Clinical Study Protocol	
Drug Substance	Durvalumab and tremelimumab
Study Code	D419EC00001
Version	6.0
Date	12 December 2022

Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

EudraCT number: 2018-003118-42

IND: CCI [redacted]

VERSION HISTORY

Version 6.0, 12 December 2022

Overall Rationale for Modification:

The purpose of this amendment is to reflect the updated study design change with the removal of the non-Hodgkins lymphoma (NHL) cohort and the capping of enrollment for the solid tumor (STO cohort). Additionally language has been added for the required treatment plan for patients remaining on treatment beyond the data cutoff (DCO).

Changes to the protocol are summarized below:

Section 1.1 Table 1 Schedule of activities for durvalumab ± tremelimumab dose-finding phase:

- Removal of bone marrow aspirate and lumbar puncture as efficacy assessment procedures given the suspension/removal of all hematological malignancies (including lymphoma); corresponding footnote referencing CSF analysis also removed [this same information is also being removed from tables 2 and 3]

Section 1.1 Table 4 Schedule of activities for patients receiving ongoing treatment beyond database cutoff (DCO)

- Insertion of a new table outlining the treatment plan, the suggested clinical monitoring, and the requirements for safety reporting and pregnancy testing.
- Following tables numbering rearranged

Section 5.2 Exclusion Criteria

- Removal of reference to exception for allogeneic transplantation for NHL patients
- Text updated to remove reference to AZ consult requirement for patient eligibility, for toxicity considerations (to align with AZ protocol standard)

Section 6.4 Concomitant Medication

- Table 16 (previously Table 15): removal of reference to use of prophylactic intrathecal chemotherapy for high-risk leukemia and NHL, given the removal of all hematological malignancies (including lymphoma) from the dose expansion phase of the study.

Section 6.6 Continued Access to Study Intervention After the End of the Study

- Updated language inserted describing the provision and the procedures for continuing treatment for patients actively receiving treatment and experiencing clinical benefit, following the completion of the study

Section 8.3.14 Safety data to be collected following the final DCO of study

- Text updated to reflect requirements for SAE and AESI reporting for patients remaining on treatment following DCO

Section 8.4.4 Medication error, Drug Abuse, and Drug Misuse and Appendix B 8 Medication error, Drug Abuse and Drug Misuse

- Text updated related to medication error definition and reported. New sections added related to description of Drug Abuse, and Drug Misuse [also updated in Appendix B]

Appendix A 1 Regulatory and ethical considerations

- Added a sub-heading "Regulatory Reporting Requirements for Serious Breaches"

Appendix A 7 Data quality assurance

- Added a paragraph related to AstraZeneca medical oversight responsibility

All Sections:

- Modifications to the study design have been made throughout the protocol to reflect the following changes to the disease cohorts, as approved by the Pediatric Committee (PDCO) of the European Medicines Agency in August 2022:
- Limiting enrollment of the STO cohort in the dose-expansions to 10 patients due to a) feasibility challenges and b) lack of activity
- Removal of the Non-Hodgkin's lymphoma cohort due to feasibility challenges; no NHL patients have been enrolled in the protocol to date.

Version 5.0, 23 April 2021

Changes to the protocol are summarized below:

Section 1.1 Table 1 Schedule of activities for durvalumab ± tremelimumab dose-finding phase:

- Footnotes describing sampling for soluble programmed cell death ligand 1, in relation to durvalumab or tremelimumab infusion, updated to clarify timings
- Radiological imaging schedule modified to allow a reduced frequency of tumor assessments, as clinically indicated, for patients achieving an objective response or stable disease still evident at 12 months (an interval of 16 weeks versus 8 weeks)
- Frequency of Tanner staging and tumor marker assessments clarified to align with the modified radiological imaging schedule

Section 1.1 Table 2 Schedule of activities for durvalumab ± tremelimumab dose-expansion phase:

- Pharmacokinetic sampling updated to remove collection of the Cycle 6 and Cycle 10 samples for durvalumab
- Immunogenicity assessment at Cycle 6 removed and replaced with assessment at Cycle 4 for durvalumab
- Testicular exam for male patients in acute lymphoblastic leukemia cohort removed
- CCI [redacted] assessments for the Hodgkin's lymphoma cohort removed (to clarify removal of this cohort from the dose-expansion phase)
- Radiological imaging schedule modified to allow a reduced frequency of tumor assessments, as clinically indicated, for patients achieving an objective response or stable disease still evident at 12 months (an interval of 16 weeks versus 8 weeks)
- Frequency of Tanner staging and tumor marker assessments clarified to align with the modified radiological imaging schedule
- Footnotes describing sampling for soluble programmed cell death ligand 1, in relation to durvalumab or tremelimumab infusion, updated to clarify timings
- Table and footnotes updated to clarify removal of the Hodgkin's lymphoma, neuroblastoma (and associated tumor marker assessments [urine catecholamines]), and other hematological malignancies cohorts from the dose-expansion phase

Section 1.1 Table 3 Schedule of activities for patients who have discontinued all study treatments (durvalumab monotherapy or durvalumab and tremelimumab combination therapy) in the dose-finding or the dose-expansion phases:

- Table and footnotes updated to reflect modified frequency of radiological efficacy assessments (an interval of 16 weeks versus 8 weeks) for patients achieving an objective response or stable disease which is still evident at 12 months

Section 1.2 Objectives and Endpoints:

- Primary objective "To determine the preliminary antitumor activity of patients from the HL dose-expansion cohort treated with durvalumab monotherapy with a q4w dosing schedule, using cohort-specific response criteria (eg, Cheson criteria, Wayne criteria, RECIST 1.1, and INRC)" and corresponding endpoints removed
- Safety objective "To determine the safety profile and tolerability of patients from the HL dose-expansion cohort treated with durvalumab monotherapy with a q4w dosing schedule" and corresponding endpoints removed
- Primary, secondary, and safety objectives (and corresponding endpoints) for the dose-expansion phase updated to reflect removal of Hodgkin's lymphoma and other hematological malignancies cohorts

Section 1.2 Overall design:

- Text updated to clarify changes to the design for the dose-expansion phase (see changes listed under 'All Sections')
- Sample size described for newly combined SARCOMA cohort; 11 patients to be enrolled in initial stage (with requirement that ≥ 40% of the patients enrolled must have soft-tissue sarcomas), followed by an additional 15 patients in the expansion stage, for a total of 26 patients

Section 1.2 Number of patients:

- Sample size for dose-expansion phase revised to clarify changes to cohorts; expected range for evaluable patients revised to 38 to 66 patients, and total number of patients (assuming 20% are non-evaluable) revised to 46 to 80 patients

Section 1.3 Schema:

- Figure 1 updated to clarify changes to the overall study design (specifically, updates to the cohorts included in the dose-expansion phase)

Section 2.3.2.1 Durvalumab:

- Risks with durvalumab treatment updated to include pemphigoid, immune thrombocytopenia, and neuromuscular toxicities (Guillain-Barré syndrome, myasthenia gravis) to reflect the latest clinical information available

Section 3 Objectives and endpoints:

- Table 4 updated to remove following primary objective and corresponding endpoints for dose-expansion phase: "To determine the preliminary antitumor activity of patients from the HL dose-expansion cohort treated with durvalumab

monotherapy with a q4w dosing schedule, using cohort-specific response criteria (eg, Cheson criteria, Wayne criteria, RECIST 1.1, and INRC)"

- Table 4 updated to remove following safety objective and corresponding endpoints for dose-expansion phase: "To determine the safety profile and tolerability of patients from the HL dose-expansion cohort treated with durvalumab monotherapy with a q4w dosing schedule"

- Table 4 updated to clarify changes to primary, secondary, and safety objectives (and corresponding endpoints) for dose-expansion phase (due to removal of Hodgkin's lymphoma and other hematological malignancies cohorts)

Section 4 Study design:

- Table 5 Disease cohorts separated into two tables (by study phase) and corresponding text updated to clarify changes to the design of the dose-expansion phase (see changes listed under 'All Sections')

- Sample size described for newly combined SARCOMA cohort; 11 patients to be enrolled in initial stage (with requirement that ≥ 40% of the patients enrolled must have soft-tissue sarcomas), followed by an additional 15 patients in the expansion stage, for a total of 26 patients

- New section titled "Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis" added (as Section 4.1.5), to describe changes to study conduct in light of disruptions, including disruption due to pandemics

Section 4.1.2 Definition of dose-limiting toxicities and stopping criteria:

- Term 'irAE' replaced with 'imAE' throughout section, for consistency with language used elsewhere in protocol

Section 5.1.2 Inclusion criteria (Malignant neoplasms of hematopoietic and lymphoid tissue and myelodysplastic syndrome):

- Section title revised to "Non-Hodgkin's lymphoma", and introductory paragraph and inclusion criterion 3 updated to reflect that only NHL (including, primary mediastinal B-cell lymphoma and anaplastic large-cell lymphoma) will be evaluated for malignant neoplasms of hematopoietic and lymphoid tissue

Section 5.2 Exclusion criteria (all patients):

- Exclusion criterion 1 revised to remove criteria for Hodgkin's lymphoma, acute myeloid leukemia, and acute lymphoblastic leukemia

Section 8 Study assessments and procedures

- Table 17 Volume of blood to be collected (by weight and including World Health Organisation limits) updated to reflect reduced number of blood samples required for research laboratory (pharmacokinetic and anti-drug antibody) assessments in the dose-expansion phase (volume from Cycle 3 until progression revised from "up to 5.5 mL" to "up to 6 mL")

Section 8.1 Efficacy Assessments:

- Radiological imaging schedule modified to allow a reduced frequency of tumor assessments, as clinically indicated, for patients achieving an objective response or stable disease still evident at 12 months (an interval of 16 weeks versus 8 weeks)

Section 8.2.4 Tanner staging:

- Frequency of Tanner staging clarified to align with the modified radiological imaging schedule

Section 8.3.13 Adverse events of special interest:

- List of adverse events of special interest observed with durvalumab ± tremelimumab updated to include neuromuscular toxicities (Guillain-Barré syndrome, myasthenia gravis) to reflect the latest clinical information available

Section 8.4.5.1 Specific toxicity management and dose modification information – Durvalumab and durvalumab + tremelimumab:

- Cross-reference to TMG document removed

Section 8.8.3 Exploratory Biomarkers:

- Requirement for collection of CCI [redacted] in patients with neuroblastoma is reflected only for patients enrolled during dose-finding phase

Section 9.2 Sample size determination (Dose-expansion phase):

- Sample size added for newly combined SARCOMA cohort; 11 patients to be enrolled in initial stage (with requirement that ≥ 40% of the patients enrolled must have soft-tissue sarcomas), followed by an additional 15 patients in the expansion stage, for a total of 26 patients

- Sample size for dose-expansion phase revised to clarify changes to cohorts; expected range for evaluable patients revised to 38 to 66 patients, and total number of patients (assuming 20% are non-evaluable) revised to 46 to 80 patients

Section 9.6 Interim analyses:

- Number of patients for evaluation of ORR updated to reflect revised sample sizes for dose-expansion cohorts (11 patients for the SARCOMA cohort and 9 patients for the NHL cohort)

Section 11 Supporting Documentation:

- Appendix titled "Actions required in cases of increases in liver biochemistry and evaluation of Hy's law" updated to include revised guidance for identifying and following-up potential Hy's law cases.

- Appendices titled "Response Criteria in Acute Myeloid Leukemia" and "Response Criteria in Acute Lymphoblastic Leukemia" deleted from Section 11

- Appendix titled "Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis, including COVID-19 Outbreak" added to Section 11

All sections:

- Modifications to the study design have been made throughout the protocol to reflect the following changes to the disease cohorts in the dose-expansion phase, as approved by the Pediatric Committee (PDCO) of the European Medicines Agency in January 2021:

  - Consolidation of the previous two sarcoma cohorts (SARC-1 [bone sarcomas] and SARC-2 [soft-tissue sarcomas]) in a single sarcoma cohort with a requirement that at least 40% of the enrollment must reflect soft-tissue sarcomas
  - Suspension of the neuroblastoma cohort due to a) lack of activity during the dose-finding phase and b) checkpoint inhibitor therapy not reflected as a target within the recent Neuroblastoma Drug Development Strategy summary issued by the Innovative Therapies for Children with Cancer and the International Society of Pediatric Oncology Europe Neuroblastoma
  - Non-Hodgkin's lymphoma cohort modified to limit enrollment to only 2 subtypes: primary mediastinal B-cell lymphoma and anaplastic large cell lymphoma
  - Suspension of the Hodgkin's lymphoma cohort due to feasibility challenges
  - Suspension of the other hematological malignancies cohort (acute leukemias, myelodysplastic syndrome) due to a) feasibility challenges with prioritization of other therapies for acute lymphoblastic leukemia and b) emergence of a regimen combining a checkpoint inhibitor with a hypomethylating agent as a more appropriate regimen for acute myeloid leukemia/myelodysplastic syndrome

- Abbreviations were updated, and minor typographical errors and inconsistencies were corrected throughout

Version 4.0, 23 March 2020

Changes to the protocol are summarized below:

Section 1.1 Table 1 Schedule of activities for durvalumab ± tremelimumab dose-finding and dose-expansion phases:

- Tremelimumab (random) sample added to End of Treatment visit; footnote added to indicate required only for patients who received a single cycle of combination therapy

Section 8.5.1 Collection of pharmacokinetic samples and determination of drug concentration:

- Text added to indicate that a tremelimumab PK sample will be collected at the End of Treatment visit

Version 3.0, 29 July 2019

Changes to the protocol are summarised below.

