Assuming the true OS HR is 0.7 and the median OS in SoC arm is 12.9 months, 532 OS events (80% maturity) will provide greater than 90% power to demonstrate statistical significance at the 2-sided alpha level of a 3.3% (with overall alpha for OS 4%), allowing for 3 interim analyses conducted at approximately 45%, 61% and 84% of the target events. The smallest treatment difference that is statistically significant will be an HR of 0.83. Assuming a recruitment period of 16 months, this analysis is anticipated to be 46 months from FPI.

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	
PFS and OS	PD-L1 TC <50% analysis set
PFS and OS	Full analysis set (ITT population)
ORR, DoR, BoR, APF12, PFS2, PROs, and symptom endpoints	PD-L1 TC <50% analysis set
ORR, DoR, BoR, APF12, PFS2, PROs, and symptom endpoints	Full analysis set (ITT population)
PFS, OS, ORR, BoR, DoR, APF12, and PFS2	PD-L1 TC <25% analysis set
PFS, OS, ORR, BoR, DoR, APF12, and PFS2	PD-L1 TC <1% analysis set
PK data	PK analysis set
PFS, OS, ORR, BoR, DoR, APF12, and PFS2	TMB high analysis set
Safety data	
Exposure	Safety analysis set
AEs	Safety analysis set
Laboratory measurements	Safety analysis set
Vital signs	Safety analysis set
ECGs	Safety analysis set

AE Adverse event; APF12 Proportion of patients alive and progression free at 12 months from randomization; BoR Best objective response; DoR Duration of response; ECG Electrocardiogram; ITT Intent-to-treat; ORR Objective response rate; OS Overall survival; PD-L1 Programmed cell death ligand 1; PFS Progression-free survival; PFS2 Time from randomization to second progression; PK Pharmacokinetic(s); PRO Patient-reported outcome; TC Tumor cell.

8.3.1 Full analysis set

The full analysis set (FAS) will include all randomized patients. 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 TC <50% analysis set

The PD-L1 TC<50% analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 TC <50% as defined by the Ventana SP263 PD-L1 IHC assay (ie, <50% PD-L1-membrane expression in tumoral tissue).

8.3.3 PD-L1 TC <25% analysis set

The PD-L1 TC<25% analysis set will include the subset of patients in the FAS whose PD L1 status is PD-L1 TC <25% as defined by the Ventana SP263 PD-L1 IHC assay (ie, <25% PD L1 membrane expression in tumoral tissue).

8.3.4 PD-L1 TC <1% analysis set

The PD-L1 TC <1% analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1 TC <1% as defined by the Ventana SP263 PD-L1 IHC assay (ie, <1% PD-L1-membrane expression in tumoral tissue).

8.3.5 TMB high analysis set

The TMB high analysis set will include the subset of patients in the FAS defined as per cut-off/threshold included in the final SAP prior to DBL with data external to Poseidon.

8.3.6 Safety analysis set

The safety analysis set will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized, according to the treatment received, that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

8.3.7 Pharmacokinetic analysis set

All patients who received at least 1 dose of IP per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set. The population will be defined by the Study Physician, Pharmacokineticist, and 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 PFS, ORR, DoR, BoR, and APF12 will be based on BICR tumor assessments according to RECIST 1.1. OS will be evaluated from all-cause mortality. Additionally, PFS2 will be defined by local clinical practice.

A sensitivity analysis of PFS will be performed using the Investigator tumor assessments.

8.4.2 RECIST 1.1-based endpoints

Blinded Independent Central Review of RECIST 1.1-based assessments

The BICR will be performed on all radiological scans of all patients. All images will be collected centrally. Prior radiotherapy reports will also be provided to the BICR to allow the selection of appropriate target lesions. The imaging scans will be reviewed by 2 independent radiologists using RECIST 1.1 and will be adjudicated, if required, by a third independent

radiologist who will choose the assessments of 1 of the 2 primary reviewers. For each patient, the BICR will define the overall visit response data (CR, PR, SD, PD, or NE). 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) will be derived from the scan dates.

Further details of the BICR will be documented in the Imaging Charter.

Investigator RECIST 1.1-based assessments

All RECIST 1.1 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).

The definitions of CR, PR, SD, and PD are given in Appendix E.

8.4.2.1 Dual primary endpoints

PFS and OS comparing durvalumab monotherapy +SoC versus SoC alone are the dual primary endpoints.

Progression-free survival

PFS (per RECIST 1.1 using BICR 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. 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 0 days unless they die within 2 visits of baseline.

The PFS time will always be derived based on scan/assessment dates 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 reviewer, where both select PD as a timepoint response and there is no adjudication for central review (BICR).

- For investigational assessments, the date of progression will be determined based on the earliest of the RECIST 1.1 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 will be recorded out of all scans performed at that assessment for the target lesions. Similarly, for non-target lesions, only the latest scan date will be recorded out of all scans performed at that assessment for the non-target lesions.

For Treatment Arms 1 and 2, patients with a single disease progression and with no further tumor assessment scans will be treated as PD in the analysis. In the absence of significant clinical deterioration, the investigational site will be advised to have the patient continue in their randomized experimental arms until radiological progression is confirmed (Appendix E). If progression is not confirmed, the patient should continue in their randomized experimental arms and on-treatment assessments.

For Treatment Arm 3, at least 1 scan documenting unequivocal radiographic progression.

CCI [redacted]

Overall survival

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.

Note: Survival calls will be made following the date of data cut-off for the analysis (these contacts should generally occur within 7 days of the data cut-off). If patients are confirmed to be alive or if the death date is after the data cut-off date, these patients will be censored at the date of data cut-off. Death dates may be found by checking publicly available death registries.

8.4.2.2 Secondary endpoints

Objective response rate

ORR (per RECIST 1.1 using BICR assessments) is defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

ORR will also be obtained using the algorithm described above for the RECIST 1.1 site Investigator tumor data.

CCI [redacted]

Duration of response

DoR (per RECIST 1.1 using BICR assessments) 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 a documented response.

Time from randomization to second progression

PFS2 will be defined as the time from the date of randomization to the earliest of the progression event 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 it may involve any of the following: objective radiological imaging, symptomatic progression, or death. Second progression status will be reviewed (q6w for the first 12 weeks relative to the date of randomization and q8w thereafter) following the progression event used for the primary variable PFS (the first progression) and status recorded. Patients who are alive and in whom a second disease progression has not been observed should be censored at the last time known to be alive, without a second disease progression, that is, censored at the latest of the PFS or PFS2 assessment date if the patient has not had a second progression or death.

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 using BICR assessments) at 12 months.

Best objective response

BoR will be calculated based on the overall visit responses from each RECIST 1.1 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 the last evaluable assessment in the absence of RECIST 1.1 progression, as determined by BICR.

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 1.1 using all BICR assessments up until the first progression event. For patients whose progression event is death, BoR will be calculated based upon all evaluable RECIST 1.1 assessments prior to death.

8.4.3 Calculation or derivation of safety variables

8.4.3.1 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 the last dose in all treatment arms, may be included in the AE summaries, but the majority of those summaries will omit those AEs observed after a patient has received further systemic non-protocol therapy for cancer. Further details will be provided in the SAP. Any events in the 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 study drug in all treatment arms will be produced. These events will not be included in AE summaries.

8.4.3.2 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 as 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.

8.4.3.3 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 a pre-dose and at least 1 post-dose value recorded
- If a CTCAE criterion does not consider changes from baseline, evaluable patients need only have 1 post-dose value recorded.

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

8.4.4 Calculation or derivation of patient-reported outcome variables

PRO questionnaires, a secondary endpoint of interest, will be assessed using the EORTC QLQ-C30 with the QLQ-LC13 module (HRQoL and lung cancer specific symptoms), CCI 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 full analysis set (FAS; ITT population) and the PD-L1<50% analysis sets, unless otherwise stated. The clinical meaningfulness threshold of the PRO analyses described below will be provided in the SAP.

8.4.4.1 EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual items (dyspnea, insomnia, appetite loss, constipation, and diarrhea), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers et al 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

Changes in score compared with baseline will be evaluated. For each subscale, if <50% of the subscale items are missing, then the subscale score will be divided by the number of non-missing items and multiplied by the total number of items on the subscales (Fayers et al 2001). 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.

Time to HRQoL/function deterioration

For the following HRQoL items of the EORTC QLQ-C30, time to deterioration will be analyzed:

- The Global Health Status/ QoL scale consisting of items 29 and 30 of the EORTC QLQ-C30. Item 29: How would you rate your overall health during the past week?

Item 30: How would you rate your overall quality of life during the past week? Patients are asked to rate their overall health and overall quality of life on a scale from 1 (very poor) to 7 (excellent).

Time to deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful deterioration that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to HRQoL/function deterioration. Patients with a single deterioration and with no further assessments will be treated as deteriorated in the analysis.

Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the HRQoL/function change could be evaluated.

Patients whose HRQoL (as measured by EORTC QLQ-C30) has not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the HRQoL/function could be evaluated. Also, if HRQoL deteriorates after 2 or more missed PRO assessment visits or if the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where HRQoL/function could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement in that symptom from baseline.

HRQoL/function improvement rate

The HRQoL/function improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement in that scale from baseline.

8.4.4.2 Lung cancer module (EORTC QLQ-LC13)

The QLQ-LC13 is a lung cancer specific module from the EORTC for lung cancer comprising 13 questions to assess lung cancer symptoms (cough, hemoptysis, dyspnea, and site-specific pain), treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication. Changes in score compared with baseline will be evaluated.

Time to symptom deterioration

For each of the following key symptom scales/items in the QLQ-LC13 and QLQ-C30, time to deterioration will be analyzed:

- Dyspnea: multi-item scale based on 3 questions: (“Were you short of breath when you rested; walked; climbed stairs?”), LC13,

- Cough: 1 item ("How much did you cough?"), LC13
- Pain: 3 individual items ("Have you had pain in your chest; your arm or shoulder; other parts of your body?"), LC13
- Appetite loss: 1 item ("Have you lacked appetite?"), C30
- Fatigue: 3 individual items ("Have you felt weak?", "Did you need to rest?", "Were you tired?"), C30

The dyspnea scale will only be used if all 3 items have been scored; otherwise the items are treated as single-item measures. The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales/single items of the EORTC QLQ-C30.

Time to symptom deterioration will be defined as the time from the date of randomization until the date of the first clinically meaningful symptom deterioration that is confirmed at a subsequent visit or death (by any cause) in the absence of a clinically meaningful symptom deterioration, regardless of whether the patient withdraws from study treatment or receives another anticancer therapy prior to symptom deterioration. Patients with single deterioration and no further assessments will be treated as deteriorated in the analysis.

Death will be included as an event only if the death occurs within 2 visits of the last PRO assessment where the symptom change could be evaluated.

Patients whose symptoms (as measured by QLQ-LC13) have not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the symptom could be evaluated. Also, if symptoms deteriorate after 2 or more missed PRO assessment visits or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where the symptom could be evaluated. If a patient has no evaluable visits or does not have baseline data they will be censored at 0 days.

Symptom improvement rate

The symptom improvement rate will be defined as the number (%) of patients with 2 consecutive assessments at least 14 days apart that show a clinically meaningful improvement in that symptom from baseline.

8.4.4.3 CCI

CCI

CCI

[redacted]

8.4.5 Calculation or derivation of pharmacokinetic variables

8.4.5.1 Pharmacokinetic analysis

The PK analyses will be performed at AstraZeneca. The actual sampling times will be used in the PK calculations. PK concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. Samples below the lower limit of quantification will be treated as missing in the analyses. The PK data collected in this study may be utilized with data from other studies for population PK and/or PKPD analyses.

8.4.5.2 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab 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.

8.4.6 CCI

CCI

[redacted]

8.5 Methods for statistical analyses

The formal statistical analysis will be performed to test the following main hypotheses:

- H0: No difference between durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone
- H1: Difference between durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone

The dual primary endpoints are PFS and OS (durvalumab monotherapy +SoC chemotherapy versus SoC chemotherapy alone) in the ITT population (with PFS using BICR assessments per RECIST 1.1).

The final (primary) PFS analysis for superiority will be performed when the following conditions have been met:

- Approximately 497 BICR PFS events from the global cohort have occurred across the durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone treatment arms (75% maturity)

The final OS analysis for superiority will be performed when the following conditions have been met:

- Approximately 532 OS events have occurred across the durvalumab monotherapy + SOC chemotherapy and SoC chemotherapy alone treatment arms (80% maturity)

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 data will be summarized and analyzed by treatment arm based on the FAS, the PD-L1 TC <50% analysis set, the PD-L1 TC <25% analysis set, the PD-L1 TC <1% analysis set, and TMB high analysis set. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized on the safety analysis set.

Results of all statistical analysis will be presented using appropriately sized CIs and 2-sided p-values, unless otherwise stated.

Table 11 details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint.

Table 11 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Progression-free survival	Stratified log-rank tests for: Dual primary analyses using BICR RECIST 1.1 assessments: – Durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone for the ITT population Secondary analysis using BICR RECIST 1.1 assessments: – Durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone for the ITT population – Durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone for PD-L1 TC <50% population (stratified only for disease stage and histology), PD-L1 TC <25% population, PD-L1 TC <1% population and TMB high population – Durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone for PD-L1 TC <50% population (stratified only for disease stage and histology), PD-L1 TC <25% population, PD-L1 TC <1% population and TMB high population Sensitivity analyses using Investigator assessments (RECIST 1.1) CCI
Overall survival	– Stratified log-rank tests for: Dual primary analysis – Durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone for the ITT population Key secondary analysis – Durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone for the ITT population – Durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone for PD-L1<50% (stratified only for disease stage and histology), PD-L1 TC <25%, PD-L1<1% and TMB high population – Durvalumab monotherapy + SoC chemotherapy and SoC chemotherapy alone for PD-L1<50% (stratified only for disease stage and histology), PD-L1 TC <25%, PD-L1<1% and TMB high population
Objective response rate	Logistic regression for: Secondary analysis for the ITT, PD-L1<50%, PD-L1 <25%, PD-L1 <1% and TMB high population using BICR RECIST 1.1 assessments Sensitivity analysis for the ITT, PD-L1<50%, PD-L1 <25%, PD-L1 <1% and TMB high population using Investigator RECIST 1.1 assessments CCI

Endpoints analyzed	Notes
Duration of response	Analysis methods as described by Ellis et al 2008 for: Secondary analysis using BICR assessments (RECIST 1.1)
Proportion of patients alive and progression free at 12 months	Hazard ratio using the Kaplan Meier estimates of progression-free survival at 12 months (following method described by Klein et al 2007)
Time from randomization to second progression	Stratified log-rank test
Time to deterioration (EORTC QLQ-C30 and QLQ-LC13 endpoints)	Stratified log-rank test

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 dual primary endpoints and the secondary endpoints included in MTP.

- The dual primary endpoints: PFS and OS (durvalumab monotherapy +SoC chemotherapy versus SoC chemotherapy alone) in the ITT population (with PFS using BICR assessments per RECIST 1.1).
- The key secondary endpoints: PFS and OS (durvalumab + tremelimumab combination therapy + SoC chemotherapy and SoC chemotherapy alone) in the ITT population (with PFS using BICR assessments per RECIST 1.1).

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 as outlined in Figure 6. According to alpha (test mass) splitting and alpha recycling, if the higher level hypothesis in the MTP is rejected for superiority, the next lower level hypothesis will then be tested. The test mass that becomes available after each rejected hypothesis is recycled to lower level hypotheses not yet rejected. 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 the dual primary endpoints and the secondary endpoints included in MTP.

The overall 5% type 1 error will be first split between the dual primary endpoints of PFS and OS so an alpha level of 1% will be allocated to the primary PFS analysis and 4% will be allocated to the primary OS analysis. If PFS primary endpoint is significant, the 1% alpha level will be recycled to the key secondary PFS comparison of Arm 1 vs Arm 3. If OS primary endpoint is significant, the 4% alpha level will be recycled to the key secondary OS comparison of Arm 1 vs Arm 3. If PFS comparison of Arm 1 vs Arm 3 is significant, the 1% alpha level will be recycled to OS comparison of Arm 1 vs Arm 3. If OS comparison of Arm 1

vs Arm 3 is significant, the 4% alpha level will be recycled to PFS comparison of Arm 1 vs Arm 3.

If both PFS and OS comparisons of Arm 1 vs Arm 3 are significant, the available alpha level may be recycled to other comparisons. The recycle scheme of these additional compariosns, if included in MTP, will be specified in SAP prior to DBL.

The primary and secondary PFS endpoints are tested at 2 timepoints, 1 interim analysis and 1 final analysis. The primary and the key secondary OS endpoints are tested at 4 timepoints: 3 interim analyses and 1 final analysis. The tests including the interim and the final analyses that are for the same comparison/endpoint (ie, shown in 1 rectangle box in Figure 6) 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 will be recycled to next MTP level.

So, if the interim or final analyses indicate superiority in the tested hypothesis, then subsequent analyses of endpoints will be performed hierarchically in accordance with the MTP strategy. The alpha level allocated to the interim or final analyses will be determined by 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 upon the proportion of information available at time of the analysis. A separate Lan DeMets (O'Brien Fleming) spending function will be used to determine the alpha level at the interim and final analyses for the next lower level of hypothesis testing under MTP based on the information proportion of that lower level of hypothesis.

If the interim results do not meet the criterion of stopping for superiority for a given hypothesis, then follow-up will continue until the next target number of events for that comparison has been observed, following which the hypothesis will be re-tested. If the hypothesis is then rejected, subsequent testing will continue hierarchically in accordance with the MTP strategy.

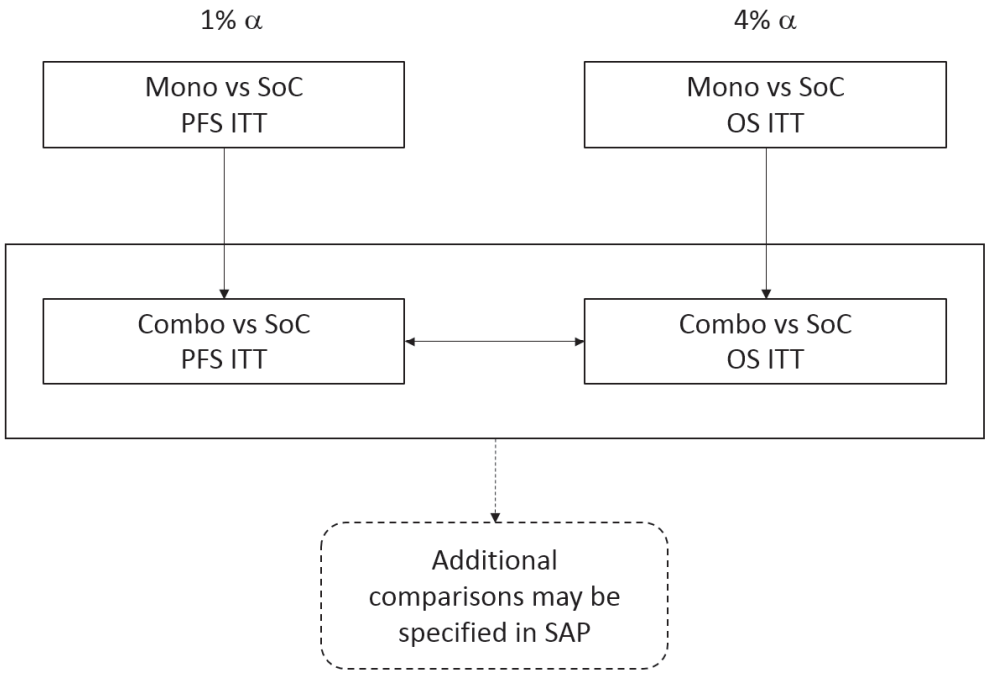
Assuming that 1% alpha level is available to a PFS hypothesis testing, if exactly 80% of the final target PFS events are available at the time of the interim, the 2 sided alpha level to be applied for the interim and final analyses of PFS would be 0.0034 and 0.009, respectively.

Assuming that 4% alpha level is available to a OS hypothesis testing, and if exactly 45%, 61% and 84% of the OS events required at the time of the final OS analysis are available at the times of the interim analyses, the 2-sided alpha level to be applied for the first interim, second interim, third interim and final analyses of OS would be 0.001, 0.0055, 0.0204 and 0.033 respectively. Refer Section 8.5.9 for details of interim analysis.

The details of the multiple testing procedure will be provided in the SAP prior to DBL.

Figure 6 shows the multiple testing framework.

Figure 6 Multiple testing procedures for controlling the type 1 error rate



Combo durvalumab + tremelimumab combination therapy + SoC chemotherapy; Mono durvalumab monotherapy + SoC chemotherapy; ITT Intent-to-treat; OS Overall survival; PFS Progression-free survival; SoC Standard of care; vs versus.

8.5.1 Analysis of the primary and key secondary variable(s)

8.5.1.1 Progression-free survival

The dual primary PFS analyses will be based on the programmatically derived RECIST 1.1 using the BICR tumor assessments. The dual primary analysis uses a stratified log-rank test adjusting for PD-L1 tumor expression (PD-L1≥ 50% versus PD-L1 <50%), histology (squamous versus non-squamous), and disease stage (Stage IVA and Stage IVB). The effect of experimental arms versus SoC arm will be estimated by the HR together with its corresponding 95% CI and p-value.

The HR and its CI can be estimated from the 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 PFS will be presented by treatment arm and PD-L1 tumor status and TMB subgroup, where appropriate. 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.

Sensitivity analyses will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled timepoints. The midpoint between the time of progression and the previous evaluable RECIST assessment will be analyzed using a log-rank test. For patients whose death was treated as PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust even in highly asymmetric assessment schedules (Sun and Chen 2010).

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following 2 or more non-evaluable tumor assessments will be included. In addition, patients who take subsequent therapy prior to progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. This analysis will be supported by a Kaplan-Meier plot of the time to censoring where the censoring indicator of the PFS analysis is reversed.

Ascertainment bias will be assessed by analyzing the site Investigator data. The stratified log-rank test will be repeated on the programmatically derived PFS using the site Investigator data based upon RECIST 1.1. The HR and CI will be presented.

If there is an important discrepancy between the primary analysis using the BICR assessments and this sensitivity analysis using Investigator assessments, the proportion of patients with site but no central confirmation of progression will be summarized; such patients have the potential to introduce bias in the central review due to informative censoring. An approach that imputes an event at the next visit in the central review analysis may help inform the most likely HR value (Fehrenbacher et al 2016, Fleischer et al 2011), but only if an important discrepancy exists.