Title Page:

- IND number updated ("~~119062~~141756")

Section 1.1 Tables 1 and 2 Schedule of activities for durvalumab ± tremelimumab dose-finding and dose-expansion phases:

- Table revised to reflect cycle length is 28 days (both tables)
- Visit window for Cycle 2, Day 1 updated to ± 4 days (both tables)
- Removed reference to targeted physical exam being based on symptoms for SoA (both tables)
- Coagulation added as a laboratory assessment with appropriate changes also made to footnotes e and f (both tables)
- Table revised to clarify when random tremelimumab PK sample is to be obtained (eg, 3 months after last dose [both tables])
- Text revised to refer to diagnostic FFPE biopsy sample as CCI [redacted]

- Footnote b updated to refer to "imaging/**staging examination**" results for clarification (both tables)
- Footnotes j and l updated to stipulate that pre-dose sample should be within 60 minutes of start of infusion (both tables)
- Testicular exam for male acute lymphoblastic leukemia patients added to physical examination (Table 2)
- Clarified details of requirements (limited sampling) for CCI [redacted] in footnote r (Table 2)

Section 1.1 Table 3 Schedule of activities for patients who have discontinued all study treatments:

- Table updated to align the total interval for AE/SAE assessments with the protocol text (ie, total interval of 90 days, to be performed at 30, 60, and 90 days)

Section 1.2 Synopsis

- Updated for consistency with changes within main body of protocol

Section 1.3 Schema

- Figure 1 updated to clarify the overall study design (primarily to provide clarity for the dose-expansion representation)

Section 2.2.2 Durvalumab:

- Information on the ongoing investigator-initiated study (durvalumab monotherapy) updated to reflect current status (also updated in Sections 2.3.2, 2.3.2.1, and 4.3.1.2)

Section 2.3.2.1 Durvalumab:

- Text revised to include the data cut-off date for monotherapy clinical studies and refer to the IB for updated information

Section 2.3.2.3 Durvalumab + tremelimumab:

- Reference to the current version of the IB added for detailed information

Section 2.3.3 Overall benefit/risk:

- Text revised to refer to the DRC rather than a committee composed by the Sponsor or designee and selected key trial Investigators

Section 3 Objectives and Endpoints:

- Study objectives updated to reflect safety and efficacy of the durvalumab and tremelimumab combination followed by durvalumab monotherapy; for HL cohort, safety and efficacy reflect durvalumab monotherapy

Section 4.1 Overall design

- Text revised to specify that pembrolizumab has also been approved for use in HL
- Dates for when the study is planned to be conducted were updated to reflect the current status

Section 4.1.1 Dose-finding phase:

- Text revised to provide description of the modified 3 + 3 design
- Figure 3 updated to clarify reduction in dose from DL 1 to DL-1

- Text revised to provide details on when adequate pediatric exposure will be declared

Section 4.1.2 Definition of dose-limiting toxicities:

- Section title revised to "Definition of dose-limiting toxicities and stopping criteria"
- List of exceptions for a dose-limiting toxicity revised to include Grade 3 hypothyroidism adequately treated with hormone replacement therapy (replacing reference to Grade 4 hypothyroidism)
- Text revised to describe hold and stopping criteria for dose-finding and dose-expansion phases, in the context of number of patients experiencing dose-limiting toxicities

Section 4.1.3 Determining a recommended Phase II dose:

- Text and Table 6 revised to describe what will be considered for dose escalation decisions and determination of RP2D

Section 4.1.4 Dose-expansion phase:

- Text revised to provide additional description of the Simon 2-stage design

Section 4.4 End of study definition:

- Text revised to indicate that study will (instead of *may*) be stopped for change in risk due to clinically significant findings

Section 5.1.1 Solid malignant tumors (except primary central nervous system malignant tumors and Section 5.1.2 Malignant neoplasms of hematopoietic and lymphoid tissue and myelodysplastic syndrome:

- Inclusion criterion 3 revised to reflect that all patients must be refractory to standard therapy and for whom, no standard of care treatments exist
- Inclusion criterion 4 revised to CCI [redacted]
- Inclusion criterion 7 revised to further define immune therapies representing prior treatments that will exclude a patient from the study, to include no prior exposure to immune checkpoint inhibitors or genetically engineered cellular therapies
- Inclusion criterion 8 revised as follows:
  - Updated hematologic parameters for solid tumor patients with bone marrow involvement

- Updated upper-limit allowed for serum bilirubin, for patients with Gilbert's syndrome
- Updated text to define acceptable renal function based on age-appropriate creatinine or, if abnormal, use of Schwartz formula to calculate or use of 24-hour urine collection or radioisotope study, to determine creatinine clearance

Section 5.2 Exclusion criteria (all patients):

- Exclusion criterion 1 revised to clarify that patients who have previously received an autologous bone marrow transplant are eligible
- Exclusion criterion 2 revised to include autoimmune myocarditis and autoimmune pneumonitis (ie, conditions with an autoimmune etiology)
- Exclusion criterion 7 revised to exclude patients with chloroma
- Exclusion criterion 12 revised to permit use of intrathecal chemotherapy as prophylaxis/management for patients with high-risk leukemia or NHL disease
- Exclusion criterion 20 revised to specify a *highly* effective birth control method should be used

Section 5.4 Screen failures

- Text revised to describe additional procedures for handling screen failures

Section 6.1.1.1 Dose-finding phase

- Text added to describe restarting treatment with the combination of durvalumab and tremelimumab for patients with initial clinical benefit, who have progressed on durvalumab monotherapy

Section 6.1.1.2 Dose-expansion phase

- Text revised to reflect combination treatment starting at Cycle 1 (total of 4 cycles, Cycles 1 to 4)
- Text added to describe restarting treatment with the combination of durvalumab and tremelimumab for patients with initial clinical benefit, who have progressed on durvalumab monotherapy

Section 6.1.2 Study Drug Administration

- Text revised to specify a low-protein binding in-line filter is to be used for study drug administration, for both durvalumab and tremelimumab infusions

Section 6.1.3 Study Drug Preparation

- Text revised to reflect that either an IV bag or syringe preparation can be used for administration of both durvalumab and tremelimumab for patients ≥20 kg

Section 6.1.3.1 Durvalumab (MEDI4736)

- Text revised to reflect the use of the 500-mg vial size

Section 6.4 Concomitant therapy

Table 14 (prohibited medications) revised as follow:

- Intrathecal chemotherapy as prophylaxis/management for patients with high-risk leukemia or NHL disease is permitted

- Reference to EGFR TKIs changed to Tyrosine-kinase inhibitors

Section 8 Study assessments and procedures:

- Text revised to reflect scheduling of treatment visits for the dose-finding phase (to align with the SoA tables)

- Section amended to include instructions for collecting blood samples for patients with a body weight of <6 kg. Current Table 16 replaced with new table with blood volumes collected by body weight and including World Health Organisation limits. Sampling prioritization details added for dose-finding and dose-expansion phases, specifically for young children

Section 8.2.1 Clinical safety laboratory assessments:

- Table 17 (footnote) revised to reflect the corrected creatinine clearance equation (Schwartz equation) and acceptable methods for creatinine clearance determinations

- Coagulation added as additional laboratory assessment in Table 18 (hematology)

Section 8.2.2 Physical examinations:

- Text revised to clarify that urogenital assessment can include testicular exam for male acute lymphoblastic leukemia patients

Section 8.2.3 Vital signs:

- Text revised to define required vital signs and observation periods required for both dose-finding and dose-expansion phases around infusions

Section 8.3.13 Adverse events of special interest:

- Neuropathy/neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis) added as an AESI

Section 8.4.5.1 Specific toxicity management and dose modification information – Durvalumab and durvalumab + tremelimumab:

- Section updated to clarify that the Dosing Modification and Toxicity Management Guidelines (TMGs) for durvalumab and tremelimumab will be provided to investigative sites as an Annex to the protocol document. The section now provides a comprehensive description and rationale for use of the TMG

Section 8.8.1 Collection of patient samples for CCI [redacted]:

- Text revised to define requirements for CCI [redacted]

Section 8.8.2 CCI [redacted]:

- CCI [redacted] will not be taken from the smallest patients

Section 8.8.3 Exploratory biomarkers:

- CCI [redacted]
- Text added to clarify that CCI [redacted] will not be taken from the smallest patients

Section 8.9: Effect of immune checkpoint inhibition in response to routine immunizations

- Text added to clarify that samples for vaccine titers will not be taken from the smallest patients

Section 9.3.2 Evaluable for response analysis set:

- Text revised for definition of evaluable for response analysis set

Section 9.3.3 Safety analysis set:

- Text revised for definition of safety analysis set

Section 9.4.1.6 Best objective response:

- Corrected reference for NHL response criteria (Cheson 2007)

Section 9.4.1.7 Disease control rate:

- Text revised to provide additional details about definition of disease control rate

Section 9.5.1 Efficacy analyses:

Table 21 revised as follows:

  - Remove reference to irRECIST
  - Correct description of analysis required for proportion alive and progression-free at 12 and 18 months, and proportion alive at 12 and 24 months

Section 9.6.1 Data Review Committee:

- Text revised to reflect requirement of DRC to perform a benefit/risk assessment at the completion of safety data analysis prior to expansion into cohort of children <1 year old; notification of health authority of decision, if necessary per local requirements

Section 11 Supporting documentation and operational considerations, Appendix A 1 Regulatory and ethical considerations and related text in synopsis:

- Text revised to include the requirement of regulatory authority (in addition to IRB/IEC) approval of protocol amendments before their implementation

Section 11 Supporting documentation and operational considerations, Appendix A 10 Standard therapies:

- List updated to include chimeric antigen receptor T-cell therapies (CAR-T) as an approved standard therapy for acute lymphoblastic leukemia

Section 11 Supporting documentation and operational considerations, Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's law:

- Text revised to include new version of Hy's Law appendix

Section 11 Supporting documentation and operational considerations, Appendix E Guidelines for evaluation of objective tumor response using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors):

- Table 23 updated to remove the term "preferred" in reference to CT scans
- Text revised in 'CT and MRI' section to indicate selection of imaging is based on clinical situation and local guidelines

All sections:

- Text revised for dose-expansion phase in all appropriate sections to reflect durvalumab will be given in combination with tremelimumab for the first 4 cycles, starting on Cycle 1, in all tumor cohorts except HL where patients will be treated with durvalumab monotherapy only
- Minor typographical errors and inconsistencies were corrected throughout.

Version 2.0, 29 November 2018

Changes to the protocol are summarised below:

Section 1.2 Synopsis, Rationale:

- Text revised to reflect the intended patient population as those with relapsed/refractory malignancies for whom there are no available standard treatment options ("This is a first time in pediatrics study primarily designed to evaluate the safety and tolerability of durvalumab and durvalumab in combination with tremelimumab at increasing doses in pediatric patients with advanced solid malignancies (including lymphomas) **who have progressed or are refractory to standard therapies** and for whom no standard of care treatments exist. Although treatment efficacy is not a primary objective of this study given its early phase nature, the patients screened for this study have no ~~curative~~**standard treatment** options and this study offers the potential of some benefit").

Section 1.2 Data Review Committee

- Summary of key tasks for the Data Review Committee updated to reflect Section 9.6.1 Data Review Committee.

Table 1 Schedule of activities for durvalumab ± tremelimumab dose-finding phase:

- Table revised to include oxygen saturation as part of vital sign assessments.

- Footnote p revised to align with infusion times in Section 6.1.2 Study Drug Administration.
- Lumbar puncture assessment included.

Table 2 Schedule of activities for durvalumab ± tremelimumab dose-expansion phase:

- Table revised to include oxygen saturation as part of vital sign assessments.
- Footnote p revised to align with infusion times in Section 6.1.2 Study Drug Administration.
- Lumbar puncture assessment included.

Table 3 Schedule of activities for patients who have discontinued all study treatments (durvalumab monotherapy or durvalumab and tremelimumab combination therapy) in the dose-finding or the dose-expansion phases:

- Table revised to include oxygen saturation as part of vital sign assessments.

Section 5.1.1 Solid Malignant Tumors Inclusion Criteria:

- Inclusion criteria 3 reworded to clarify the patient type and disease characteristics for patients with solid malignant tumors ("**Patients must have a histopathologic confirmation of malignancy. Patients must have progressed or are refractory to standard therapies, and for whom no standard of care treatments exist**").

Section 4.1.2 Definition of Dose-Limiting Toxicities:

- Text revised to provide clarify the definition of a dose-limiting toxicity ("Any of the AE's listed below encountered between Cycle 1 Day 1 and Cycle 2 Day 28 (ie, 56 day DLT monitoring period for combination therapy) and in the opinion of the Investigator is thought to be attributable to durvalumab or/and tremelimumab**, given a reasonable possibility based on temporal exposure to IP and for which an alternate etiology does not exist or cannot be identified**, will be classified as DLTs.").
- The parameters for hematologic and non-hematologic dose-limiting toxicities were revised after discussion with the Food and Drug Administration.

Section 4.1.3 Determining a recommended Phase II dose:

- Text revised to clarify the basis for decisions about the recommended Phase II dose ("A DRC will be established prior to the initiation of the study to review all the data, with a primary emphasis on safety and PK, to establish RP2D to be further explored in the dose-expansion phase of the study. **Decisions about RP2D doses for the start of expansion cohorts will be based on safety assessments from at**

least 3 patients followed up for 4 cycles or 90 days post the combination of durvalumab and tremelimumab given on Cycle 2 Day 1. More details on the DRC constitution are described in Section 9.6.1.").

Section 8 Study Assessments and Procedures, Dose Finding Phase

- Infusion times updated to align with Section 6.1.2 Study Drug Administration.

Section 8.2.3 Vital signs:

- Text revised so that peripheral oxygen saturation is assessed a every clinic visit along with the remaining vital signs.

Section 9.6.1 Data Review Committee:

- Additional item included in list of key tasks for the Data Review Committee members (**"6. Perform a benefit/risk assessment at the completion of safety data analysis for children <1 years of age prior to enrolling a patient less than 12 months of age; notify FDA of decision"**).

Section 11 Supporting Documentation and Operational Considerations:

- Appendix titled "Standard Therapies" added to Section 11 to detail expected standard therapies these patients have received for their disease prior to entering this study.