CCI [redacted]

Subgroup analyses will be conducted comparing PFS (per RECIST 1.1) between experimental arms versus SoC arm 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 (PD-L1 TC ≥50% versus TC <50%)
- Histology (squamous versus non-squamous)
- Chemotherapy (abraxane doublet versus pemetrexed doublet versus gemcitabine doublet)
- Smoking (current smoker, former smoker, never smoker)
- Race (Asian versus non-Asian)

- PD-L1 using cutpoints of 1% and 25% tumor expression (<1% versus ≥1%, and <25% versus ≥25%)
- TMB (high vs low)
- PS status (0 versus 1)
- Brain metastasis (Yes vs No)
- Disease stage (stage IVa versus stage IVb)

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 PFS.

Unless there is a marked difference between the results of the statistical analyses of the PFS from the BICR data and that of the site Investigator tumor data, these subgroup analyses will only be performed on the PFS endpoint using the BICR data.

Cox proportional hazards modeling will be employed to assess the effect of covariates on the HR estimate. Before embarking on more detailed modeling, an initial model will be constructed containing treatment and the stratification factors alone to ensure that any output from the Cox modeling is likely to be consistent with the results of the stratified log-rank test.

Interactions between treatment and stratification factor will also be tested to rule out any qualitative interaction using the approach of Gail and Simon (Gail and Simon 1985).

Additionally, for each subgroup, the HR (for the treatment comparisons of interest) and 95% CI will be calculated from a single model that contains treatment and subgroup. These will be presented on a forest plot including the HR and 95% CI.

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 PFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

Censoring rules will be provided in the SAP.

8.5.1.2 Overall survival

OS will be analyzed using a stratified log-rank tests, using the same methodology as described for the primary PFS endpoint. The effect of experimental arms versus SoC arm will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm and PD-L1 tumor status and TMB subgroup, where appropriate. 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.

The boundaries (ie, adjusted alpha levels) for the treatment comparison at the interim and final analyses for OS will be derived based upon the exact number of OS events using the Lan and DeMets approach that approximates the O'Brien Fleming spending function (see Section 8.2).

CCI [redacted]

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 using the BICR tumor data. The ORR will be compared between experimental arms versus SoC arm 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 CI and p-value (based on twice the change in log-likelihood resulting from the addition of a treatment factor to the model). This analysis will be performed in the ITT, PD-L1 <50%, PD-L1 <25%, PD-L1 <1%, and TMB high populations.

This analysis of ORR will be repeated using the results of the programmatically derived ORR using the site Investigator tumor data based upon RECIST 1.1 as a sensitivity analysis to confirm the results of the primary analysis derived from the eCRFs.

CCI [redacted]

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 for all patients (ie, the FAS). For each treatment arm, best overall response (BoR) will be summarized by n (%) for each category (CR, PR, SD, PD, and NE). No formal statistical analyses are planned for BoR.

8.5.2.2 Duration of response

In order to analyze the DoR between the experimental arms and the SoC arm, the expected duration of response (EDoR) will be derived for each treatment arm (Ellis et al 2008) using

the BICR tumor data. The EDoR is the product of the proportion of patients responding to treatment and the mean DoR in responding patients and provides an estimate based on all randomized patients. Treatments will be compared by calculating the ratio of EDoRs, using an appropriate probability distribution (to be specified in the SAP) for DoR in responding patients. Additionally, 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). Further details will be provided in SAP.

8.5.2.3 Proportion of patients alive and progression free at 12 months

The APF12 will be summarized (using the Kaplan-Meier curve) and presented by treatment arm. APF12 will be compared between experimental arms and SoC arm by using the Kaplan-Meier estimator of PFS at 12 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 events 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).

8.5.2.4 Patient-reported outcomes

EORTC QLQ-C30

Time to deterioration will be analyzed using a stratified log-rank test, using the same methodology as described for the primary PFS endpoint.

The effect of experimental arms versus SoC arm will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

A summary of the symptom improvement rate for each of the 3 symptom scales and the 5 individual symptom items will be produced. Similarly, a summary of QoL/function improvement rate for each of the 5 function scales (physical, role, emotional, cognitive, and social) and global health status/QoL will be produced.

Summaries of the original and the change from baseline values of each symptom scale/item, the global HRQoL score, and each functional domain will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal item will also be produced for each treatment arm.

EORTC QLQ-LC13

Time to deterioration in the ITT population will be analyzed using a stratified log-rank test, using the same methodology as described for the primary PFS endpoint.

The effect of experimental arms versus SoC arm will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

A summary of the symptom improvement rate for each of the 6 individual-symptom items will be produced.

Summaries of the original and the change from baseline values of each symptom (dyspnea, cough, hemoptysis, chest pain, arm/shoulder pain, and/or other pain) and each treatment-related symptom (sore mouth, dysphagia, peripheral neuropathy, and alopecia) will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate. Summaries of the number and percentage of patients in each response category at each visit for each ordinal-symptom item will also be produced for each treatment arm.

For PRO symptoms and HRQoL endpoints, the overall type I error (5% [2-sided]) will be controlled across the 5 primary PRO measures of cough, dyspnea, and pain as assessed by the EORTC QLQ-LC13 and fatigue and appetite loss as assessed by the EORTC QLQ-C30 using the Bonferroni-Holm procedure (Holm 1979).

The physical functioning and overall health status domains of the EORTC QLQ-C30 are furthermore pre-specified endpoints of interest.

CCI [redacted]

8.5.3 CCI [redacted]

CCI [redacted]

8.5.4 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 durvalumab + tremelimumab combination therapy will be produced separately, if required.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to durvalumab + tremelimumab combination therapy, durvalumab monotherapy, and SoC alone will be summarized. Time on study; durvalumab + tremelimumab combination therapy, durvalumab monotherapy, and SoC dose delays/interruptions; and SoC dose reductions will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

8.5.5 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day, and a summary will be provided for all evaluable patients in the PK analysis population.

8.5.6 Immunogenicity analysis

Immunogenicity results will be listed by patient, and a summary of the number and percentage of patients who develop detectable anti-durvalumab and anti-tremelimumab antibodies will be provided. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab and anti-tremelimumab antibodies.

CCI [redacted]

8.5.7 CCI

CCI

8.5.8 CCI

CCI

8.5.9 Interim analysis

Interim monitoring for safety will be conducted by the IDMC. Details of the plan and communication process will be provided in the SAP and the IDMC Charter.

In addition, one interim analysis of PFS will be performed when approximately 80% of the target PFS events have occurred. Three interim analyses of overall survival (OS) will be performed; the first at the time of the interim PFS analysis (approximately 45% of the target OS events), the second at the time of the primary PFS analysis (approximately 61% of the target OS events) and the third when approximately 84% of the target OS events have occurred. The interim analyses will be performed for the analyses specified in multiple testing procedure, refer to Section 8.5. It is expected that global recruitment will have completed prior to the results of the interim analyses being available.

The Lan DeMets spending function that approximates an O'Brien Fleming approach will be used to account for multiplicity introduced by including the interim analysis for superiority (Lan and DeMets 1983).

The alpha level that is spent at the interim and final analyses for the PFS analyses will be calculated using the Lan DeMets spending function separately. If exactly 80% of the target events are available at the time of each interim comparison (368 out of 465 events occurred in Arm1 and 3, ITT population;397 out of 497 events occurred in Arm 2 and 3, ITT population), with overall 2-sided alpha levels of 0.01, the 2-sided alpha level to be applied for the interim and final analyses of each PFS would be 0.0034 and 0.009, respectively.

The alpha level that is spent at the interim and final analyses for the OS analyses will be calculated using the Lan DeMets spending function separately. If exactly 45% of the target events are available at the time of the first interim comparison (243 out of 532 events occurred in Arm 1 and 3 or Arm 2 and 3, ITT population and if exactly 61% of the target events are available at the time of the second interim comparison (328 out of 532 events occurred in Arm 1 and 3 or Arm 2 and 3, ITT population), and if exactly 84% of the target events are available at the time of the third interim comparison (449 out of 532 events occurred in Arm 1 and 3 or Arm 2 and 3, ITT population), with overall 2-sided alpha levels of 0.04, the 2-sided alpha level to be applied for the first interim, second interim, third interim and final analyses of each OS analysis would be 0.001, 0.0055, 0.0204 and 0.033 respectively.

If the interim analyses indicate superiority, subsequent analyses of other endpoints will be performed in accordance with the hierarchical multiple testing strategy described in Section 8.5.

8.6 China cohort

It is planned to randomize up to 180 patients from China, including up to 135 patients with PD-L1 TC <50%, before global enrollment completion. This is to ensure adequate Chinese patient participation to satisfy CFDA requirements to evaluate consistency in safety and efficacy in Chinese patients. If China enrollment cannot complete prior to the last patient first visit (LPFV) of the global cohort, then the following portion of this section will be applied.

The global cohort will enroll approximately 2000 patients to randomize approximately 1000 patients. The China cohort consists of all patients from sites in China and enrolled prior to the last patient last visit of the global cohort. The China cohort has up to 180 randomized patients, including up to totally 135 patients with PD-L1 TC <50%. The global cohort consists of all patients recruited by the documented date of LPFV of the global cohort. Global recruitment will be complete once approximately 1000 patients have been randomized. The recruitment across all sites will then be closed except for those sites in China, where recruitment of patients will continue. Hence, a patient randomized in the China cohort prior to the LPFV of the global cohort enrollment will be included in both the global FAS and the China FAS. A patient randomized in the China cohort after the LPFV of the global cohort enrollment will be included only in the China FAS.

Per CFDA guidance, in addition to the evaluation of the global cohort data for primary, secondary and safety objectives, evaluation of consistency in efficacy and safety in Chinese and Asian populations is required to facilitate the benefit-risk assessment for Chinese patients. Hence, the safety and efficacy data in the China cohort will be analyzed separately where the same endpoint definitions (as described in Section 8.4) and the same analysis methods (as detailed in Section 8.5) are applied.

The China FAS will include all patients randomized in the China cohort and will be used for all China-only efficacy analyses.

The China safety analysis set will consist of all patients recruited in the China cohort who received at least 1 dose of study treatment and for whom post-dose data are available.

Efficacy analyses for the China cohort will be performed when the PFS and/or OS data from the patients from China are of similar maturity at which significant clinical efficacy is established in the global cohort, eg, if PFS efficacy is established at the PFS interim analysis, a similar maturity will be used for the consistency evaluation.

All statistical analyses will be considered exploratory and only performed if sufficient numbers of events or patients are available (eg, ≥20 OS or PFS events). Unless specified otherwise, descriptive statistics only will be presented. No adjustment for multiplicity will be made and the procedure for hierarchical testing detailed in Section 8.5 will not be followed. PFS and OS efficacy evaluation for the China cohort will be performed once, respectively.

Details of the China cohort and Asian population analyses, including the vendor to perform the analyses, will be specified in the China supplementary SAP, which is to be finalized before the global cohort data locks for analysis.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first patient is enrolled in the study, an AstraZeneca representative will review and discuss the requirements of the clinical study protocol and related documents with the investigational staff and train them in any study-specific procedures and IVRS/IWRS, WBDC, and any ePRO systems to be utilized.

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

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

9.2 Monitoring of the study

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

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, data are being accurately and timely recorded in the eCRFs, biological samples are handled in accordance with the Laboratory Manual, and 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 that withdrawal of informed consent for the use of the patient's biological samples is reported, 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 Investigators or other staff at the centers need information and advice about the study conduct.

9.2.1 Source data

Refer to the CSA for location of source data.

9.2.2 Study agreements

The Principal Investigator 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 the 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 Principal Investigator should be in place before any study-related procedures can take place or before any patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the CSA.

9.3 Study timetable and end of study

The Investigator will be notified by AstraZeneca when recruitment is complete.