Version 1.1, 11 October 2018

Changes to the protocol are summarised below:

Table 1 Schedule of activities for durvalumab ± tremelimumab dose-finding phase:

- Footnote (r) revised to state that the tumor markers for germ cell tumors are CCI [redacted]

Table 2 Schedule of activities for durvalumab ± tremelimumab dose-expansion phase:

- Table revised to show that tremelimumab infusions will be performed at Cycles 2, 3, 4 and 5 only.
- Footnote (t) revised to state that the tumor markers for germ cell tumors are CCI [redacted]

Section 5.1.2

- Typographical error corrected for inclusion criterion 3 ("Patients must have pathologically confirmed relapsed ~~**or relapsed**~~ or refractory advanced hematological malignancies including lymphoma and acute leukemia…")

Section 6.1.1.1

- Typographical error corrected ("…tremelimumab will be co-administered with durvaluma**a**b.")

Section 6.1.2

- Typographical error corrected ("On days when both durvalumab and treme**l**i~~u~~mumab are scheduled...")

Section 8.8.3 Exploratory biomarkers:

- Text revised to state that the tumor markers for germ cell tumors are CCI [redacted]

Version 1.0, 11 September 2018
Initial creation

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.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The procedures for the screening and treatment periods in this study are presented in

- Table 1 for the dose-finding phase
- Table 2 for the dose-expansion phase
- Table 3 for the procedures for the follow-up period (for patients off study treatment).
- Table 4 for the procedures (management, reporting) for patients receiving ongoing treatment beyond database cutoff

The timing of the vital signs assessments should be such that it allows the blood draw eg, pharmacokinetic (PK) blood sample, to occur at the timepoints indicated in the schedule of activities (SoAs). Whenever electrocardiograms (ECGs), vital signs, 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 the SoAs. Vital signs should always be assessed before blood draws.

For both durvalumab monotherapy or durvalumab in combination with tremelimumab

- Patients may delay dosing under certain circumstances:
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either immune or non-immune-related adverse events (AEs).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - A treatment delay of up to 14 days is permitted in the event that any AEs prevent the patient from starting the following cycle as planned.

Table 1 Schedule of activities for durvalumab ± tremelimumab dose-finding phase

	Screening	Cycle 1 (28 days)			Cycle 2 (28 days)			Cycle 3 to progression (each cycle is 28 days)	End of Treatment visit	For details, see Section
Day of cycle	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Visit window[a]			**±3 days**	**±3 days**	**±4 days**	**±3 days**	**±3 days**	**±4 days**		
Informed consent										
Informed consent/ assent: study procedures[b]	X									5.1
Study procedures										
Physical exam (full)	X									8.2.1
Targeted physical exam		X	X	X	X	X	X	X	X	8.2.1
Vital signs (including peripheral oxygen saturation)	X	X	X	X	X	X	X	X	X	8.2.3
Weight		X			X			X		8.2.1
Height		X			X			X		8.2.1
Tanner staging		X	To be measured at visits where tumor efficacy assessments are made (see Section 8.1) until progression							8.2.4
ECG[c] *(single)*	X	As clinically indicated								8.2.5
Concomitant medications (including vaccines)	X	X	X	X	X	X	X	X	X	6.4
Demography, including baseline characteristics and tobacco use[d]	X									
Eligibility criteria	X									5.1, 5.2

	Screening	Cycle 1 (28 days)			Cycle 2 (28 days)			Cycle 3 to progression (each cycle is 28 days)	End of Treatment visit	For details, see Section
Day of cycle	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Visit window[a]			**±3 days**	**±3 days**	**±4 days**	**±3 days**	**±3 days**	**±4 days**		
Laboratory assessments										
Clinical chemistry[e]	X	X[f]		X	X		X	X	X	Table 19
Hematology[e]	X	X[f]		X	X		X	X	X	Table 20
Coagulation		X[f]								Table 20
TSH[g], (if abnormal free T4[h] ±free T3)	X	X			X			X	X	Table 19
Urinalysis	X	X		X	X		X	X	X	Table 21
Hepatitis B and C and HIV	X									8.2.1
Pregnancy test[i]	X	X			X			X	X	8.2.1
Durvalumab PK sample (serum)		X[j,k] Pre- and post-infusion of Durva	X	X	X[j,k] Pre-[l] and post-infusion of Durva			X[j,k] Pre- and post-infusion of Durva[l] in C4, C6, C8, C10, and C12		8.5
Tremelimumab PK sample (serum)					X[j,k] Pre- and post-infusion of Treme	X	X	X Pre- and post-infusion of Treme in C3, C4, and C5[j,k] Random sample in C8[m]	X[t]	8.5
Durvalumab immunogenicity assessment ADA (serum)		X[j] Pre-infusion of Durva only						C6[j] Pre-infusion of Durva only		8.5
Tremelimumab immunogenicity assessment ADA (serum)					X[j] Pre-infusion of Treme only			C5[j] and C8[m] Pre-infusion of Treme only		8.5

	Screening	Cycle 1 (28 days)			Cycle 2 (28 days)			Cycle 3 to progression (each cycle is 28 days)	End of Treatment visit	For details, see Section
Day of cycle	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Visit window[a]			**±3 days**	**±3 days**	**±4 days**	**±3 days**	**±3 days**	**±4 days**		
Monitoring										
Performance Score (Lansky or Karnofsky)[a]	X	X	X	X	X	X	X	X	X	8.2.7
AE/SAE assessment[c]	X	X	X	X	X	X	X	X	X	8.3
IP administration										
Durvalumab infusion[f,p]		X			X			X		6.1.1 6.1.2
Tremelimumab infusion[f,p]					X			C3, C4 and C5 only		6.1.1 6.1.2
Other assessments and assays										
CCI [redacted]										

	Screening	Cycle 1 (28 days)			Cycle 2 (28 days)			Cycle 3 to progression (each cycle is 28 days)	End of Treatment visit	For details, see Section
Day of cycle	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Visit window[a]			**±3 days**	**±3 days**	**±4 days**	**±3 days**	**±3 days**	**±4 days**		
Efficacy evaluation										
Radiological efficacy assessments[s]	Days -21 to -1	On-study tumor assessments occur every 8 weeks ± 1 week (always relative to the date of first dose), until radiological progression plus an additional regularly scheduled follow-up scan. For patients who achieve an objective response (CR, PR) or stable disease, and for whom the response is still evident at 12 months, subsequent tumor assessments are to occur every 16 weeks. Unscheduled assessments can be performed at any time during the study, as clinically indicated, based on signs and symptoms								8.1

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

Note: Patients who restart combination therapy (having subsequently progressed on durvalumab monotherapy following the completion of 4 months of combination therapy) should complete the same assessments starting from the Cycle 2 Day 1 of the dose-finding phase, with the exception of the PK, ADA, blood for CCI [redacted] analysis, and tumor biopsies.

[a] Visit windows are relative to the first day of each cycle.

[b] Written informed consent/assent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. 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's parent(s)/legally authorized representative(s). However, all screening laboratory assessments must have been obtained within 28 days of Cycle 1 Day 1 and imaging/staging examination results must have been obtained within 21 days of Cycle 1 Day 1. The unique enrollment code will be obtained after ICF signature. Dose-finding phase will be manually supplied.

[c] Any clinically significant abnormalities detected require a confirmatory ECG result.

[d] Tobacco use will be collected at the Investigator's discretion.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[f] Results for LFTs, electrolytes, full blood count, urea, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing. If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 1 (unless performed within 3 days prior to Day 1).

[g] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1. TSH to be measured every 4 weeks from baseline.

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

[i] For females of childbearing potential only. A urine or serum pregnancy test is acceptable. Females of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of IP and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

[j] Predose within 60 minutes of start of the 1st infusion.

[k] Within 10 minutes of the end of the 2nd infusion.

[l] During the combination treatment period, predose samples for durvalumab PK samples should ideally be taken in the window after tremelimumab has been infused and before durvalumab is infused, within 60 minutes of start of infusion. However, sampling prior to tremelimumab infusion is also acceptable, if considered necessary for logistical/operational reasons.

[m] The C8 follow-up tremelimumab PK and ADA sample will be taken 3 months (±1 week) after the last dose of this IP (meets requirement in Table 3).

[n] Karnofsky scale to be used for patients ≥16 years of age; Lansky scale to be used for patients ≥1 and <16 years of age.

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

[p] During the combination portion of treatment, tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour after the end of the tremelimumab infusion. See Section 6.1.2 (Study Drug Administration).

[q] See Section 8.8.1 for details around collection, requirement, and exemption for samples for CCI

[r] CCI

[s] See Section 6.1.4 and Section 8.1 for additional details. Imaging modalities appropriate for the tumor type under consideration should be performed and the corresponding objective criteria used to monitor efficacy: solid tumors (RECIST 1.1 [Appendix E], and INRC for neuroblastoma [Appendix F]). Confirmatory scans will be required.

[t] A tremelimumab sample is required for patients at the EoT visit who only received a single dose (cycle) of tremelimumab in combination with durvalumab. Preferably, this sample should be collected approximately 30 days after the final tremelimumab infusion, but can be collected at any time after the final (day 15) tremelimumab PK sample.

ADA Anti-drug antibody; AE Adverse event; C Cycle; CR Complete response; CSF Cerebrospinal fluid; D Day; Durva Durvalumab; ECG Electrocardiogram; FFPE Formalin-fixed paraffin-embedded; HIV Human immunodeficiency virus; ICF Informed consent form; IM Intramuscular; INRC International Neuroblastoma Response Criteria; IP Investigational product; LFT Liver function test; LP Lumbar puncture; mRNA Messenger ribonucleic acid; NA Not applicable; CCI PK Pharmacokinetics; PR Partial response; qXw Every X weeks; RECIST Response Evaluation Criteria In Solid Tumors; SAE Serious adverse event; CCI Treme Tremelimumab; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone; W Week.

Table 2 Schedule of activities for durvalumab ± tremelimumab dose-expansion phase

	Screening	Cycle 1 (28 days)			Cycle 2 (28 days)		Cycle 3 to progression (each cycle is 28 days)	End of Treatment visit	For details, see Section
Day of cycle	**-28 to -1**	**1**	**8**	**15**	**1**	**15**	**1**		
Visit window[a]			**±3 days**	**±3 days**	**±4 days**	**±3 days**	**±4 days**		
Informed consent									
Informed consent/assent: study procedures[b]	X								5.1
Study procedures									
Physical exam (full)	X								8.2.1
Targeted physical exam		X	X	X	X	X	X	X	8.2.1
Vital signs (including peripheral oxygen saturation)	X	X	X	X	X	X	X	X	8.2.3
Weight		X			X		X		8.2.1
Height		X			X		X		8.2.1
Tanner staging		X	To be measured at visits where tumor efficacy assessments are made (see Section 8.1), until progression						8.2.4
ECG[c] *(single)*	X	As clinically indicated							8.2.5
Concomitant medications (including vaccines)	X	X	X	X	X	X	X	X	6.4
Demography, including baseline characteristics and tobacco use[d]	X								5.1
Eligibility criteria	X								5.1, 5.2
Laboratory assessments									
Clinical chemistry[e]	X	X[f]		X	X	X	X	X	Table 19
Hematology[e]	X	X[f]		X	X	X	X	X	Table 20
Coagulation		X[f]							Table 20

	Screening	Cycle 1 (28 days)			Cycle 2 (28 days)		Cycle 3 to progression (each cycle is 28 days)	End of Treatment visit	For details, see Section
Day of cycle	**-28 to -1**	**1**	**8**	**15**	**1**	**15**	**1**		
Visit window[a]			**±3 days**	**±3 days**	**±4 days**	**±3 days**	**±4 days**		
TSH[g], (if abnormal free T4[h] ± free T3)	X	X			X		X	X	Table 19
Urinalysis	X	X		X	X	X	X	X	Table 21
Hepatitis B and C and HIV	X								8.2.1
Pregnancy test[i]	X	X			X		X	X	8.2.1
Durvalumab PK sample (serum)		X[j,k] Pre- and post-infusion of Durva	X	X	X[j,k] Pre[l]- and post-infusion of Durva		Pre- and post-infusion of Durva in C4[l], C8, C12		8.5
Tremelimumab PK sample (serum)		X[j,k] Pre- and post-infusion of Treme	X	X	X[j,k] Pre- and post-infusion of Treme		X C4 Pre- and post-infusion of Treme[j,k] Random sample in C7[m]		8.5
Durvalumab immunogenicity assessment ADA (serum)		X[j] Pre-infusion of Durva only[l]					C4[j] Pre-infusion of Durva only		8.5
Tremelimumab immunogenicity assessment ADA (serum)		X[j] Pre-infusion of Treme only					C4[j] Pre-infusion of Treme only Random sample in C7[m]		8.5
Monitoring									
Performance Score (Lansky or Karnofsky)[n]	X	X	X	X	X	X	X	X	8.2.7
AE/SAE assessment[o]	X	X	X	X	X	X	X	X	8.3

	Screening	Cycle 1 (28 days)			Cycle 2 (28 days)		Cycle 3 to progression (each cycle is 28 days)	End of Treatment visit	For details, see Section
Day of cycle	**-28 to -1**	**1**	**8**	**15**	**1**	**15**	**1**		
Visit window[a]			**±3 days**	**±3 days**	**±4 days**	**±3 days**	**±4 days**		
IP administration									
Durvalumab infusion[f,p]		X			X		X		6.1.1 6.1.2
Tremelimumab infusion[f,p]		X			X		C3 and C4 only		6.1.1 6.1.2
Other assessments and assays									
CCI [redacted]		[redacted]	[redacted]		[redacted]		[redacted]		[redacted]
Blood sample for vaccine antibody titer measurements (blood)[q]		X	At least 4 weeks after vaccination					X	8.9
CCI [redacted]									

	Screening	Cycle 1 (28 days)			Cycle 2 (28 days)		Cycle 3 to progression (each cycle is 28 days)	End of Treatment visit	For details, see Section
Day of cycle	**-28 to -1**	**1**	**8**	**15**	**1**	**15**	**1**		
Visit window[a]			**±3 days**	**±3 days**	**±4 days**	**±3 days**	**±4 days**		
Efficacy evaluations									
Radiological efficacy assessments[u]	X	On-study efficacy assessments occur every 8 weeks ± 1 week (always relative to the date of first dose), until radiological progression plus an additional regularly scheduled follow-up scan. This schedule MUST be followed regardless of any delays in dosing. For patients who achieve an objective response (CR, PR) or stable disease, and for whom the response is still evident at 12 months, subsequent tumor assessments are to occur every 16 weeks. Unscheduled assessments can be performed at any time during the study, as clinically indicated, based on signs and symptoms							8.1

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

Note: Patients who restart combination therapy (having subsequently progressed on durvalumab monotherapy following the completion of 4 months of combination therapy) should complete the same assessments starting from Cycle 1 Day 1 of the dose-expansion phase, with the exception of PK, ADA, tumor biopsies, blood for CCI [redacted] analysis, blood for CCI sequencing, and CCI [redacted].

[a] Visit windows are relative to the first day of each cycle.

[b] Written informed consent/assent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. 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's parent(s)/legally authorized representative(s). However, all screening laboratory assessments must have been obtained within 28 days of Cycle 1 Day 1 and imaging/staging examination results must have been obtained within 21 days of Cycle 1 Day 1. The unique enrollment code will be obtained after ICF signature, through the IRT/RTSM.

[c] Any clinically significant abnormalities detected require a confirmatory ECG result.

[d] Tobacco use will be collected at the Investigator's discretion.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[f] Results for LFTs, electrolytes, full blood count, urea, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing. If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 1 (unless performed within 3 days prior to Day 1).

[g] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1. TSH to be measured every 4 weeks from baseline.

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

[i] For females of childbearing potential only. A urine or serum pregnancy test is acceptable. Females of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of IP and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

[j] Predose within 60 minutes of start of the 1st infusion.

[k] Within 10 minutes of the end of the 2nd infusion.

[l] During the combination treatment period, predose samples for durvalumab PK samples should ideally be taken in the window after tremelimumab has been infused and before durvalumab is infused, within 60 minutes of start of infusion. However, sampling prior to tremelimumab infusion is also acceptable, if considered necessary for logistical/operational reasons.

[m] The C7 follow-up tremelimumab PK and ADA sample will be taken 3 months (±1 week) after the last dose of this IP (Table 3).

[n] Karnofsky scale to be used for patients ≥16 years of age; Lansky scale to be used for patients ≥1 and <16 years of age.

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

[p] During the combination portion of treatment, tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour after the end of the tremelimumab infusion. See Section 6.1.2 (Study Drug Administration).

[q] Blood sample for antibody titer measurement will be taken from all patients at C1D1 and from at least 14 patients on durvalumab plus tremelimumab combination therapy. At Cycle 1 Day 1, samples will be collected before tremelimumab infusion. Afterwards, a new sample should be collected at least 4 weeks after a vaccine has been given and end of treatment visit. Upon confirmation that a sufficient number of samples has been successfully analyzed, sites will be informed so that further collection of samples can be discontinued.

[r] Blood samples for CCI will be collected for at least 10 patients receiving durvalumab plus tremelimumab combination therapy.

[s] See Section 8.8.1 for details around collection, requirement, and exemption for CCI.

[t] The following tumor markers will be assessed in this study: alpha-fetoprotein for patients with hepatoblastoma and CCI for patients with germ cell tumors.

[u] See Section 6.1.4 and Section 8.1 for additional details. Imaging modalities appropriate for the tumor type under consideration should be performed and the corresponding objective criteria used to monitor efficacy: solid tumors (RECIST 1.1 [Appendix E]). Confirmatory scans will be required.

ADA Anti-drug antibody; AE Adverse event;C Cycle; CR Complete response; CSF Cerebrospinal fluid; D day; Durva Durvalumab; ECG Electrocardiogram; FFPE Formalin-fixed paraffin-embedded; HIV Human immunodeficiency virus; ICF Informed consent form; IM Intramuscular; IP Investigational product; Interactive Response Technology (IRT); Randomization and Trial Supply Management (RTSM); LFT Liver function test; LP Lumbar puncture; CCI; NA Not applicable; CCI; PK Pharmacokinetics; PR Partial response; qXw Every X weeks; RECIST Response Evaluation Criteria In Solid Tumors; SAE Serious adverse event; CCI; Treme tremelimumab; T3 Triiodothyronine; T4 Thyroxine; CCI; TSH Thyroid-stimulating hormone; W Week.

Table 3 Schedule of activities for patients who have discontinued all study treatments (durvalumab monotherapy or durvalumab and tremelimumab combination therapy) in the dose-finding or the dose-expansion phases

	Time since last dose of IP				
	Day (±3)	Months (±1 week)			For details, see Section
Evaluation	30	2	3	4 months and every 2 months thereafter (±2 weeks)	
Physical examination (full)	X				8.2.1
Vital signs (temperature, respiratory rate, blood pressure, pulse, and peripheral oxygen saturation)	X	X	X		8.2.3
Weight	X	X	X		8.2.1
Pregnancy test[a]	X	X	X		8.2.1
AE/SAE assessment	X	X	X		8.3
Concomitant medications	X	X	X		6.4
Performance Score (Lansky or Karnofsky) performance status[b]	X				8.2.7
Subsequent anticancer therapy[c]	X	X	X	X	8.1.2
Survival status[d]	X	X	X	X	8.1.2
Hematology	X	X	X		Table 20
Clinical chemistry	X	X	X		Table 19
TSH[e] (if abnormal free T4 ± free T3)	X	X	X		Table 19
Durvalumab PK sample (serum)[f]			X		8.5
Tremelimumab PK sample (serum)[f]			X		8.5
Durvalumab immunogenicity assessment ADA (serum)[f]			X		8.5

	Time since last dose of IP				
	Day (±3)	Months (±1 week)			For details, see Section
Evaluation	**30**	**2**	**3**	**4 months and every 2 months thereafter (±2 weeks)**	
Tremelimumab immunogenicity assessment ADA (serum)[f]			X		8.5
Radiological efficacy assessments[g]	Efficacy assessments occur every 8 weeks (or every 16 weeks for patients who achieve an objective response [CR, PR] or stable disease disease and for whom the response is still evident at 12 months) ± 1 week relative to the date of first dose, until radiological progression plus an additional regularly scheduled follow-up scan or death (whichever comes first). Additional scans to be completed per standard practice post-progression				7.1

Note: Patients who permanently discontinue drug for reasons other than objective PD should continue to have objective response assessments performed every 8 weeks ± 1 week (when clinically indicated) thereafter until PD plus an additional follow-up assessment or death (whichever comes first). For patients who achieve an objective response (CR, PR) or stable disease and for whom the response is still evident at 12 months, subsequent tumor assessments are to occur every 16 weeks. If a patient is discontinued for PD, then the patient should have 1 additional follow-up assessment performed 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.

[a] For females of childbearing potential only. A urine or serum pregnancy test is acceptable.
[b] Karnofsky scale to be used for patients ≥16 years of age; Lansky scale to be used for patients ≥1 and <16 years of age.
[c] Details of any treatment **for the malignancy under study** (including surgery) post the last dose of IP must be recorded in the CRF. At minimum, collect the start date and description of the subsequent anticancer therapy.
[d] Patients/parents/legally authorized representatives may be contacted in the week following data cut offs to confirm survival status. Details of any treatment for **the malignancy under study** (including surgery) post the last dose of IP must be recorded in the CRF.
[e] Free T4 ± free T3 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[f] PK and immunogenicity samples for durvalumab and tremelimumab are collected 90 days (3 months) (±7 days) after the last dose of that IP (eg, if the last dose of tremelimumab is at C4D1 [12 weeks], then the follow-up samples for tremelimumab PK/ADA will be taken 90 days ± 7 days after that date, so equivalent to C7D1 [24 weeks] of durvalumab monotherapy; if the last dose of durvalumab is, for example, at C8D1, then the follow-up samples for durvalumab PK/ADA will be taken 90 days ± 7 days after that date.
[g] See Section 7.1 for additional details. Imaging modalities appropriate for the tumor type under consideration should be performed and the corresponding objective criteria used to monitor efficacy.

ADA Anti-drug antibody; AE Adverse event; CR Complete response; CRF Case report form; IP Investigational product; NA Not applicable; PD progression of disease; PK Pharmacokinetics; PR Partial response; SAE serious adverse event; T3 Triiodothyronine; T4 Thyroxine; TSH Thyroid-stimulating hormone.

Table 4 Schedule of activities for patients receiving ongoing treatment beyond final data cutoff (DCO)

IP Administration	
Durvalumab administration	Every 28 days until disease progression (or meeting criteria for treatment discontinuation)
Laboratory assessments	
Clinical chemistry	Standard of care, per local clinical practice
Hematology	Standard of care, per local clinical practice
TSH	Standard of care, per local clinical practice
Required Monitoring and Reporting	
SAE reporting	Any time during study treatment and up until 90 days after the last durvalumab infusion. If an event occurs after the 90-day period and is considered to be due to a late onset toxicity to study treatment, it should be reported as a SAE.
AESI reporting	Any time during study treatment and up until 90 days after the last durvalumab infusion.. If an event occurs after the 90-day period and is considered to be due to a late immune-related toxicity to study treatment, it should be reported as an AESI.
Pregnancy testing	For females of childbearing potential: Monthly while on study treatment and then monthly x 3 following the completion of study treatment.
Pregnancy reporting	Any time during study treatment
Overdose reporting	Any time during study treatment
Efficacy evaluation	

Radiological efficacy assessments	Imaging schedule as standard of care, per local clinical practice

1.2 Synopsis

International Co-ordinating Investigator:

PPD

Address: PPD
, London, WC1N 3JH, United Kingdom

Protocol Title: Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies.

Rationale: This is a first time in pediatrics study primarily designed to evaluate the safety and tolerability of durvalumab and durvalumab in combination with tremelimumab at increasing doses in pediatric patients with advanced solid malignancies who have progressed or are refractory to standard therapies and for whom no standard of care treatments exist. Although treatment efficacy is not a primary objective of this study given its early phase nature, the patients screened for this study have no standard treatment options and this study offers the potential of some benefit.

The study will also characterize the PK of durvalumab and durvalumab in combination with tremelimumab in children and adolescents and explore potential biological activity and immunogenicity by assessing pharmacodynamics, anti-drug antibody (ADA) levels, and anti-tumor activity. The results from this trial will form the basis for decisions for potential future pediatric studies.

Objectives and Endpoints

Primary Objective (Dose-finding phase):	Endpoint/Variable:
To determine the adult equivalent exposure/MTD/recommended Phase II pediatric dose of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy.	Based on PK parameters (including C_{max}, C_{min}, AUC, and others), identify the adult equivalent exposure/MTD of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy, among children and young adults from birth to <18 years of age with advanced solid tumors using a q4w dosing schedule. Time of RP2D assessment will be at the end of the dose-finding phase, when sufficient numbers of evaluable samples have been accrued.

Objectives and Endpoints

To determine the safety profile of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy	Identify the safety and tolerability of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy at the adult equivalent exposure/MTD among children and young adults from birth to <18 years of age with advanced solid tumorsusing a q4w dosing schedule. Endpoints include AEs, vital signs, physical examinations, ECGs, and laboratory evaluations.
Primary Objective (Dose-expansion phase):	**Endpoint/Variable:**
To determine the preliminary antitumor activity of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy, at the recommended dose, using cohort-specific response criteria (eg, RECIST 1.1).	Objective response rate as determined by the Investigator assessed RECIST 1.1 or alternative pre-specified tumor-specific response rates for different scoring systems. Assessment of antitumor activity will be specific to tumor cohort, eg, Investigator assessed RECIST 1.1. Additional efficacy endpoints that will be collected include DoR, BoR, DCR, PFS, APF12, and APF18 based on RECIST 1.1 assessed by the Investigator, and OS, OS12, and OS24 as appropriate to each individual cohort.
Secondary Objective (Dose-finding and Dose-expansion phases):	**Endpoint/Variable:**
To describe the PK of durvalumab and tremelimumab in combination and durvalumab as monotherapy following combination therapy, in children and young adults with solid tumors, or hematological malignancies.	Individual durvalumab and tremelimumab concentrations in serum, and PK parameters including C_{max}, C_{min}, AUC, and other parameters where appropriate.
To determine the immunogenicity of durvalumab and tremelimumab in combination and durvalumab as monotherapy following combination therapy, in children and young adults with solid tumors.	CCI [redacted]

Objectives and Endpoints

To determine the immunogenicity of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy, in children and young adults with hematological malignancies.	CCI [redacted]
To measure effects on immune checkpoint inhibition in response to routine immunizations (dose-expansion phase only).	Individual antibody titer measurements CCI [redacted]
To evaluate immune activation and counts of NK-, B- and T-cells.	CCI [redacted]
Safety objective:	**Endpoint/variable:**
To determine the safety profile and tolerability of patients from dose-expansion cohort(s) treated with durvalumab in combination with tremelimumab with a q4w dosing schedule.	Adverse events, vital signs, physical examinations, ECGs, and laboratory evaluations.
Exploratory objective:	**Endpoint/variable:**
To collect biomarker and immune response data in patients treated with durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy.	The endpoints related to candidate predictive and/or prognostic biomarkers will focus on CCI [redacted], acknowledging that pediatric patients with advanced cancer have limitations on CCI [redacted] that can be harvested for correlative studies. If technically feasible the current translational plan will include assessment of: CCI [redacted]

Objectives and Endpoints

	In addition, an exploratory assessment related to biomarkers will be performed based on the availability of CCI to examine the relationship between a patient's health CCI prior to treatment as well as any modulations which may occur during and/or following treatment relative to clinical outcome, as applicable. If samples are available, assays may include: CCI
To compare RECIST 1.1 with irRECIST as assessment methodologies for clinical benefit of durvalumab and durvalumab in combination with tremelimumab.	Progression-free survival (and ORR) according to RECIST 1.1 and irRECIST (irRECIST will only be used as an exploratory endpoint).