The end of the study is defined as "the last visit of the last patient undergoing the study". The study started in Quarter 2 2017 (first patient enrolled). The last patient in the global cohort was enrolled in Quarter 3 2018. The estimated date of last patient completed in the China cohort will be later than the estimated date of last patient completed in global cohort. The study is expected to end by Quarter 4 2023. The end of the study is defined as "the last visit of the last patient undergoing the study".

Data collection during long-term follow up until study end:

After the final analysis of OS for superiority is conducted, ongoing patients in the study will continue to be followed for long-term data collection

1) Following DCO for the final analysis of superiority for OS for approximately 12 months:
There will be reduced schedule of assessments to allow collection of safety data (for safety reporting) and survival data for long-term follow-up (as per Table 12)

2) Subsequent to safety reporting :
There will be only limited assessments to allow collection of safety data and survival data for long-term follow-up (as per Table 13)

- Subjects continuing Durvalumab and Tremelimumab with or without pemetrexed maintenance therapy (Arms 1 and 2) & subject receiving pemetrexed maintenance therapy (Arm 3) should continue to receive study treatment until objective disease progression, unless contraindicated per the Investigator (see Section 3.9, 7.2.2)

- Subjects in survival follow-up should continue further visits for survival assessment (see section 5.1.2).

- All AEs/SAEs collection (see section 6).

Table 12 Schedule of study assessments and relevant eCRF pages to be completed during Long-term follow-up (up to approximately 12 months after DCO for final analysis of OS for superiority)

(* Visit windows and timepoints for assessments should be performed as per details outlined in Table 2 for patients ongoing study treatment and in Table 3 for patients in follow-up period.)

Assessment	Relevant eCRF page
Durvalumab, Tremelimumab & Pemetrexed Exposure (applicablefor patients continuing Durvalumab, Tremelimumab or Pemetrexed treatment post final analysis of OS for superiority)	EX, EX4, EX7, EX8
Discontinuation (applicable for patients continuing Durvalumab, Tremelimumab & Pemetrexed treatment post final analysis of OS for superiority)	DOSDISC, DOSDISC1, DOSDISC4, DOSCDISC7, DOSDISC8
Survival assessment	SURVIVE
Statement of death	DEATH
Subsequent anti-cancer therapy	CAPRX1, CAPRXR2
CCI	
All AEs/SAEs experienced by patients whilst receiving treatment or within 90 days of treatment discontinuing. If SAE is reported then all data relevant to the SAE (e.g. concomitant medications, laboratory data, dosing data, new medical or surgical history) should be submitted under "Description of AE" as part of the SAE report	AE, SERAE
WHO/ECOG Performance Status	PSTAT
Vital signs[a]	VS
Full physical examination	PE
12-lead ECG[b]	EG
Laboratory assessments Including 1) Clinical Chemistry[c] 2) Hematology[c] 3) APTT and INR[c] 4) TSH, free T3, and free T4 [c, d] 5) Urinalysis 6) Pregnancy Test[e]	LB, LB3, LB4, LB5, LB6, PREG

a Body weight will be recorded along with vital signs.
b Any clinically significant cardiovascular findings require confirmation by ECG.
c Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion (samples must have been obtained within 3 days prior to the infusion).
d Free T_3 and free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
e Pregnancy test will be performed in women of childbearing potential only. A urine or serum pregnancy test is acceptable.

Table 13 Schedule of study assessments and relevant eCRF pages to be completed during long-term follow-up (12 months after DCO for final analysis of OS for superiority)

(* Visit windows and timepoint for assessment should be performed as per details outlined in Table 2 for patients onoing study treatment and in table 3 for patients in follow-up period.)

Assessment	Relevant eCRF page
Durvalumab, Tremelimumab & Pemetrexed Exposure (applicable for patients continuing Durvalumab, Tremelimumab or Pemetrexed treatment post final analysis of OS for superiority)	EX, EX4, EX7, EX8
Discontinuation (applicable for patients continuing Durvalumab, Tremelimumab & Pemetrexed treatment post final analysis of OS for superiority)	DOSDISC, DOSDISC1, DOSDISC4, DOSCDISC7, DOSDISC8
Survival assessment	SURVIVE
Statement of death	DEATH
Subsequent anti-cancer therapy	CAPRX1, CAPRXR2
CCI	
All SAEs experienced by patients whilst receiving treatment or within 90 days of treatment discontinuing. If SAE is reported then all data relevant to the SAE (e.g. concomitant medications, laboratory data, dosing data, new medical or surgical history) should be submitted under "Description of AE" as part of the SAE report	SERAE
WHO/ECOG Performance Status	PSTAT

The study may be terminated at individual centres once there are no longer any patients being treated or in overall survival follow up or once the final DCO for the study has cored and all queries at that centre have been resolved.

Also, 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 involving durvalumab and/or tremelimumab.

9.4 Data management by AstraZeneca or delegate

Data management will be performed by AstraZeneca Data Management Centre staff according to the Data Management Plan.

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

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 WHO Drug Dictionary. Classification coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Centre.

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.

Data collection per section 9.3 will continue post DCO for final analysis of OS for superiority for collection of limited data in long term survivors.

When all data have been coded, validated, signed, and locked, a clean file will be declared. Any treatment-revealing data may be added thereafter, 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 associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) 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 Council for Harmonisation (ICH)/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

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

10.3 Ethics and regulatory review

An EC/IRB should approve the final study protocol, including the final version of the Informed Consent Form 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 EC/IRB, and the Principal Investigator to the Investigator and study site staff.

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

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

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

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

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

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

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

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure that each patient is notified that he 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 that each patient provides a signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure that 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.

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 Principal Investigator and AstraZeneca.

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

The amendment is to be approved by the relevant EC/IRB and, if applicable, 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 Principal Investigator. 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 required by local regulations, any administrative change will be communicated to or approved by each EC/IRB.

For sites in Japan: Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca. If it is necessary for the Clinical Study Protocol to be amended, the new version of the Clinical Study Protocol 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 Clinical Study Protocol amendment requires a change to a particular center's Informed Consent Form, then AstraZeneca and the center's IRB should be notified by the Principal Investigator. Approval of the revised Informed Consent Form by AstraZeneca and by the IRB is required before the revised form is used.

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 purposes of an audit or inspection are to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and to determine whether data were recorded, analyzed, and accurately reported according to the Clinical Study Protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

11. LIST OF REFERENCES

Aaronson et al 1993
Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

Alexandrov et al 2013
Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Blankin AV et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415-21.

CCI

Antonia et al 2016a
Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Onc 2016;17(6):299-308.

Antonia et al 2016b
Antonia SJ, Kim SW, Spira AI, Ahn MJ, SHI Ou, Stjepanovic N et al. Safety and clinical activity of durvalumab (MEDI4736), an anti-PD-L1 antibody, in treatment-naïve patients with advanced non–small-cell lung cancer. J Clin Oncol 2016;34(suppl; abstr 9029).

Bergman et al 1994
Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M; EORTC Study Group on Quality of Life. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials.
Eur J Cancer 1994;30A(5):635-42.

Bonomi 2010
Bonomi PD. Implications of key trials in advanced nonsmall cell lung cancer.
Cancer 2010;116(5):1155-64.

Borghaei et al 2018
Borghaei H, Hellmann MD, Paz-Ares L, Ramalingam SS, Reck M, O'Byrne KJ et al. Nivolumab + Ipilimumab, Nivolumab + Chemotherapy, and Chemotherapy in Chemo-Naïve Patients With Advanced Non-Small Cell Lung Cancer and <1% Tumor PD-L1 Expression: Results From CheckMate 227. J Clin Oncol 36, 2018 (Suppl: abstr 9001).

Brahmer et al 2012
Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.
N Engl J Med 2012;366(26):2455-65.

Burman et al 2009
Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni-based multiple tests. Stat Med 2009;28(5):739-61.

Carbone et al 2017
Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M et al. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. N Engl J Med 2017;376(25):2415-26.

Ciuleanu et al 2009
Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomized, double-blind, phase 3 study. Lancet 2009;374(9699):1432-40.

Cox 1972
Cox DR. Regression models and life-tables. J Royal Stat Society 1972;Series B 34(2):187-220.

D'Addario et al 2010
D'Addario G, Fruh M, Reck M, Baumann P, Klepetko W, Felip E et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up.
Ann Oncol 2010;21(Suppl 5):116-9.

Dunn et al 2004
Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting.
Annu Rev Immunol 2004;22:329-60.

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.

Ellis et al 2008
Ellis S, Carroll KJ, Pemberton K. Analysis of duration of response in oncology trials.
Contemp Clin Trials 2008;29(4):456-65.

CCI

Fayers et al 2001
Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A; EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.

Fairman et al 2014
Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C et al. Pharmacokinetics of durvalumab, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumours. Journal of Clinical Oncology, 2014 ASCO Annual Meeting Abstracts;32(5s): (suppl; abstr 2602).

FDA Guidance 2011
Food and Drug Administration. Guidance for Industry: Clinical trial endpoints for the approval of non-small-cell lung cancer drugs and biologics. June 2011. Available from: URL: http://www.fda.gov/downloads/Drugs/Guidances/UCM259421.pdf. Accessed 21 May 2014.

Fehrenbacher et al 2016
Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, Phase 2, randomised, controlled trial. Lancet 2016;387(10030):1837-46.

Fife and Bluestone 2008
Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev 2008;224:166-82.

Fleischer et al 2011
Fleischer F, Gaschler-Markefski B, Bluhmki E. How is retrospective independent review influenced by investigator-introduced informative censoring: a quantitative approach. Stat Med 2011;30(29):3373-86.

Gail and Simon 1985
Gail M, Simon R. Tests for qualitative interactions between treatment effects and patient subsets. Biometrics 1985;41(2):361–72.

Gainor 2016
Gainor JF. Moving programmed death-1 inhibitors to the front lines in non-small-cell lung cancer. J Clin Oncol. 2016;34(25):2953-5.

Garassino et al 2016
Garassino MC, Vansteenkiste J, Kim JH, Lena H, Mazieres J, Powderly J et al. Durvalumab in ≥3rd-line locally advanced or metastatic, EGFR/ALK wild-type NSCLC: results from the Phase 2 ATLANTIC study. IASLC 17th World Conference on Lung Cancer. 2016.

Garon et al 2015
Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP et al. KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372(21):2018-28.

Gettinger et al 2015
Gettinger SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA et al. Overall survival and long-term safety of nivolumab (anti-programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non-small-cell lung cancer. J Clin Oncol 2015;33(18):2004-12.

Glimm et al 2009
Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. Stat Med 2009;29(2):219-28.

GLOBOCAN 2012
GLOBOCAN. Lung cancer, estimated incidence, mortality and prevalence worldwide in 2012. International Agency for Research on Cancer, World Health Organization; Lyon, 2012 [cited 16 April 2015]. Available from: URL: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

Gandara et al 2018
Gandara DR, Paul SM, Kowanetz M, Schleifman E, Zou W, Li Y, Rittmeyer A et al. Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab. Nature Medicine 2018, Available from: URL: https://doi.org/10.1038/s41591-018-0134-3.

Hellmann et al 2017
Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol 2017;18(1):31-41.

Hellmann et al 2018
Hellmann MD, Ciuleanu T-E, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. NEJM.org (posted on April 16, 2018, DOI: 10.1056/NEJMoa1801946).

CCI [redacted]

Hirano et al 2005
Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity.
Cancer Res 2005;65(3):1089-96.

Holm 1979
Holm S. A simple sequentially rejective multiple test procedure.
Scand J Statistics 1979;6:65-70.

Howlander et al 2014
Howlander N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, et al. SEER cancer statistics review, 1975-2011. Bethesda (MD): National Cancer Institute. Available from: URL:http://seer.cancer.gov/csr/1975_2011/. Based on November 2013 SEER data submission (posted to the SEER web site, April 2014).