ADA Anti-drug antibody; AE Adverse event; APF12 / APF18 Proportion of patients alive and progression-free at 12 / 18 months from first dose of IP; AUC Area under the plasma drug concentration-time curve; BoR Best objective response; CD Cluster of differentiation; C_{max} Maximum serum concentration; C_{min} Minimum serum concentration; DCR Disease control rate; DoR Duration of response; ECG Electrocardiogram; CCI ; IFN Interferon; irRECIST immune-related Response Evaluation Criteria in Solid Tumors; MTD Maximum tolerated dose; NK Natural killer; ORR Objective response rate; OS Overall survival; CCI PK Pharmacokinetics; q4w Every 4 weeks; RECIST Response Evaluation Criteria in Solid Tumors; RP2D Recommended Phase II dose; CCI .

Overall design:

Open-label, non-randomized, international, multicenter study investigating durvalumab in combination with tremelimumab (q4w for 4 cycles only) followed by durvalumab monotherapy (q4w) in pediatric patients from birth to <18 years of age with relapsed or refractory malignant solid tumors. Durvalumab in combination with tremelimumab will be examined in all solid malignant tumors (except primary central nervous system tumors).

The study will be conducted in 2 sequential phases: a dose-finding phase, followed by a dose-expansion phase.

Each treatment cycle is 28 days.

Phase I: Dose-finding phase

The dose-finding phase of the study will be conducted using a modified 3 + 3 design to determine whether durvalumab and tremelimumab can be administered safely in pediatric patients and if adult exposures can be achieved. Pediatric patients with relapsed or refractory malignant solid tumors (osteosarcoma and Ewing sarcoma [SARC-1], rhabdomyosarcoma, non-rhabdomyosarcoma, and other sarcomas [SARC-2], neuroblastoma [NB]), other solid tumors (STO), will be enrolled in 2 arms:

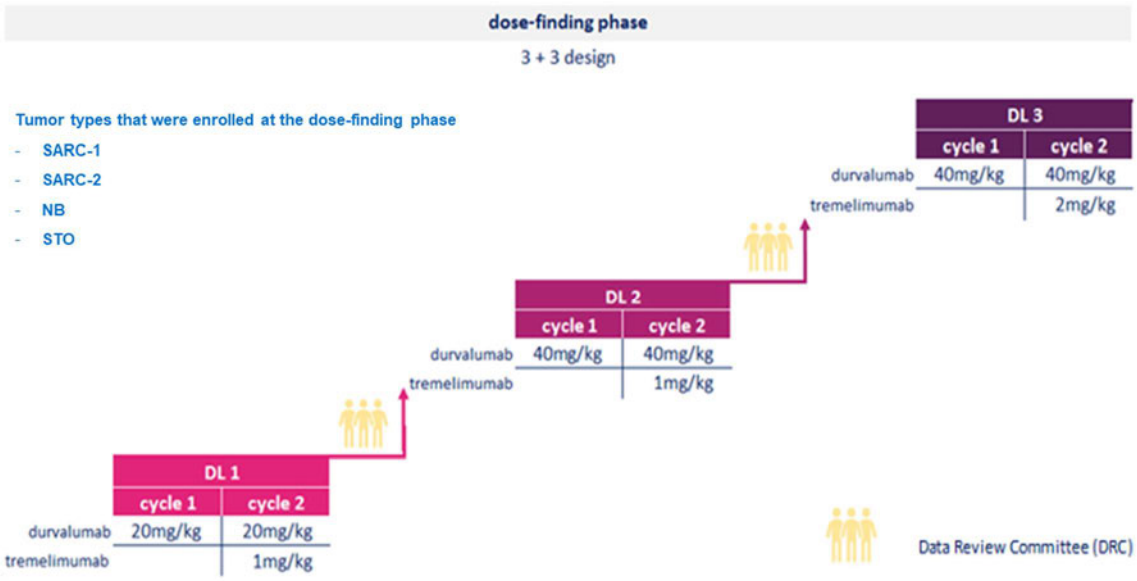
- Arm A: patients weighing ≥35 kg
- Arm B: patients weighing <35 kg.

Patients will be treated in Cycle 1 with durvalumab monotherapy, Cycles 2 to 5 with durvalumab combined with tremelimumab, and from Cycle 6 with durvalumab alone until progression of disease (PD).

Based on the available clinical and PK data and simulations, the administration of an adult weight-adjusted dose in children with a body weight of ≥35 kg is anticipated to result in PK and target engagement profiles similar to adults. However, patients with a body weight less than 35 kg, may have exposures lower than those in adults, and thus may require higher doses to achieve exposures similar to adults. Consequently dose-finding will be conducted in 2 body weight-based arms (ie patients, ≥35 kg and <35 kg) in parallel. Based on emerging data during the conduct of the study, cohorts may also be backfilled to provide further assessment of safety and PK in specific age groups and to ensure a broad representation of ages/weights at a given dose level (DL).

Three DLs may be explored in each of the arms as outlined in the figure below. Dose level 1 will be 100% of the recommended adult dose of both durvalumab and tremelimumab administered as weight-adjusted doses. The doses and schedules are as follows:

1. Cycle 1 (durvalumab monotherapy): durvalumab 20 mg/kg
2. Cycles 2 to 5 (durvalumab in combination with tremelimumab): durvalumab 20 mg/kg and tremelimumab 1 mg/kg (4 cycles administered every 28 days)
3. From Cycle 6 onwards, treatment will continue until a discontinuation criterion is met, with durvalumab monotherapy administered at 20 mg/kg every 28 days.



This figure shows the maximum doses for durvalumab at DLs 2 and 3 (40 mg/kg) and tremelimumab at DL 3 (2 mg/kg). Lower doses may be tested, depending on the obtained PK modeling data.
DL Dose level; NB Neuroblastoma; SARC-1 Osteosarcoma and Ewing sarcoma; SARC-2 Rhabdomyosarcoma, non-rhabdomyosarcoma, and other sarcomas; STO Solid tumor other.

A Data Review Committee (DRC) will be established prior to the initiation of the study to review all the data, including with a primary emphasis on safety and PK, to make decisions on dose escalations and determination of a recommended Phase II dose (RP2D) to be further explored in the dose-expansion phase.

Dose escalation decisions will aim to identify the RP2D for durvalumab and tremelimumab in combination. Dose escalation decisions and determination of RP2D will mainly consider safety assessments from at least 3 patients followed up for 4 cycles, to include a single cycle of durvalumab and 3 cycles of the combination of durvalumab and tremelimumab (for a total of 120 days). This includes assessment of pre-defined dose-limiting toxicities (DLTs) in the first 2 cycles.

A de-escalation step may occur for durvalumab or tremelimumab, with reduced doses of 15 mg/kg and 0.75 mg/kg, respectively, if DL 1 is considered not tolerated. Furthermore, if exposure of durvalumab or/and tremelimumab proves inadequate, intermediate DLs may also be tested.

In addition, 3 patients older than 2 years of age must be treated with durvalumab in combination with tremelimumab and clear the DLT period before children less than 2 years old may be enrolled in the dose-finding phase.

Phase II: Dose-expansion phase

The dose-expansion phase will be conducted using a Simon 2-stage optimal design with an additional provision to include 1 mixed disease cohort (other malignant solid tumors).

Once the RP2D has been established, patients will be recruited to each of the following cohorts:

1. SARCOMA (bone sarcomas: osteosarcoma, Ewing sarcoma; soft-tissue sarcomas [≥ 40% of enrollment]: rhabdomyosarcoma, non-rhabdomyosarcoma, and other sarcomas)

2. STO (other solid tumors).

For the SARCOMA cohort, the initial stage will allow 11 evaluable patients, to be dosed in this disease-specific cohort. If 2 or more responses in either of these cohorts are observed, additional patients will be accrued, as part of the second stage, into the corresponding expansion cohort; 15 patients will be accrued into the SARCOMA expansion cohort for a total of 26 evaluable patients. If there has been ≤1 objective response in the SARCOMA cohort (11 patients), at the time that evaluable patients dosed in the initial stage have been followed/assessed for at least 3 cycles, the cohort will be discontinued for lack of benefit.

For the STO cohort, 10 evaluable patients will be enrolled into this mixed-disease cohort; Simon rules are not applicable for this cohort.

Study period:

Date of first patient enrolled: Q1 2019.

Estimated date of last patient completed: Q1 2023.

Number of patients:

Dose-finding phase: The final sample size in the dose-finding phase will depend on the number of DLTs and on the number of DLs to be explored. In addition, any patients not evaluable will be replaced in order to have the required number of patients evaluable at each DL. A minimum of 12 patients is anticipated to be dosed, to enable exploration of one DL in both patients weighing 35 kg and greater, and patients weighing under 35 kg. If all 3 DLs are used at both weight-based arms, then 36 evaluable patients would be necessary to complete the dose-finding phase. If approximately 20% of patients need to be replaced due to non-evaluability, then a maximum of 45 patients will be enrolled on the dose-finding cohorts.

Dose-expansion phase:

- Following a Simon 2-stage optimal design, a total of 26 evaluable patients (11 evaluable patients in the initial stage and an additional 15 patients in the second stage), are expected to be enrolled in the SARCOMA cohort.

- The STO cohort is planned to recruit 10 evaluable patients.

With the above considerations, the sample size for evaluable patients in the dose-expansion phase is expected to range from 38 to 66. Assuming that about 20% of patients may not be evaluable for objective response rate (ORR), the total number of patients dosed in the dose-expansion phase may range from approximately 46 to 80.

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be dosed. Patients may be rescreened a single time.

Treatments and treatment duration:

Durvalumab + tremelimumab combination therapy (dose-finding phase):

- Durvalumab monotherapy, administered as a single cycle, will be given via intravenous (IV) infusion at Cycle 1. Patients will receive durvalumab in combination with tremelimumab via IV infusion q4w, starting on Cycle 2, for up to a maximum of 4 doses/cycles. Four weeks after the last infusion of the combination, treatment continues with durvalumab monotherapy q4w until clinical or confirmed PD, or other discontinuation criteria is met, whichever comes first.

Durvalumab + tremelimumab combination therapy (dose-expansion phase):

- Durvalumab in combination with tremelimumab via IV infusion q4w will be given for up to a maximum of 4 doses/cycles. Four weeks after the last infusion of the combination, treatment continues with durvalumab monotherapy q4w until clinical or confirmed PD, or other discontinuation criteria is met, whichever comes first.

Duration of treatment

Unless specific treatment discontinuation criteria are met, patients will continue therapy until clinical progression/deterioration or confirmed radiological progression, and scanning/tumor assessments continue throughout treatment until radiological progression plus an additional follow-up scan (if clinically feasible).

Progression during treatment

All patients will receive 4 cycles of durvalumab in combination with tremelimumab (Cycles 2 to 5 in the dose-finding phase and Cycles 1 to 4 in the dose-expansion phase). Treatment with durvalumab alone will be continued q4w until clinical progression or confirmed radiological progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

If a patient progresses while receiving durvalumab monotherapy after receiving an initial 4 cycles of the combination of durvalumab and tremelimumab, such patients may restart treatment with the combination treatment for 4 additional cycles.

Follow-up of patients post discontinuation of study drug

Patients who have discontinued treatment due to toxicity or symptomatic deterioration, clinical progression, or who have commenced subsequent anticancer therapy will be followed for PK and survival. Efficacy assessments are to be done according to Table 3 (ie, until radiological progression plus an additional regularly scheduled follow-up scan or death; whichever comes first).

Survival

All patients in the study will be followed up for survival.

Data Review Committee:

A DRC will be established prior to the initiation of the study and will review the safety and PK data. The DRC membership will comprise of participating Investigators and representatives from both AstraZeneca (Pharmacovigilance Scientists for durvalumab and tremelimumab, PK Scientist, Study Physician and Biostatistician) and IQVIA (Study Physician, Safety Physician and Biostatistician). On a case-by-case basis, the DRC may also seek advice from pediatric oncologists with the required site specialization expertise.

Recommendations and decisions will be made through consensus of opinion amongst the DRC members with all decisions being documented and distributed to DRC members.

The key tasks of the DRC members will be to review the data recorded in the clinical database in conjunction with the PK data to:

1. Determine whether DLTs have occurred
2. Decide whether additional patients should be added to a cohort
3. Recommend de-escalating a dose that was poorly tolerated or escalating a dose if PK exposures inferior to those observed in adults, were achieved
4. Declare that dose finding is complete
5. Recommend a Phase II dose to be explored in the dose-expansion phase of the study
6. Perform a benefit/risk assessment at the completion of safety data analysis for children <1 year old prior to enrolling a patient less than 1 year old; notify local health authority of decision, if applicable, as per local requirements
7. Put enrollment on hold
8. End the study.

During the dose-expansion phase, the DRC will review safety, tolerability, PK, and efficacy data to make consensual decisions on cohort expansion or closure, and end the study, among others.

Statistical methods

There is no formal statistical testing for the dose-finding phase of the study.

The dose-expansion phase of the study will formally test the following hypothesis:

- H0: ORR $\leq$10%
- H1: ORR >10%.

The test will be performed for the SARCOMA cohort and it will be done at the 1-sided 5% level. No formal statistical testing will be performed for the STO cohort.