IASLC Staging Manual in Thoracic Oncology 2016
Rami-Porta R, ed. Staging manual in thoracic oncology (2nd edition; includes 8th edition tumor, node, and metastasis classification (TNM) information for lung cancer, plural mesothelioma, thymic malignancies, and carcinoma of the oesophagus and of oesophagogastric Junction). IASLC 2016. (Available on request).

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade.
Proc Natl Acad Sci USA 2002;99(19):12293-7.

Juergens et al 2016
Juergens RA, Hao D, Laurie SA, Mates M, Tehfe M, Bradbury P, et al. Pemetrexed / cisplatin + durvalumab +/- tremelimumab in patients with advanced non-squamous NSCLC: A CCTG phase IB study - IND.226 Cohort 1. IASLC 17th World Conference on Lung Cancer. 2016.

Keir et al 2008
Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity.
Annu Rev Immunol 2008;26:677-704.

Klein et al 2007
Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med 2007;26(24):4505-19.

Lan and DeMets 1983
Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.

Langer et al 2016
Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17(11):1497-1508.

Larkin et al 2015
Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373(1):23-34.

CCI

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-α monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet 2013;52(11):1017-27.

NCCN 2014
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 4.2014. Available from: URL: www.nccn.org.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275-84.

Nishino et al 2013
Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: Immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013;19(14):3936-43.

Okazaki and Honjo 2007
Okazaki T and Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19(7):813-24.

CCI

Okudaira et al 2009
Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12(4):252-64.

Paz-Ares et al 2013
Paz-Ares LG, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31(23):2895-902.

Pazdur 2008
Pazdur R. Endpoints for assessing drug activity in clinical trials. Oncologist 2008;13(Suppl 2):19-21.

CCI

Pisters and LeChevalier 2005
Pisters KM, LeChevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol 2005;23(14):3270-8.

Postow et al 2015
Postow MA, Chesney J, Pavlick AC, Robert C, Grossman K, McDermott D et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372(1):2006-17.

Powles et al 2014
Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515(7528):558-62.

Qin et al 2016
Qin A, Coffey DG, Warren EH, Ramnath N. Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer.
Cancer Med 2016;5(9):2567-78.

Reck et al 2014
Reck M, Popat S, Reinmuth N, De Ruysscher D, Kerr KM, Peters S; ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):iii27-39.

Reck et al 2016
Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer.
N Engl J Med. 2016;375(19):1823-33.

Rizvi et al 2015a
Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with nonsmall cell lung cancer (NSCLC). J Clin Oncol 2015;33:Abstract 8032.

Rizvi et al 2015b
Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ et al. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer.
Science 2015;348(6230):124-8

Rizvi et al 2016
Rizvi NA, Hellmann MD, Brahmer JR, Juergens RA, Borghaei H, Gettinger S et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2016;34(25):2969-79.

CCI

Sandler et al 2006
Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer.
N Engl J Med 2006;355(24):2524-50.

Scagliotti et al 2008
Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer.
J Clin Oncol 2008;26(21):3543-51.

Schadendorf et al 2013
Schadendorf D, Hodi FS, Robert C et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma [abstract 24]. Presented at European Cancer Congress 2013 (ECCO-ESMO-ESTRO); 27 September to 01 October 2013; Amsterdam, The Netherlands.

Schiller et al 2002
Schiller JH, Harringdon D, Belani CP, Langer C, Sandler A, Krook J et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer.
N Engl J Med 2002;346(2):92-8.

Segal et al 2015
Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015;33:Abstract 3011.

Socinski et al 2016
Socinski MA, Creelan B, Horn L, Reck M, Paz-Ares L, Steins M et al. CheckMate026: A phase 3 trial of nivolumab vs investigator's choice of platinum-based doublet chemotherapy as first-line therapy for stage IV/recurrent programmed death ligand 1–positive NSCLC.
ESMO 2016.

CCI

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody.
Cancer Immunol Res 2015;3(9):1052-62.

Sun and Chen 2010
Sun X, Chen C. Comparison of Finkelstein's Method with the conventional approach for interval-censored data analysis. Stat Biopharm Res 2010;2(1):97-108.

Tarhini and Kirkwood 2008
Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. Expert Opin Biol Ther 2008;8(10):1583-93.

Topalian et al 2012
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer.
N Engl J Med 2012;366(26):2443-54.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012-24.

Wang et al 2014
Wang E, Kang D, Bae KS, Marshall MA, Pavlov D, Parivar K. Population pharmacokinetic and pharmacodynamics analysis of tremelimumab in patients with metastatic melanoma.
J Clin Pharmacol 2014;54(10):1108-16.

Whitehead and Whitehead 1991
Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 1991;10(11):1665-77.

Wolchok et al 2013
Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369(2):122-33

Zhang et al 2008
Zhang C, Wu S, Xue X, Li M, Qin X, Li W et al. Anti-tumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV.
Cytotherapy. 2008;10(7):711-9.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18-28.

Appendix A Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the 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 an SAE, 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 judgment 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 judgment must be used.

- Angioedema not severe enough to require intubation but requiring IV 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, 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.

Appendix B 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, for example, 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, for example, 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:

- UN3373 - Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

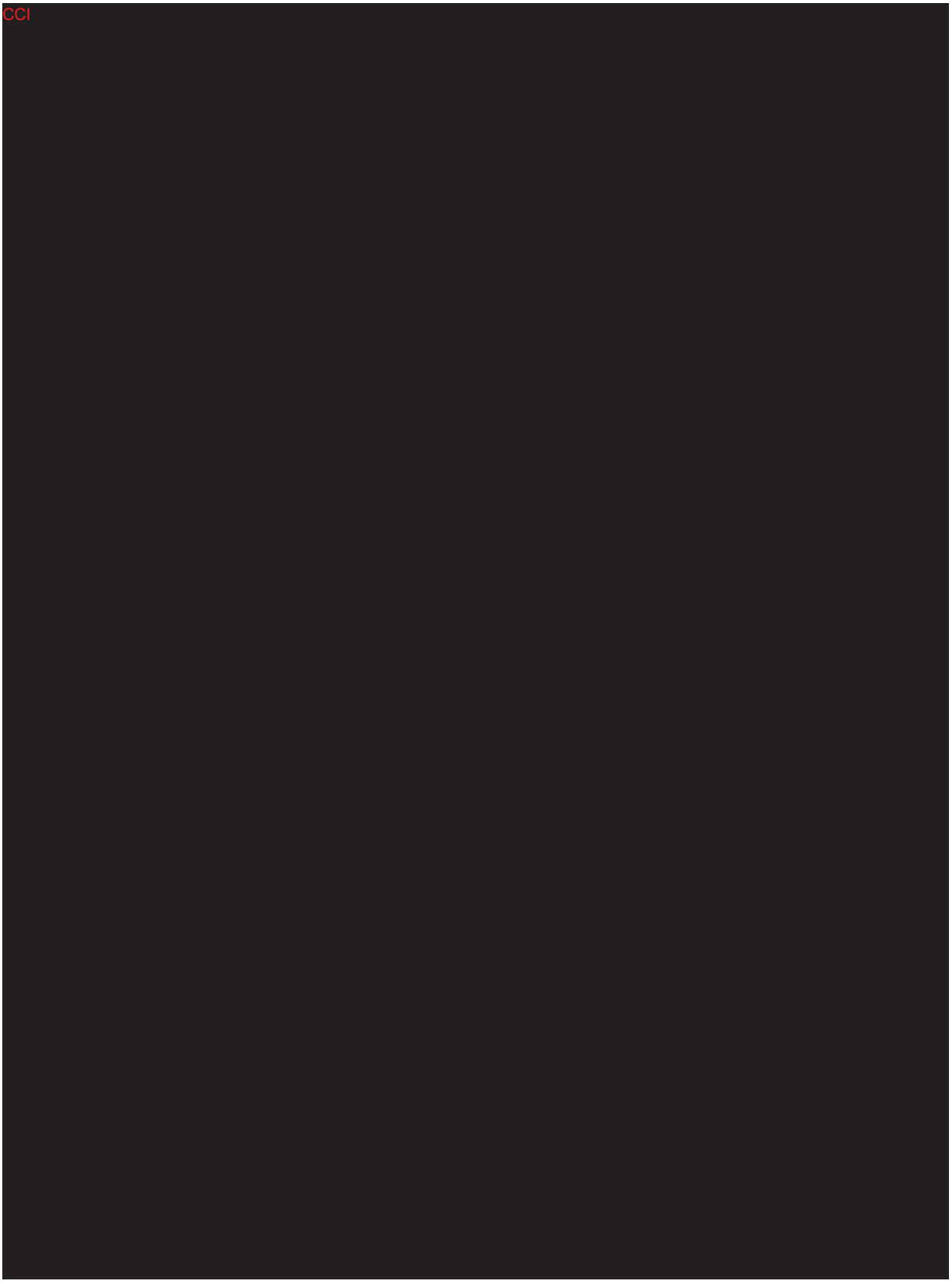
Exempt are all other materials with minimal risk of containing pathogens.

- 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.

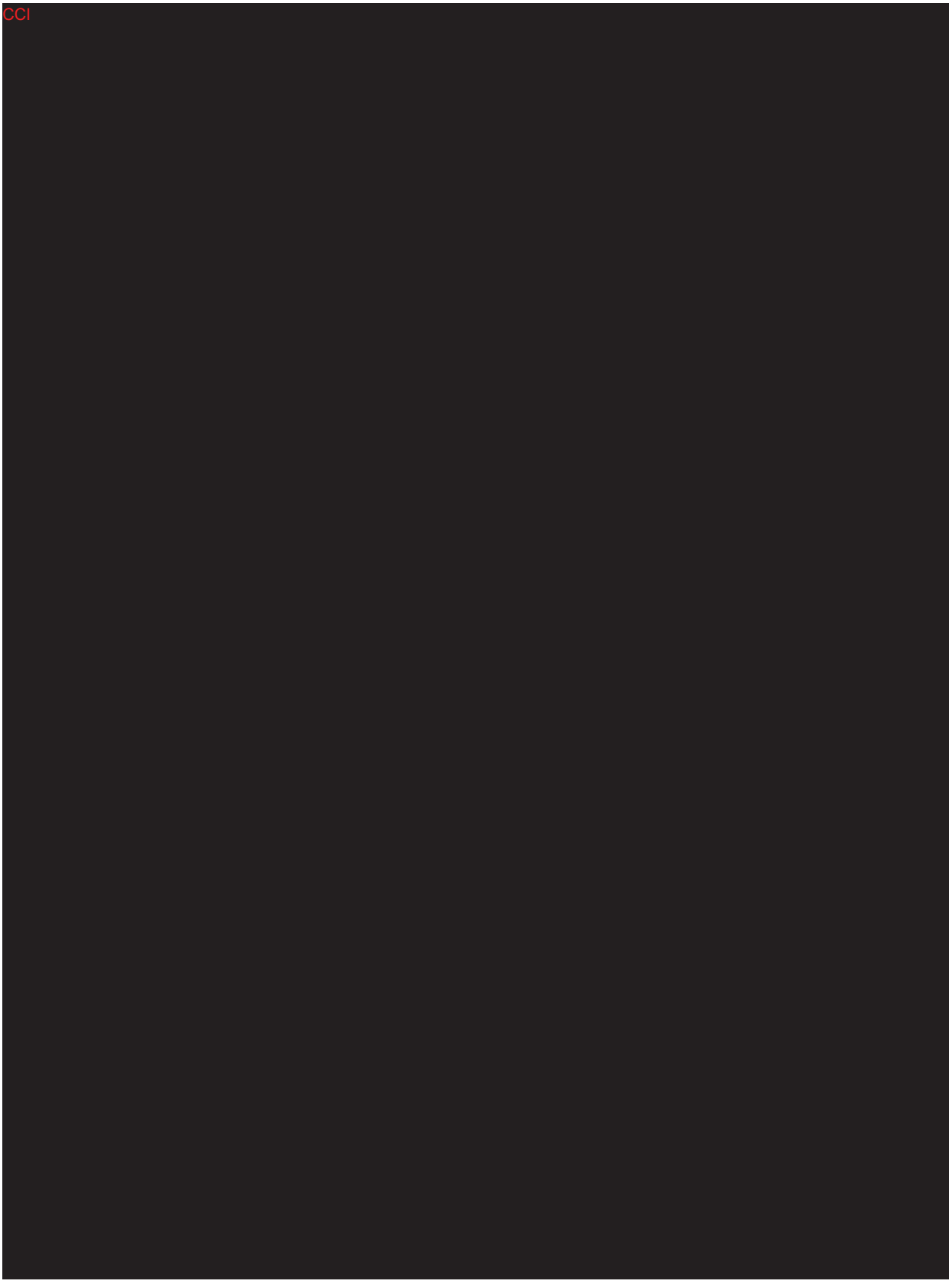
Appendix C [redacted]

[redacted]

CCI



CCI



Appendix D Hy's Law

ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

D1. 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 biochemistry. Specific guidance on managing liver abnormalities can be found in Sections 5.2.1 and 6.3.8 of the protocol.