Five analysis sets will be used for data analysis:

- The full analysis set (FAS) will include all patients who were assigned to treatment and received at least 1 dose of study treatment. The FAS (or subset of the FAS specified below) will be used for all efficacy analyses. Patients will be summarized and analyzed according to their assigned study treatment, regardless of the treatment actually received.
- Evaluable for response analysis set is a subset of patients in the FAS who had measurable disease at baseline.
- The safety analysis set (SAS) will consist of all patients who received any amount of study treatment. Safety data will be summarized using the SAS according to the treatment received.
- The DLT evaluable analysis set is a subset of the SAS for the dose-finding phase of the study. It includes all patients enrolled in the dose-finding phase of the study who receive the protocol-assigned treatment with durvalumab + tremelimumab and complete the safety follow-up through the DLT evaluation period (Cycle 1 + Cycle 2) or experience a DLT during the DLT evaluation period.
- The PK analysis set will consist of all patients who receive at least 1 dose of IP per the protocol for whom any postdose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses.
  The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

The analysis of the primary endpoint, ORR, and the analyses of the secondary endpoints, progression-free survival (PFS), duration of response (DoR), and disease control rate (DCR), will be based on the site Investigator assessments using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for solid tumors. Immune-related Response Evaluation Criteria will also

be assessed for ORR and PFS. In addition, OS, another secondary endpoint, will also be evaluated.

The 2 phases of the study will be summarized and analyzed separately. For the dose-finding phase, summaries will be presented by DL. For the dose-expansion phase, summaries and analyses will be presented by cohort.

Methods for statistical analysis:

The following table presents the analyses planned for the efficacy endpoints. All tumor-related endpoints will be analyzed using Investigator RECIST 1.1 assessments.

Pre-planned statistical analyses to be conducted

Endpoints analyzed	Notes
Objective response rate	Exact 90% 2-sided CI (Mid-P)
Duration of response	Median estimated from KM curve
Disease control rate	Exact 90% 2-sided CI (Mid-P)
Best objective response	n (%) of patients in each response category
Progression-free survival	Median estimated from KM curve
Overall survival	Median estimated from KM curve
Proportion alive and progression-free at 12 months	90% 2-sided CI estimated from KM curve
Proportion alive and progression-free at 18 months	90% 2-sided CI estimated from KM curve
Proportion alive at 12 months	90% 2-sided CI estimated from KM curve
Proportion alive at 24 months	90% 2-sided CI estimated from KM curve

CI Confidence interval; KM Kaplan-Meier.

No multiplicity adjustment will be applied.

Safety and tolerability data will be presented by DL in dose-finding phase and by cohort in dose-expansion phase, using the SAS. Data from all cycles of treatment will be combined in the presentation of safety data.

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, physical examinations and exposure to durvalumab + tremelimumab combination therapy, and durvalumab monotherapy. Time on study, durvalumab + tremelimumab combination therapy, and durvalumab monotherapy dose delays will also be summarized.

Pharmacokinetic data will be summarized and analyzed based on the PK analysis set.

Pharmacokinetic concentration data will be listed for each patient and each dosing day and a summary will be provided for all evaluable patients.

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable anti-durvalumab and anti-tremelimumab antibodies. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab or anti-tremelimumab antibodies.

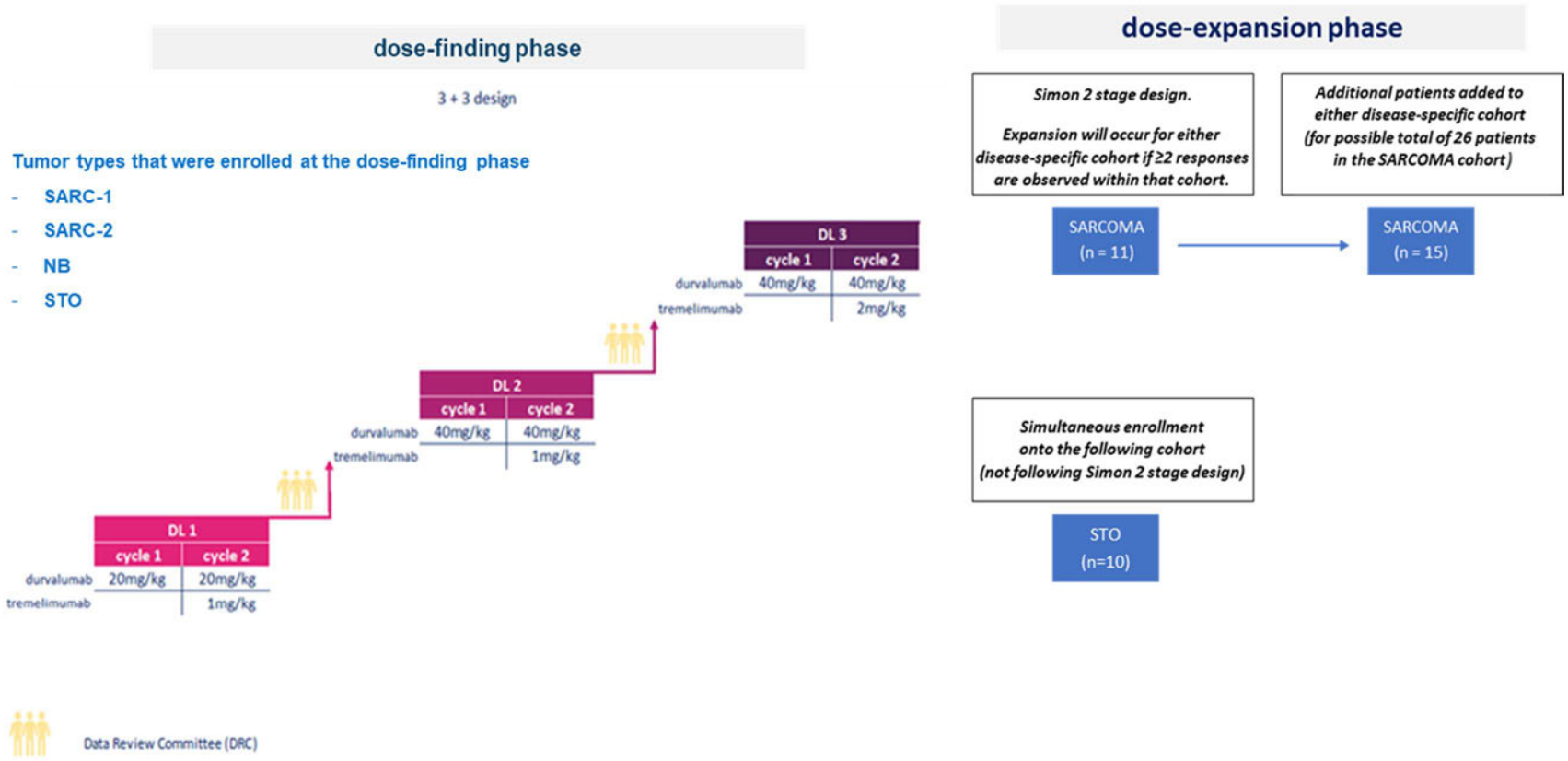
Vaccine individual antibody titer data and CCI [redacted] data will be listed for each patient and a summary will be provided.

The relationship of CCI [redacted] to clinical outcomes (including but not restricted to) of ORR, DCR, PFS and OS will be presented.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



This figure shows the maximum doses at dose-finding for durvalumab at DLs 2 and 3 (40 mg/kg) and tremelimumab at DL 3 (2 mg/kg). Lower doses may be tested, depending on the obtained PK modeling data

DL Dose level, NB Neuroblastoma; SARC-1 Osteosarcoma and Ewing sarcoma; SARC-2 Rhabdomyosarcoma, non-rhabdomyosarcoma, and other sarcomas; SARCOMA Osteosarcoma and Ewing sarcoma, and Rhabdomyosarcoma, non-rhabdomyosarcoma, and other sarcomas; STO Solid tumor other.

2. INTRODUCTION

According to the RARECARE dataset (website: http://www.rarecare.eu), the most common extracranial solid tumors in children (aged 0 to 14 years) include neuroblastoma (NB), Wilms tumor, and sarcomas, including rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma. Survival rates are highly variable with the type of solid tumor, although high overall survival (OS) rates are reported at 1 year (92%) and 5 years (76%) overall.

Pediatric hematopoietic and lymphoid malignancies are typically of an aggressive type, with acute lymphoblastic leukemia being the most common childhood cancer. According to RARECARE, other prevalent cancers of this type in ages 0 to 14 years include non-Hodgkin's lymphoma (NHL), Hodgkin's lymphoma (HL), and acute myeloid leukemia. Data from RARECARE also show high survival rates in children with HL (99% at 1 year) and remains high 5 years after diagnosis. For other lymphoid tumors, survival is also relatively high (>70%).

Standard therapy for solid and hematological pediatric tumors includes various combinations of surgery, cytotoxic chemotherapy, and radiation. These treatments can have detrimental consequences to a developing child, and many survivors carry a substantial burden of long-term morbidities. With improved survival rates, children with cancer are likely to live longer, with the risk of long-term toxicity being an important crucial factor. In addition, there is an overall unmet medical need for more effective therapies for pediatric patients who have relapsed/refractory disease. Attractive alternatives would include biological agents that do not include toxic chemotherapy and target alternative carcinogenesis pathways that may have acquired resistance from the previous therapies. Immune checkpoint inhibitors may be such candidates, with promising and positive outcomes in adults with melanoma, lung cancer, bladder cancer, gastric cancer, microsatellite instability in colorectal cancer, and other malignancies (SIOPE briefing, 2015).

2.1 Study rationale

Therapeutic options are lacking for the treatment of relapsed/refractory solid tumors and hematological malignancies in the pediatric population. Additionally, conventional pediatric therapies often produce long-term side effects. Therapies with less frequent and non-overlapping long-term side effect profiles would likely improve the quality of life of these patients.

Based on results of immune checkpoint inhibitor therapies in adults with relapsed/refractory solid tumors and lymphomas (see Section 2.2.1), durvalumab monotherapy or durvalumab plus tremelimumab combination therapy may represent an effective treatment for the pediatric population. The proposed study will evaluate durvalumab in combination with tremelimumab in pediatric patients with refractory/relapsed solid tumors and lymphoid malignancies.

This study has been discussed and agreed with the European Medicines Agency (EMA) Paediatric Committee (PDCO) and forms a key commitment as part of the Pediatric Investigation Plan.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab and tremelimumab is provided in the respective Investigator's Brochures (IBs).

2.2.1 Immunotherapies

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

Programmed cell death ligand 1 (PD-L1) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The programmed cell death 1 (PD-1) receptor (cluster of differentiation [CD]279) is expressed on the surface of activated T-cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and programmed cell death ligand 2 (PD-L2) (B7-DC; CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to a 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 immune cells (ICs). This activity overcomes PD-L1-mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

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

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

Pre-clinical data have now been added to 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 first granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies for the treatment of a number of malignancies in adult patients, including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer, squamous cell carcinoma of the head and neck, and urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

It is anticipated, based on preliminary efficacy signals for anti-PD-1/PD-L1 antibodies in pediatric indications, that immunotherapy agents could also play an important role in the treatment of relapsed/refractory solid tumors and hematological malignancies in the pediatric population, which are currently lacking. Presently the following data are available to support use of immunotherapy agents in pediatric patients.

A Phase I/II study of pembrolizumab in pediatric patients with advanced melanoma or a PD-L1+ advanced, relapsed, or refractory solid tumor or lymphoma. As of 07 November 2016, 1 patient each with HL, adrenocortical carcinoma, mesothelioma, and glioblastoma had partial response (PR) for an objective response rate (ORR) of 6.1% (95% confidence interval [CI], 1.7-14.8); 7 (10.6%) patients had stable disease (SD) for a disease control rate (DCR) of 16.7% (95% CI, 8.6-27.9). Median progression-free survival (PFS) and OS were 1.8 months and 9.2 months, respectively; 12-month PFS was 10.2% and OS was 40.5% (Geoerger et al 2017a).

Ipilimumab, an anti CTLA-4 inhibitor is approved by the FDA for the treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older) and for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab (USPI). Ipilimumab in combination with nivolumab is being pursued in a Phase I/II study of known pediatric patients with relapsed/refractory solid tumors (Davis et al 2017).

In a Phase I/II study assessing the safety, pharmacokinetic and preliminary activity of atezolizumab in pediatric and young adult patients with refractory/relapsed solid tumors concluded as of 19 July 2016 that the PK and safety profile of atezolizumab is similar to that in

adults. Two in 5 patients with HL had a PR and the only patient with atypical rhabdoid tumor had an unconfirmed PR.

There is a significant unmet medical need for new effective therapies for pediatric patients and these preliminary data suggest immunotherapy agents and combinations thereof may provide alternative effective cancer therapies for young adults and children. There is also strong rationale and support from the EMA PDCO and clinical experts to evaluate the synergistic activity of combined anti-PD-L1 and CTLA-4 targeting to activate the patient's native immune system against their cancer.

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G 1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T-cells and CD80 (B7.1) on 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 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 interferon (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 towards 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 adult 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 4.3.1.2 and Section 8.3.13. Refer to the current durvalumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

There is an ongoing study evaluating durvalumab monotherapy in pediatric patients. CCI [redacted], a Phase I, open-label, single institution study to assess the safety, tolerability and PK of durvalumab in pediatric patients with relapsed or refractory solid tumors, lymphoma and central nervous system tumors, is an externally sponsored, investigator-initiated single center study at University of Southern California, Los Angeles, USC Medical Center. Patients ≥12 months and ≤18 years of age at the time of study enrollment will be administered a starting dose of 10 mg/kg every 2 weeks (q2w). To date, 13 children (age range: 3 to 16 years) have been enrolled onto the investigator-initiated study evaluating durvalumab as monotherapy. Safety data from 11 evaluable patients have revealed no dose-limiting toxicities (DLTs). The Data Safety Monitoring Board, which convened in December 2018, did not indicate any safety concerns and recommended the study to proceed as planned. Efficacy data are incomplete at this time, as this study is still ongoing. Plans are to enroll an additional 4 patients onto the study, to fill the remaining age-based cohorts.

2.2.3 Tremelimumab

Tremelimumab is a human IgG2 mAb that is directed against CTLA-4; CD152), 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.