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.

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

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

The Investigator participates, together with AstraZeneca clinical project representatives, in the review and assessment of cases meeting PHL criteria to agree 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 Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting procedures.

D2. Definitions

Potential Hy's Law (PHL)

AST or ALT ≥3 × 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.

D3. 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

Local laboratories being used:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see 2 definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

D4. Follow-up

a. Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol

b. Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

Determine whether PHL criteria were met at any study visit prior to starting study treatment (see Section 6.3.8)

Notify the AstraZeneca representative who will then inform the central Study Team

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data.

- Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician
- Complete the 3 Liver eCRF Modules as information becomes available
- # A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

D5. 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.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent 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.

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

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

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

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

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

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

D6. 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 patients' 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 '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 TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

D7. 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 Section "Actions required when Potential Hy's Law Criteria are met before and after starting study treatment?" of this Appendix.

If **No**: follow the process described in Appendix D, Section D4 for reporting PHL as a n SAE.

- 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 Section D4 for reporting PHL as a n SAE.

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 TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

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

Appendix E Guidelines for Evaluation of Objective Tumor Response

GUIDELINES FOR EVALUATION OF OBJECTIVE TUMOR RESPONSE USING RECIST 1.1 CRITERIA (RESPONSE EVALUATION CRITERIA IN SOLID TUMORS, VERSION 1.1)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009) for this study with regards to Investigator assessment of tumor burden including protocol-specific requirements for this study. Additional special guidance is provided for determination of confirmation of radiological progression.

Definition of measurable, non-measurable, target and non-target lesions

Only patients with measurable target disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion which has not been previously irradiated.

Tumor lesions selected for screening biopsy should not be selected as target lesions (TLs), unless imaging occurred at least ~2 weeks after biopsy, allowing time for healing.

Measurable:

A lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis[1] diameter of ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[2]).
- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.
- Previously irradiated lesions[3] (see exception below for Target lesions)

---

1 The short axis is defined as the longest axis perpendicular to long axis

2 Nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as non-target lesions (NTLs).

3. Localised post-radiation changes which affect lesion sizes may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and should be selected as NTL at baseline and followed up as part of the NTL assessment.

- Brain metastasis

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 TLs.

Target lesions:

A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as TLs at baseline. Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or multilobed organ (eg, lung) is each considered as a single organ.

If there are no other target lesions available, previously irradiated lesions may be considered measurable and selected as TLs provided they fulfil the other criteria for measurability. Tumor lesions selected for screening biopsy should not be selected as TLs, unless imaging occurred at least ~2 weeks after biopsy, allowing time for healing.

Non-target lesions:

Additional measurable lesions not recorded as TL and non-measurable lesions (or sites of disease) should be identified as NTLs at baseline.

Methods of assessment

- The same method of assessment on the same imaging 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 14, and those excluded from tumor assessments for this study are highlighted with the rationale provided.

Table 14 Summary of methods of assessment

Target lesions	Non-target lesions	New lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan
		FDG-PET

CT Computed tomography; FDG-PET ^{18}F-Fluoro-deoxyglucose positron emission tomography; MRI Magnetic resonance imaging.

CT and MRI
CT and MRI, each preferably with intravenous (IV) contrast, are generally considered to generate the best currently available and reproducible images for measurement of TL, assessment of NTL, and identification of any new lesions.

It is recommended that CT examinations of the chest and abdomen (including the entire liver and both adrenal glands) will be used to assess tumor burden at baseline and follow-up visits. Any other areas of disease involvement (eg, pelvis, brain) 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) is appropriate. In patients with severely compromised renal function a non-contrast CT examination of the chest and abdomen is appropriate. For brain lesion assessment, MRI with IV contrast is the preferred method over IV 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 time points per patient.

Clinical examination
Clinical examination of tumors (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Chest X-ray

Chest X-ray assessment will not be used for assessment of TL. Chest X-ray can, however, be used to assess NTL and to identify the presence of new lesions.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTL and to identify the presence of new bone lesions.

Ultrasound
Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible method, does not provide an accurate assessment of tumor size, and it is

subjective and operator dependent. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Endoscopy and laparoscopy
Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Tumor markers
Tumor markers on cytological or histological (biopsy) samples will not be used for tumor response assessments as per RECIST 1.1.

Histology and Cytology
Histology on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any fluid accumulation/effusion (e.g. ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment in this study. An effusion that appears or significantly worsens (from trace to large) radiologically by CT/MRI anatomical scans will be considered to be disease progression due to New Lesions or progression of NTLs, respectively.

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.

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 may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan which cannot be verified with correlative imaging (CT, MRI, X-ray) of the same anatomical region shall not be the only trigger for a progressive disease (PD) assessment at that timepoint.

FDG-PET scan
^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scans may be used as a method for identifying new lesions, according to the following algorithm: New lesions will be recorded where there is positive ^{18}F-Fluoro-deoxyglucose uptake[3] not present on baseline or prior 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 or prior FDG-PET scan available, and no evidence of new lesions on CT/MRI scans

3

then follow-up CT/MRI assessments should be continued, scheduled as per protocol or clinical indicated, in order to verify new lesions.

At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT scan 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 tumor assessments. Caution that the PET portion of the PET/CT could introduce additional data that may bias an Investigator if it is not routinely or serially performed.

Tumor response evaluation

Schedule of evaluation

The methods of assessment of tumor burden used at baseline CT/MRI scans of the chest and abdomen (including the entire liver and both adrenal glands) must be used at each subsequent follow-up assessment. Additional imaging may be performed based on the signs and symptoms of the patient, eg, new lesions at follow-up.

Baseline assessments should be performed no more than 28 days before the date of randomization, and ideally should be performed as close as possible to the start of IP. Efficacy by RECIST 1.1 for all patients will be assessed according to the schedules described in Table 2 and Table 3 of the CSP. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled imaging visits.

For patients who discontinue study drug due to toxicity in the absence of clinical progression or unequivocal radiologic evidence of progression, tumor assessments should be continued according to the original imaging schedule (Table 2 and Table 3 of the CSP).

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. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter 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 TL will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TL will be calculated and reported as the follow-up sum of diameters.

Special cases:

- For TL 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 TL has completely disappeared, the longest diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.
- 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, definitive radiotherapy, embolization, surgery, etc during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST case report form for that time-point and in all subsequent TL assessments (see 'Not evaluable' in Table 15). If a TL has been completely removed (surgery) or disappears following an intervention, the diameter should be recorded as 0 mm.

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor visit response for TL (see Table 15).

Table 15 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	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 at follow-up were not assessed or not evaluable (eg missing anatomy) 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

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; 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 16).

Table 16 Evaluation of non-target lesions

Complete response	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	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	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.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; 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 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 one 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. 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 previously new lesion has been assessed as unequivocal and then the progression date should be declared using the date of the initial scan when the new lesion first appeared.

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.

If a TL has completely disappeared and a lesion appears in the same location on a subsequent scan, it will be recorded as a New Lesion.

Symptomatic deterioration
Symptomatic (clinical) 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 radiological evidence of disease progression at that time should continue to undergo tumor assessments where clinically feasible on their regular imaging schedule.

Evaluation of overall visit response
The overall visit response will be derived using the algorithm shown in Table 17.

Table 17 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.

Confirmation of Radiological Progression

Patients who are clinically stable at an initial RECIST 1.1-defined PD can continue to receive study treatment at the discretion of the Investigator and patient. A subsequent follow-up scan is collected after the initial RECIST 1.1-defined PD, preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD, and the Confirmation of Radiological Progression criteria described below are applied for tumor assessments of this follow-up scan. Patients with confirmed radiological PD who continue to receive study treatment at the discretion of the Investigator (following consultation with AstraZeneca) and patient can receive treatment until no longer having clinical benefit and should continue on their regular imaging schedule.

Confirmation of Radiological Progression Criteria:

Confirmation of radiological progression guidelines are used to evaluate scans subsequent to a prior radiological PD. An immediate prior RECIST 1.1-defined radiologic PD would be considered confirmed if any of the following criteria are met in the subsequent follow-up scan (acquired preferably at the next regularly scheduled imaging visit but no sooner than 4 weeks after the RECIST 1.1-defined PD scan):

- ≥20% increase in the sum diameters of TLs compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir
- *and/or* significant progression (worsening) of NTLs at the follow-up scan timepoint compared with the immediate prior timepoint
- *and/or* additional (brand) new unequivocal lesions at the follow-up scan timepoint
- *and/or* significant progression (worsening) of pre-existing new lesions at the follow-up scan timepoint compared with the immediate prior timepoint

Note: In order to have confirmed radiological progression, there should be 2 consecutive PDs, the first PD by RECIST 1.1 and the second PD using the confirmation of radiological progression criteria (above). If radiologic progression is not confirmed, in the absence of significant clinical deterioration, then the patient may continue with assessments until the next RECIST 1.1-defined PD, which will also require a follow-up scan evaluated using the confirmation of radiological progression criteria. **If the first PD (by RECIST 1.1) is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

Central Review

All images will be collected, quality checked, and stored centrally by an Imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A blinded independent central review (BICR) of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator RECIST 1.1 assessments will not be shared with the central

reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the Investigator.

Further details of the BICR will be documented in the Independent Review Charter, (also referred to as 'Imaging Charter').

Specifications for radiological anatomical imaging
These notes are recommendations for use in clinical studies. The use of standardized protocols for CT and MRI allows comparability both within and between different studies, irrespective of where the examination has been undertaken.

If specified, all images will be collected, quality checked and stored centrally by the imaging CRO appointed by AstraZeneca. Guidelines for image acquisition, anonymization/deidentification, 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.

Also if specified, further details of the BICR will be documented in the Independent Review Charter (also referred to as the 'Imaging Charter').