Details on the safety profile of tremelimumab monotherapy are summarized in Section 2.3.2.2. Refer to the current tremelimumab IB for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK available in adult patients. Tremelimumab monotherapy has not been studied in pediatric patients and therefore no clinical data are available. The pre-clinical studies summarized in the IB are considered adequate to support use of tremelimumab in pediatric patients, this has been endorsed by the EMA's PDCO.

2.2.4 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, AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

To date, more than 3000 adult patients have received the combination using a number of doses and dosing schedules. No pediatric patients have been studied under this combination.

The clinical safety profile of durvalumab in adult patients has been consistent with immune-system activation, and is largely manageable. Toxicity studies with tremelimumab and tremelimumab in combination with durvalumab, or other same-class competitor anti-PD-1 or anti-CTLA-4 agents as single agents or in combination in adult patients with solid tumor and hematological malignancies indicate that generalized immune activation and consequent immune-mediated adverse events (imAEs) are the most likely clinical toxicities. The target organs identified in clinical trials in adult advanced cancer patients are now generally known and management guidelines have been established (Weber et al 2012, Kumar et al 2017). These safety risks are expected to be equally relevant for pediatric patients.

Although endocrinopathies are not among the most common imAEs reported in adults, they can be very severe and diagnostically challenging, may require endocrinology consultation and hormone replacement therapy, and may not be reversible. One might consider that irreversible imAE would be of particular significance to a pediatric population treated with anti-PD-1/PD-L1 and anti-CTLA-4 therapies.

Immune checkpoint inhibitors have been shown to enhance ex vivo effector T-cell responses from patients with chronic viral, bacterial, or parasitic infection, including human immunodeficiency virus (HIV), tuberculosis, and malaria. Although the data from clinical trials in infectious diseases are still sparse, these inhibitors are being considered as potential treatments for chronic infections, especially when combined with therapeutic vaccines

(Dyck and Mills 2017). However, the risk of infection among adult or pediatric patients receiving immune checkpoint blockade is unknown. Case reports of opportunistic infections among adult patients with melanoma receiving the CTLA-4 inhibitor ipilimumab have been described (Kyi et al 2014). Del Castillo et al., retrospectively identified serious infection in 7.3% of 740 patients at a single institution who received immune checkpoint blockers. The main risk factors were receipt of corticosteroids and/or infliximab (Del Castillo et al 2016).

Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in Section 2.3.2.3. The dosing strategy applied for this study was based on simulations and preliminary PK results from study CCI [redacted] (please refer to Section 4.3.1 for details). Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of pre-clinical and clinical information including safety, efficacy, and PK.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of durvalumab and tremelimumab may be found in the respective IBs.

See Section 9.6.1 for information regarding the Data Review Committee (DRC).

2.3.1 Potential benefits

2.3.1.1 Durvalumab

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancer. In a number of these cancers, including lung (Mu et al 2011), renal (Krambeck et al 2007, Thompson et al 2005, Thompson et al 2006), pancreatic (Loos et al 2008, Nomi et al 2007, Wang et al 2010), and ovarian cancers (Hamanishi et al 2007), the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. On the other hand, the levels of tumor-infiltrating cells, and more specifically cytotoxic T-cells, have been correlated with improved prognosis in a number of cancers including colorectal, melanoma, and lung cancers (Pages et al 2010), suggesting that an antitumor immune response is beneficial to patients.

There is limited preclinical data examining the expression of PD-1 or PD-L1 in pediatric tumors. However, emerging research has shown that PD-L1 is expressed on murine embryonal rhabdomyosarcoma cell lines (Highfill et al 2014) and on human osteosarcoma cell lines (Shen et al 2014). Additionally, PD-1 expression on tumor-infiltrating lymphocytes has been correlated with advanced disease in patients with osteosarcoma (Zheng et al 2015). Finally, unpublished data has shown that PD-L1 is upregulated and expressed on tumor-infiltrating lymphocytes in a mouse model of NB. These early data suggest a potential role for PD-1/PD-L1 inhibitory agents in pediatric sarcomas and NB, which are prevalent tumors in pediatric populations.

Therapeutically, there is emerging data using PD-1/PD-L1 pathway inhibitors in patients with lymphomas, cancers that cross over into the pediatric population. PD-1 is overexpressed in Reed-Sternberg cells, the malignant cells of HL, and its blockade has been examined in adults and shown to be both tolerable and with therapeutic activity in patients with HL who were at

least 18 years of age (Ansell et al 2015). In diffuse large B-cell lymphomas (DLBCL), also seen in pediatric patients, high levels of soluble PD-L1 (sPD-L1) in the blood portends a poorer prognosis, suggesting a potential therapeutic role in patients with DLBCL (Rossille et al 2014). There is an ongoing study evaluating durvalumab monotherapy in pediatrics ([redacted]). This is a Phase I, open-label, single institution study to assess the safety, tolerability, and PK of durvalumab in pediatric patients with relapsed or refractory solid tumors, lymphoma, and central nervous system tumors. No efficacy data have been retrieved from this study, and no other studies with durvalumab have been conducted in pediatric patients to date.

2.3.1.2 Durvalumab + tremelimumab

The combination of PD-1/PD-L1 inhibition with blockade of the non-redundant and complementary checkpoint CTLA-4 is supported by strong pre-clinical evidence, and also by efficacy results in advanced melanoma patients in Phase I to III trials, as manifest by rapid, durable responses in a high proportion of patients (Curran et al 2010, Larkin et al 2015, Postow et al 2015).

Although there are preliminary efficacy signals for anti-PD-1/PD-L1 antibodies in pediatric indications, pediatric tumors likely have significant biological difference from the adult tumors where there has been clinical activity. Combining anti-PD-L1 and CTLA-4 therapy could therefore provide alternative therapy to overcome the potential limitations of single agent anti-PD-1/PD-L1 agents against pediatric tumors that may have low levels of PD-L1 expression or have low mutational loads and potentially inadequate neo-antigen expression. Furthermore, combination therapy, may also result in fewer and less severe long-term side effects in long-term survivors compared with multi-modality therapies that include chemotherapy (Johnpulle et al 2016, Ramelyte et al 2017, Metro et al 2017). Anti-PD-1/PD-L1 and anti-CTLA-4 therapies may be associated with uncommon but long-lasting endocrine complications such as hypophysitis, hypothyroidism, and diabetes mellitus, with special significance to long-term surviving pediatric populations (Boutros et al 2016). Careful evaluation of the full safety profile and tolerability of durvalumab monotherapy and durvalumab in combination with tremelimumab administered on the every 4 week (q4w) schedule will be critical to ultimate evaluation of risk-benefit treatment decisions.

2.3.2 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 tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on normal tissues.

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

It is still too early to describe the specific toxicity profiles for durvalumab monotherapy and durvalumab in combination with tremelimumab in pediatric patients. However, data from other immune checkpoint inhibitors and limited data from study [redacted] (ongoing study evaluating durvalumab monotherapy in pediatrics) have shown safety profiles in pediatric patients consistent with those observed in adults:

- A total of 145 pediatric patients have been treated with atezolizumab without major safety concerns (personal communication, Raphael Rousseau MD, PhD, Genetech/Roche)
- A total of 125 patients aged 1 to 17 years have been treated with pembrolizumab without major safety concerns (Geoerger et al 2017a)
- Pediatric patients have been treated with ipilimumab at higher doses than the 1 mg/kg tremelimumab doses, including 11 patients younger than 12 years of age (Merchant et al 2016)
- A total of 39 pediatric patients have been treated with nivolumab alone or in combination with ipilimumab without major safety concerns (Davis et al 2017)
- A total of 13 pediatric patients treated with durvalumab, 10 mg/kg q2w and 15 mg/kg q2w, so far suggest the safety and tolerability profile is similar to that described in durvalumab reference safety information.

The safety profile of durvalumab and durvalumab in combination with tremelimumab is expected to follow the same pattern as other immune checkpoint inhibitors in regards to imAEs.

2.3.2.1 Durvalumab

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

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

In monotherapy clinical studies, AEs reported very commonly include events such as fatigue, diarrhea, nausea and vomiting, decreased appetite, and muscle and joint pain. As of 03 November 2017, a total of 5% to 10% of adult patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed and updated summary of the monotherapy data including AEs, serious adverse events (SAEs), and National Cancer Institute (NCI)

Common Terminology Criteria for Adverse Events (CTCAE) 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 (see Section 8.4.5).

From review of the ongoing CCI [redacted] study, there were no new safety risks identified (see Section 2.2.2).

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

2.3.2.2 Tremelimumab

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

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

In monotherapy clinical studies in adults, AEs typically reported very commonly include events such as diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab, and approximately 45% of patients experienced an SAE. Please see the current version of the IB for a detailed summary of monotherapy data, including AEs, SAEs, and NCI CTCAE 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.

2.3.2.3 Durvalumab + tremelimumab

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose-expansion Study CCI [redacted] in adult patients with non-small cell lung cancer, is being studied in a number of other ongoing clinical studies in a

number of different indications, and has to date shown a manageable safety and tolerability profile. Please see the current version of the IB for detailed information on these studies.

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20 mg/kg and a tremelimumab dose of 1 mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from Study [redacted], from 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 typically reported very commonly were fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, peripheral edema, weight decreased, hyponatremia, and rash. Please see the current version of the durvalumab IB for a detailed summary of combination therapy data, including AEs, SAEs, and NCI CTCAE Grade 3 to 5 events reported across the durvalumab program, including durvalumab in combination with tremelimumab.

Approximately 15% of adult patients experienced an AE that resulted in permanent discontinuation of investigational product (IP), and approximately 15% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study Investigator.

The durvalumab and tremelimumab combination has not yet been evaluated in the pediatric population.

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

2.3.3 Overall benefit/risk

The overall risk/benefit of this study has been well considered and favors the conduct of the proposed study.

There is significant unmet need for therapies for pediatric patients with relapsed refractory solid tumors and hematological malignancies and in fact the patients eligible for this study have no viable therapeutic options. The clinical benefit associated with inhibition of the PD-1/PD-L1 pathway (alone or combined with inhibition of CTLA-4) is well documented for adult cancers. Many pediatric tumors bear hallmarks predicting sensitivity to immune checkpoint inhibitor therapies, including the presence of IC infiltrates, expression of PD-L1 in tumor and/or infiltrating IC (Geoerger et al 2017a, Geoerger et al 2017b) and high mutation burden in some cases (Marabelle et al 2015). Checkpoint inhibitors alone or in combination have been used safely in pediatric patients (Davis et al 2017), although early indications suggest that at least some solid tumors are not responsive to checkpoint inhibitor monotherapy. Therefore, the

proposed strategy of combination therapy with durvalumab and tremelimumab warranted. The potential risks of durvalumab, tremelimumab and the combination of these agents are well known and mitigation strategies are available. Overall, the potential benefits to this therapeutically underserved pediatric population outweigh the known potential risks based on the AEs in patients treated with durvalumab monotherapy and durvalumab + tremelimumab.

The safety of patients in this study will be assessed by the DRC.

3. OBJECTIVES AND ENDPOINTS

Table 5 Study objectives

Primary Objective (Dose-finding phase):	**Endpoint/Variable:**
To determine the adult equivalent exposure/MTD/recommended Phase II pediatric dose of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy.	Based on PK parameters (including C_{max}, C_{min}, AUC, and others), identify the adult equivalent exposure/MTD of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy, among children and young adults from birth to <18 years of age with advanced solid tumors, using a q4w dosing schedule. Time of RP2D assessment will be at the end of the dose-finding phase, when sufficient numbers of evaluable samples have been accrued.
To determine the safety profile of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy.	Identify the safety and tolerability of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy at the adult equivalent exposure/MTD among children and young adults from birth to <18 years of age with advanced solid tumors, using a q4w dosing schedule. Endpoints include AEs, vital signs, physical examinations, ECGs, and laboratory evaluations.
Primary Objective (Dose-expansion phase):	**Endpoint/Variable:**
To determine the preliminary antitumor activity of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy, at the recommended dose, using cohort-specific response criteria (eg, RECIST 1.1).	Objective response rate as determined by the Investigator assessed RECIST 1.1 or alternative pre-specified tumor-specific response rates for different scoring systems.

	Assessment of antitumor activity will be specific to tumor cohort, eg, Investigator assessed RECIST 1.1. Additional efficacy endpoints that will be collected include DoR, BoR, DCR, PFS, APF12, and APF18 based on RECIST 1.1 assessed by the Investigator, and OS, OS12, and OS24 as appropriate to each individual cohort.
Secondary Objective (Dose-finding and Dose-expansion phases):	**Endpoint/Variable:**
To describe the PK of durvalumab and tremelimumab in combination and durvalumab as monotherapy following combination therapy, in children and young adults with solid tumors, or hematological malignancies.	Individual durvalumab and tremelimumab concentrations in serum, and PK parameters including C_{max}, C_{min}, AUC, and other parameters where appropriate.
To determine the immunogenicity of durvalumab and tremelimumab in combination and durvalumab as monotherapy following combination therapy, in children and young adults with solid tumors.	CCI [redacted]
To determine the immunogenicity of durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy, in children and young adults with hematological malignancies.	
To measure effects on immune checkpoint inhibition in response to routine immunizations (dose-expansion phase only).	Individual antibody titer measurements CCI [redacted]
To evaluate immune activation and counts of NK-, B- and T-cells.	CCI [redacted]
Safety objective:	**Endpoint/variable:**
To determine the safety profile and tolerability of patients from dose-expansion cohort(s) treated	Adverse events, vital signs, physical examinations, ECGs, and laboratory evaluations.

with durvalumab in combination with tremelimumab with a q4w dosing schedule.	
Exploratory objective:	**Endpoint/variable:**
To collect biomarker and immune response data in patients treated with durvalumab in combination with tremelimumab and durvalumab as monotherapy following combination therapy.	The endpoints related to candidate predictive and/or prognostic biomarkers will focus on CCI, acknowledging that pediatric patients with advanced cancer have limitations on total sample volumes that can be harvested for correlative studies. If technically feasible the current translational plan will include assessment of: CCI In addition, an exploratory assessment related to biomarkers will be performed based on the availability of CCI specimens to examine the relationship between a patient's health and CCI as well as any modulations which may occur during and/or following treatment relative to clinical outcome, as applicable. If samples are available, assays may include: • CCI
To compare RECIST 1.1 with irRECIST as assessment methodologies for clinical benefit of durvalumab and durvalumab in combination with tremelimumab.	Progression-free survival (and ORR) according to RECIST 1.1 and irRECIST (Note: irRECIST will only be used as an exploratory endpoint).