CT Scan
CT scans of the chest and abdomen should be contiguous throughout all the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST 1.1 are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. **Anatomic coverage:** Optimal anatomic coverage for most solid tumors is the chest and abdomen. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency not only of tumor measurements but also identification of new disease.

b. **IV contrast administration**: Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination. An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. It is very important that the same technique be used at baseline and on follow- up examinations for a given patient. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or

non-enhanced) should be performed should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of TLs on a different modality and interpretation of non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodine contrast media is medically contraindicated at baseline or at any time during the course of the study then the recommended methods are: CT thoracic (chest) examination without contrast and abdominal (and pelvic) MRI with contrast. If MRI cannot be performed then CT without IV contrast is an option for the thorax and abdomen (and pelvis) examination. For brain imaging, MRI with IV contrast is the preferred method.

c. Slice thickness and reconstruction interval: It is recommended that CT scans be performed at 5mm contiguous slice thickness and this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study. All images from each examination should be included in the assessment and not "selected" images of the apparent lesion.

MRI Scan

MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen (and other anatomies eg pelvis, neck) with T1 and T2 weighted imaging along with gadolinium-enhanced imaging can be performed. The field of view, matrix, number of excitations, phase encoding steps, use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. CT of the chest is typically recommended over MRI due to significant motion artefacts (heart, major blood vessels, breathing) associated with MRI. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques if possible.

For these reasons, CT is the imaging modality of choice.

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

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌊ ⌊ ⌊

Your birthdate (Day, Month, Year): ⌊ ⌊ ⌊ ⌊ ⌊ ⌊ ⌊ ⌊

Today's date (Day, Month, Year): 31 ⌊ ⌊ ⌊ ⌊ ⌊ ⌊ ⌊ ⌊

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

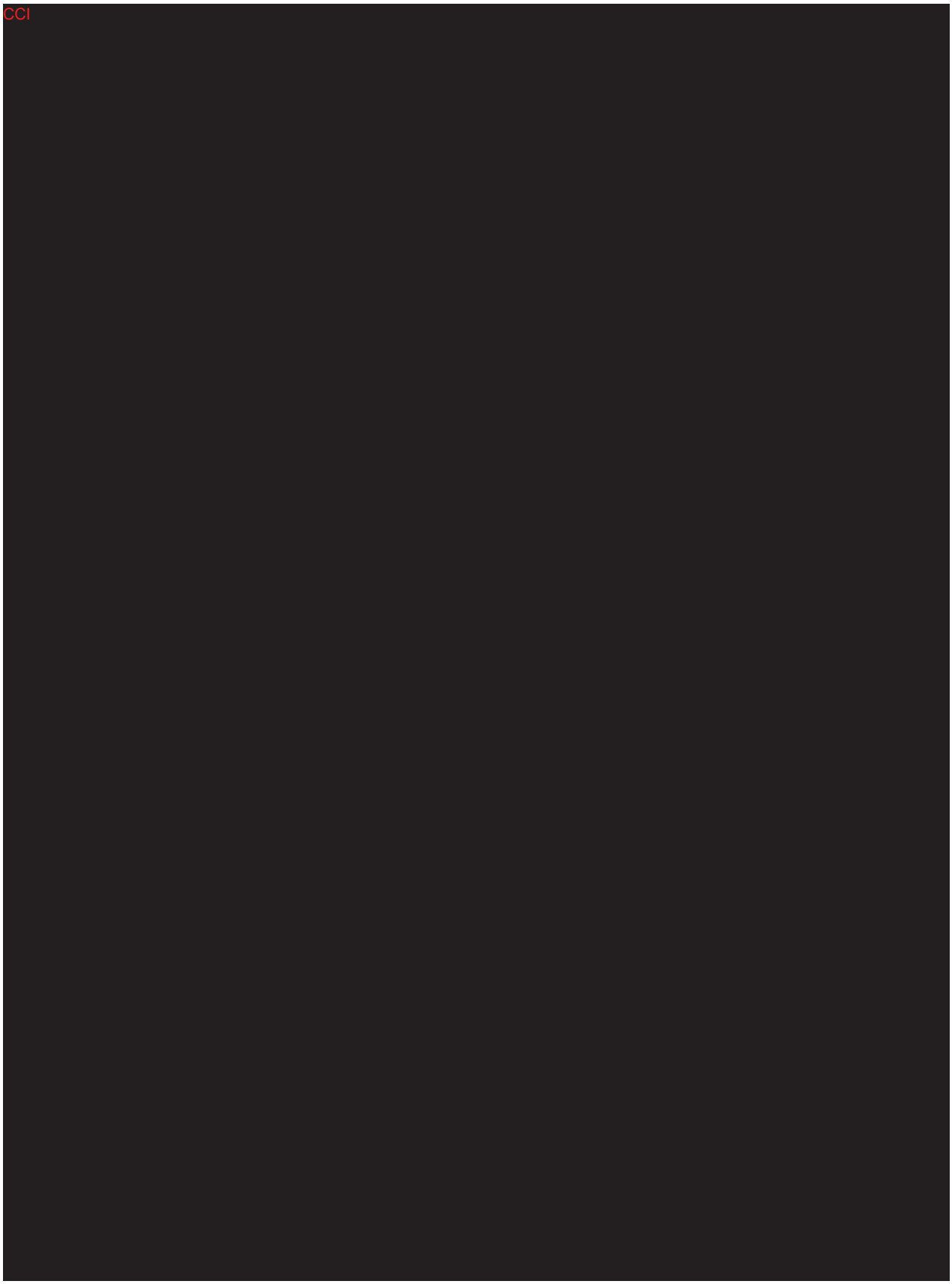
ENGLISH

EORTC QLQ - LC13

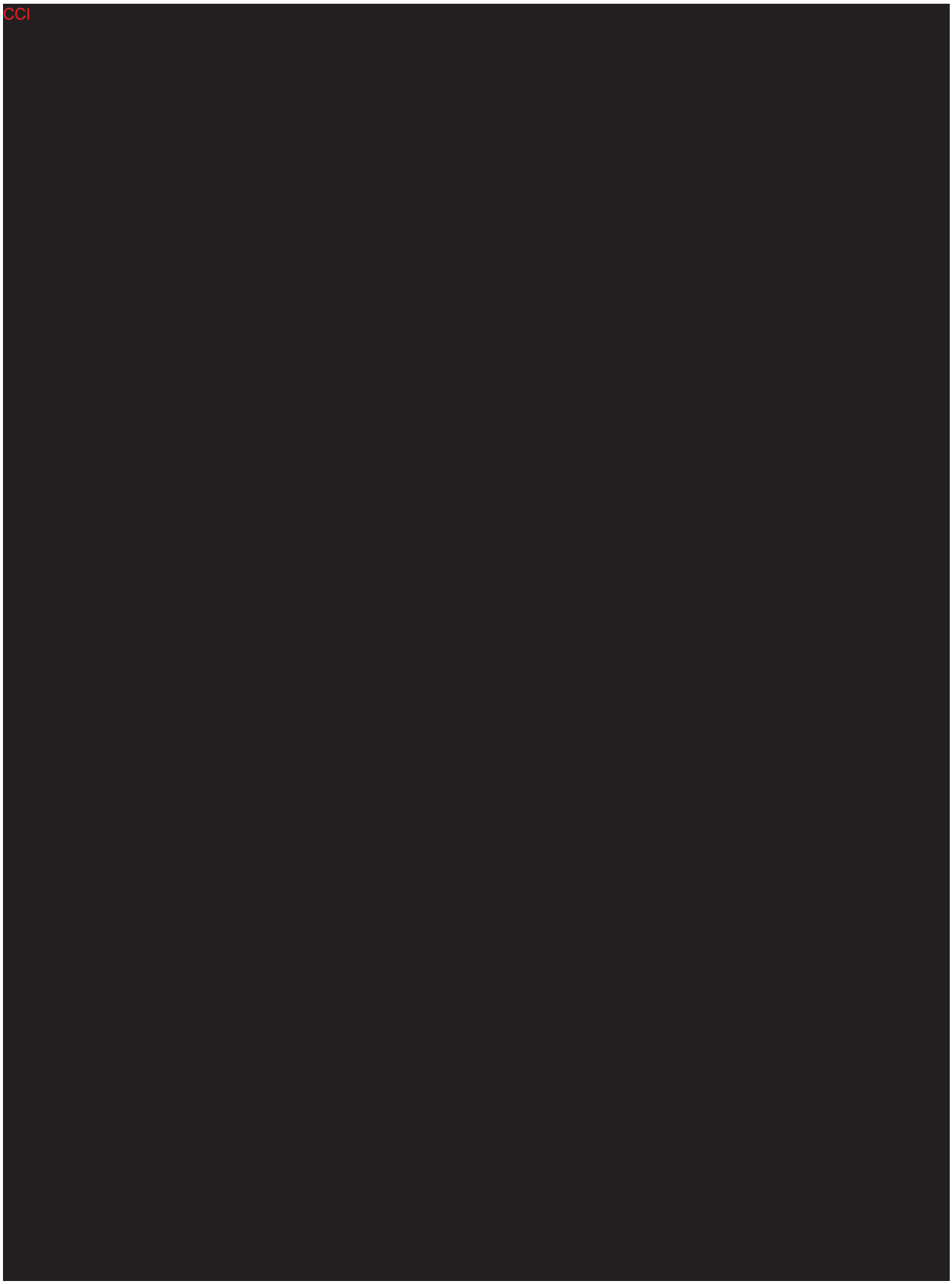
Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

CCI



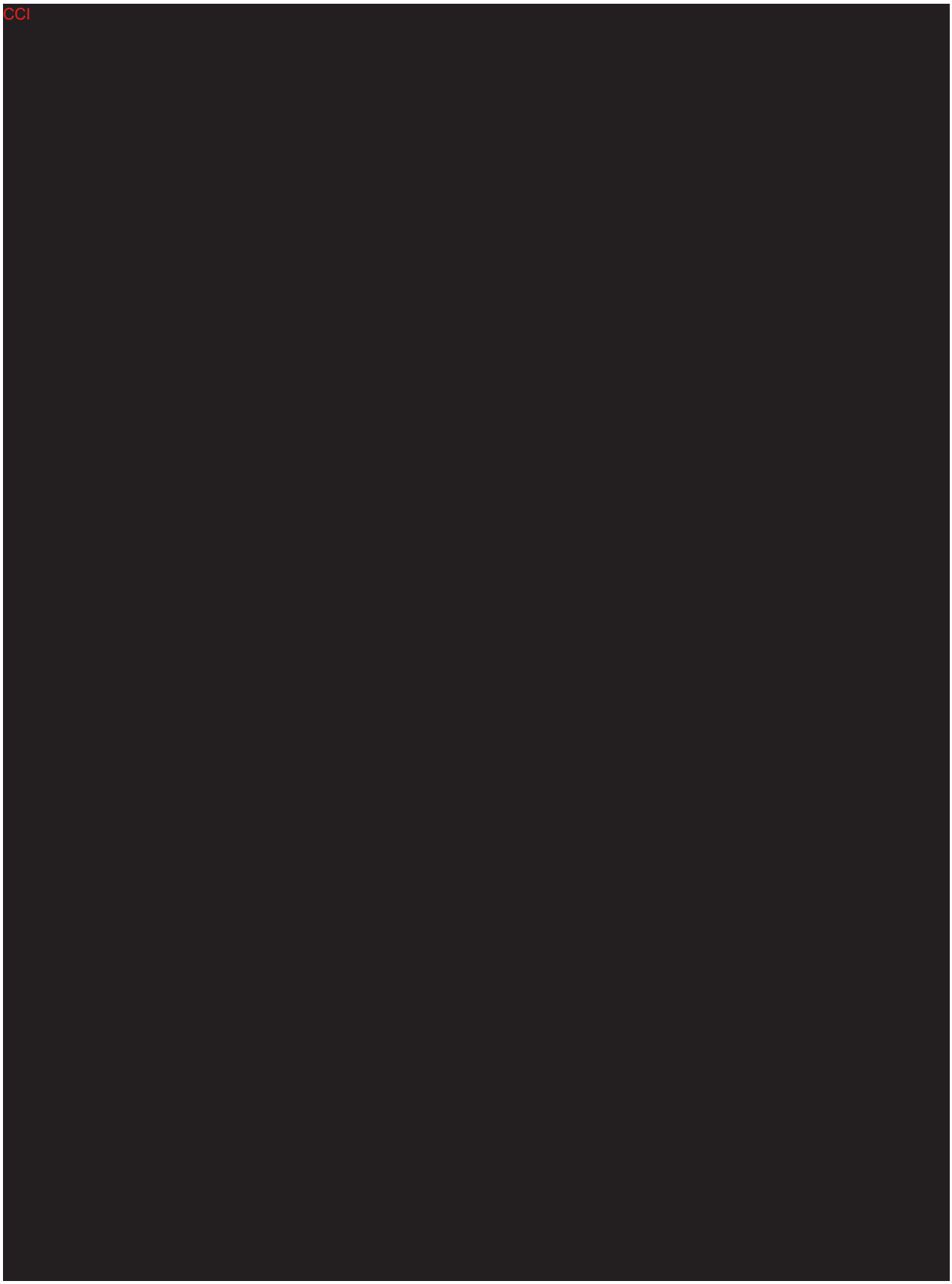
CCI



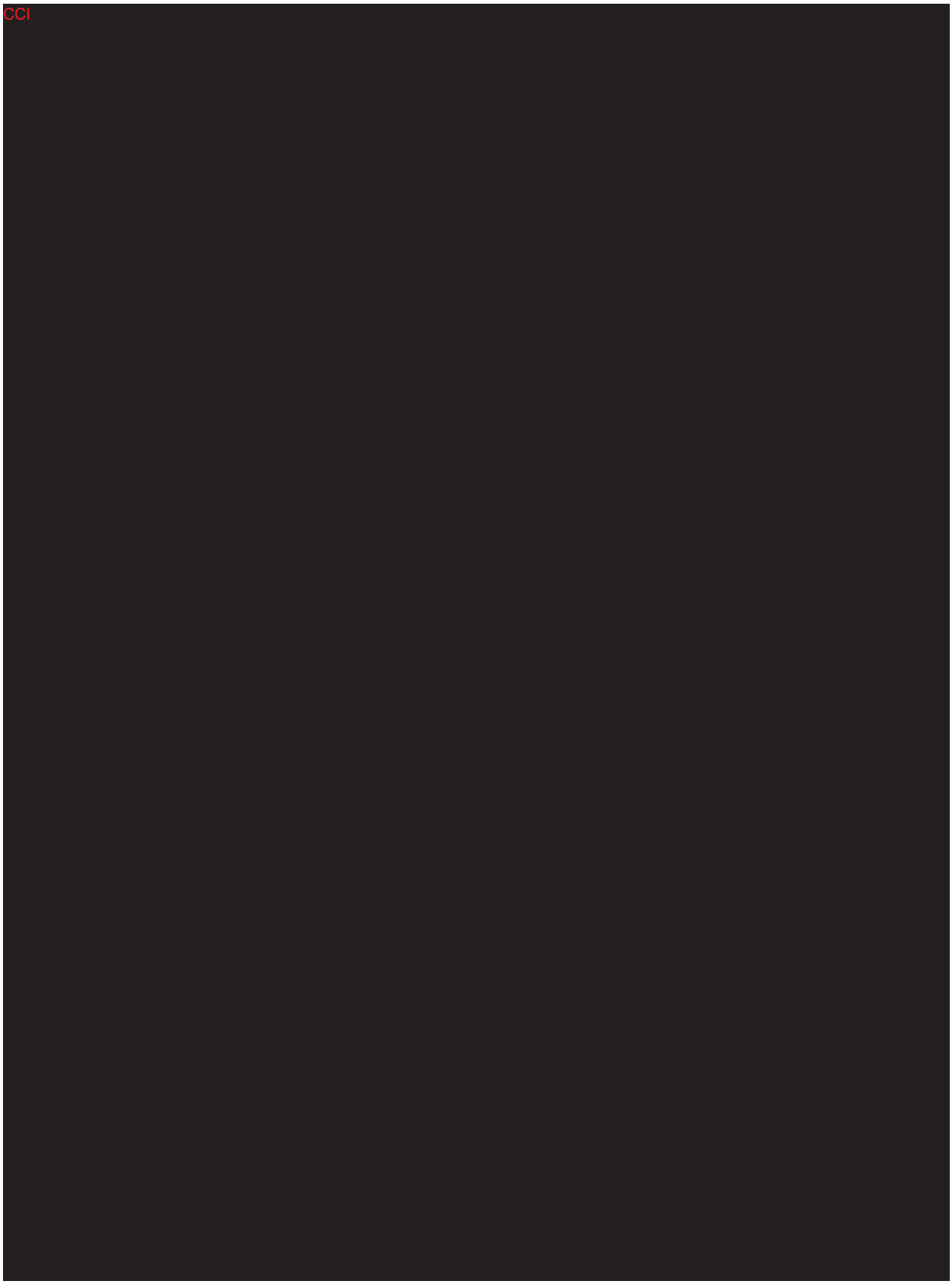
CCI

[redacted]

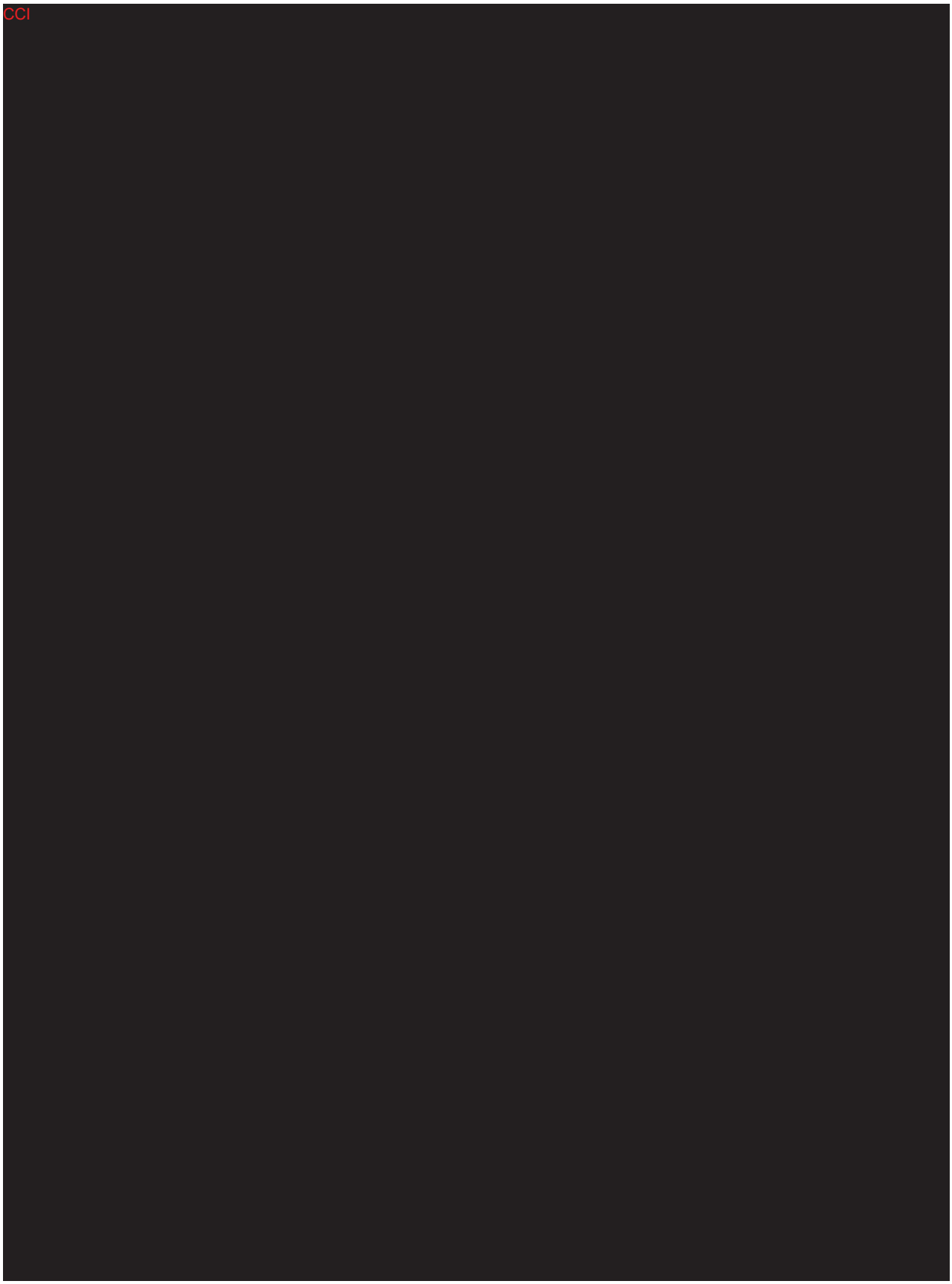
CCI



CCI



CCI



Appendix G Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the sponsor.

G 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections 0 to 0. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

G 2 Rescreening of Participants to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study clinical lead.

In addition, during study disruption there may be a delay between confirming eligibility of a participants and either enrolment into the study or commencing of dosing with study intervention. If this delay is outside the screening window specified in Section 4.1 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 3.10.1. The procedures detailed in Section 4.1 must be undertaken to confirm eligibility using the same randomisation number as for the participant.

G 3 Home or Remote Visit to Replace On-site Visit (Where Applicable)

A qualified HCP from the study site or TPV service may visit the participants home/or other remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

G 4 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow AEs, concomitant medication to be reported and documented.

G 5 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

G 6 COVID-19 Risk Assessment

The safety of participants is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study participants.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Participants enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to participants receiving standard of care. Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section 0). With these measures in place, it is considered that the anticipated potential benefits for the participants enrolled in this study outweigh the potential risks. All implemented measures prioritise trial participant safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [EMA 2020]).

Notably, participants with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 3.2, Exclusion Criterion 1).

G 7 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section 0 provides a dose modification and management plan for participants with confirmed or suspected COVID-19 who are being treated with study intervention durvalumab and tremelimumab. The risk-benefit assessment should be carefully considered for each participant enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for participants and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

G 8 New Participant Enrolment (Only applicable for China tail)

Study sites may continue to recruit new participants into the study provided the following activities to preserve study integrity can be met:

Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new participants effectively and in compliance with the protocol.

Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criterion 1 (see CSP Section 3.2), participants with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such participants (including those who have confirmed COVID 19) should not be included for study participation.

G 9 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the participants' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

G 10 Ongoing Participants

Participants receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

G 10.1 If a Participant has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.
- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.
- If COVID-19 is ruled out, study intervention may be resumed per the CSP.
- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

G 10.2 Participants with Confirmed COVID-19

Participants with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab/tremelimumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual participant's presentation (Curigliano et al 2020).

G 10.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

G 10.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for participants in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

G 11 References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d419mc00004-csp-v6		
Document Title:	D419MC00004 Clinical Study Protocol version 6	
Document ID:	Doc ID-003513330	
Version Label:	8.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
14-Jul-2021 09:44 UTC	PPD	Content Approval
12-Jul-2021 18:54 UTC		Content Approval
13-Jul-2021 13:42 UTC		Content Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.