ADA Anti-drug antibody; AE Adverse event; APF12 / APF18 Proportion of patients alive and progression-free at 12 / 18 months from first dose of IP; AUC Area under the plasma drug concentration-time curve; BoR Best objective response; CD Cluster of differentiation; C_{max} Maximum serum concentration; C_{min} Minimum serum

concentration; DCR Disease control rate; DoR Duration of response; ECG Electrocardiogram; CCI [redacted]; IFN Interferon; irRECIST immune-related Response Evaluation Criteria in Solid Tumors; MTD Maximum tolerated dose; CCI [redacted]; ORR Objective response rate; OS Overall survival; CCI [redacted]; PFS Progression-free survival; PK Pharmacokinetics; q4w Every 4 weeks; RECIST Response Evaluation Criteria in Solid Tumors; RP2D Recommended Phase II dose CCI [redacted].

4. STUDY DESIGN

4.1 Overall design

This is an open-label, non-randomized, international, multicenter study investigating durvalumab in combination with tremelimumab followed by durvalumab monotherapy in pediatric patients from birth to <18 years of age with relapsed or refractory malignant solid tumors.

The study will be conducted in approximately 7 countries involving approximately 20 investigative centers. It was initiated in Q1 2019. The last-patient-last-visit for the final analysis is estimated to occur in Q1 2023.

This study will be conducted in 2 parts: a dose-finding phase (Phase I) followed by a disease specific expansion phase (Phase II). The purpose of this study is to identify the recommended Phase II dose (RP2D) that will be taken forward to determine preliminary antitumor activity of durvalumab in combination with tremelimumab in solid malignant tumors, using disease specific response criteria.

Table and Table lists the cohorts into which these malignancies will be grouped for both the dose-finding and dose-expansion phases of the study.

Table 6 Disease cohorts for dose-finding phase

Cohort	Type of cancer
SARC-1	Bone sarcomas: osteosarcoma or Ewing sarcoma
SARC-2	Soft-tissue sarcomas: rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, other sarcomas
NB	Neuroblastoma
STO	Other solid tumors (not represented in the other solid tumor cohorts)

Table 7 Disease cohorts for dose-expansion phase

Cohort	Type of cancer
SARCOMA	Bone sarcomas: osteosarcoma, Ewing sarcoma; Soft-tissue sarcomas: rhabdomyosarcoma, non-rhabdomyosarcoma soft-tissue sarcoma, other sarcomas
STO	Other solid tumors (not represented in the other solid tumor cohorts)

Note: Patients with soft-tissue sarcomas must account for ≥ 40% of those enrolled in the SARCOMA cohort.

During the dose-finding phase (I), durvalumab will be given as monotherapy for 1 cycle followed by the addition of tremelimumab for the next 4 cycles. For the dose-expansion phase (II), durvalumab will be given in combination with tremelimumab for the first 4 cycles, starting on Cycle 1. When durvalumab is given in combination with tremelimumab, a maximum number of four 28-day cycles of tremelimumab will be permitted, followed by durvalumab monotherapy administered q4w. Study treatment will be administered until clinical or confirmed disease progression (determined by the Investigator against tumor-specific objective criteria) or until any of the other discontinuation criteria are met, whichever comes first. Tumor-specific objective response (OR) criteria are provided in Appendix F for NB, and Appendix E for solid tumors (Response Evaluation Criteria in Solid Tumors [RECIST 1.1]).

However, if in the opinion of the Investigator, a patient received clinical benefit from treatment with the combination of durvalumab and tremelimumab and subsequently progressed whilst on durvalumab maintenance monotherapy, such patients may restart treatment with the combination of durvalumab and tremelimumab for 4 cycles. A patient who meets these criteria should be reconsented and receive another 4 cycles of tremelimumab while continuing durvalumab treatment.

The immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) are also provided in Appendix G. Note: The incorporation of the irRECIST appendix in this protocol is only meant to serve as a supplement for treating physicians to help in their clinical decision-making in situations where tumor response, based on RECIST 1.1, is in doubt.

The study outline is provided in Figure 1. The objectives and endpoints, as well as the projected number of patients who will participate in this study, including the assumptions underlying the sample size calculations, are provided in Section 3 and Section 9.2, respectively.

4.1.1 Dose-finding phase

The dose-finding phase of the study will be conducted using a modified 3 + 3 design to determine whether durvalumab and tremelimumab can be administered safely in children and if adult exposures can be achieved. Dose finding will only be assessed in patients with relapsed or refractory solid malignant tumors including osteosarcoma and Ewing sarcoma (SARC-1), rhabdomyosarcoma, non-rhabdomyosarcoma, and other sarcomas (SARC-2), NB, other solid tumors (STO). Starting doses of durvalumab and tremelimumab will be 100% of the recommended adult dose as a weight-adjusted dose administration. The dose-finding phase will seek to identify the RP2D for durvalumab monotherapy and durvalumab given in combination with tremelimumab. Pediatric patients with relapsed or refractory malignant solid tumors, will be enrolled and treated in 2 arms, based on patient weight: Arm A for patients ≥35 kg and Arm B for patients <35 kg.

As seen in Section 4.3.1, available PK data are consistent with simulation-based predictions and indicate that administration of an adult weight-adjusted dose to children with body weight ≥35 kg will result in a PK profile very similar to the observed profile in adults. These findings also suggest that the target engagement and saturation are likely to be similar between adults and children. However, simulation-based predictions indicate that children with body weight <35 kg will have exposures that are lower than the predicted profile in adults, thus requiring higher doses to reach adult equivalent exposures. Therefore, during the dose-finding phase of this study, the recommended adult weight-adjusted durvalumab and tremelimumab doses will be examined in 2 weight-based cohorts separated by a cutoff weight of 35 kg. Based on emerging data during the conduct of the study, cohorts may also be backfilled to provide further assessment of safety and PK in specific age groups and to ensure a broad representation of ages/weights at a given dose level (DL).

At least 1 patient representing each of the following pediatric age subsets will be enrolled: birth to 5 years, 6 to 11 years and 12 to <18 years. However, patients under 2 years of age will only be enrolled after at least 3 pediatric patients older than 2 years of age have been dosed with durvalumab and tremelimumab and have cleared the DLT observation period and have been evaluated by the DRC. Additionally, at least 1 day between first patient and subsequent patients dosed at each DL is required.

Three DLs may be explored in each of the treatment arms (detailed DLs can be seen in Table , Table 11, Table 12, and Table 13). The starting doses (DL 1) will be 100% of the recommended adult dose of both durvalumab and tremelimumab administered as weight-adjusted doses. The doses and schedules are as follows:

1. Cycle 1 (durvalumab monotherapy): durvalumab 20 mg/kg

2. Cycles 2 to 5 (durvalumab in combination with tremelimumab): durvalumab 20 mg/kg and tremelimumab 1 mg/kg (4 cycles administered every 28 days)

3. From Cycle 6 onwards, treatment will continue until a discontinuation criterion is met, with durvalumab monotherapy administered at 20 mg/kg every 28 days.

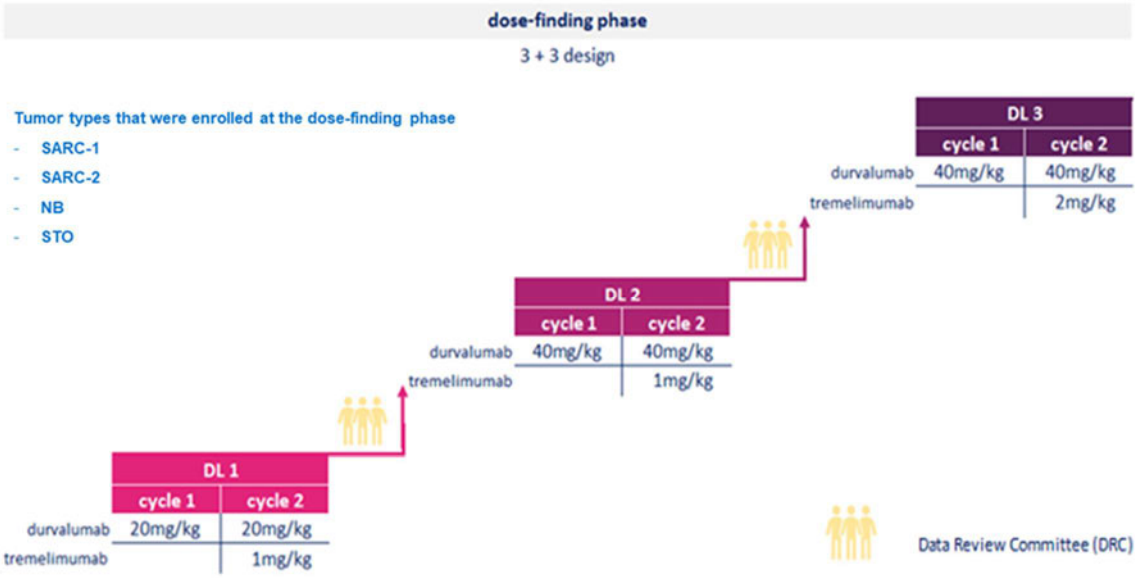
From Cycle 2 onwards, a treatment delay of up to 14 days is permitted between consecutive cycles to manage any side-effects. If a treatment delay of more than 14 days is required, the start of the cycle that had to be delayed must be skipped until the planned Day 1 of the next cycle. No dose reductions are permitted.

The pediatric PK will be considered equivalent to the adult PK when the lower limit of the 80% CI of the pediatric exposure (as measured by the area under the plasma drug concentration-time curve from Day 0 to Day 28 [AUC_{0-28}]) is more than 50% of the adult exposure. Adequate exposure will be declared only if ≥80% (5 of 6 patients at a dose level) achieve acceptable adult exposure PK, as defined. Durvalumab and tremelimumab will be escalated sequentially with durvalumab first followed by tremelimumab.

The degree of dose escalation at DLs 2 and 3 will be determined based on the review of all the safety and emerging PK data. It is anticipated that dose ranges of 24 to 40 mg/kg and 1.2 to 2 mg/kg for durvalumab and tremelimumab, respectively, will be explored in DLs 2 and 3 (the maximum dose of durvalumab that will be explored is 40 mg/kg).

Dose escalation will follow a modification of the standard 3 + 3 design. For Arm A (weight ≥35 kg), a total of 6 patients will be enrolled into this cohort; additional dose levels will only be evaluated if PK data indicate inadequate exposure to that of an adult. For Arm B (weight <35 kg), if none of the 3 patients experience a DLT, then 3 additional patients will be treated at the next dose level. If 1 or more patients experience a DLT, the 3 additional patients (for a total of 6 patients) will be treated at the same dose level. Dose escalation will continue using the same rules-based approach until at least 2 patients among a cohort of 3 or 6 patients experience a DLT, at which time, DLT will be established.

Figure 2 Dose-finding: escalation schema



This figure shows the maximum doses for durvalumab at DLs 2 and 3 (40 mg/kg) and tremelimumab at DL 3 (2 mg/kg). Lower doses may be tested, depending on the obtained PK modeling data.
DL Dose level; NB Neuroblastoma; SARC-1 Osteosarcoma and Ewing sarcoma; SARC-2 Rhabdomyosarcoma, non-rhabdomyosarcoma, and other sarcomas; STO Solid tumor other.

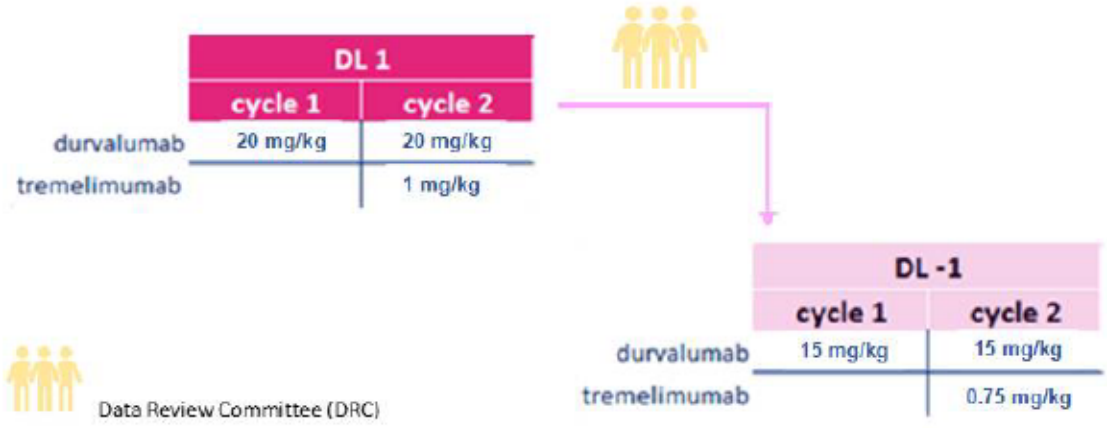
As indicated in Figure 2, DL 2 will assess an increased dose of durvalumab while holding tremelimumab dosing at 1 mg/kg.

If at DL 1, durvalumab exposure is adequate and tremelimumab exposure is too low, DL 2 can be skipped and tremelimumab alone will be escalated to DL 3 with durvalumab dosing staying at 20 mg/kg (100% of the recommended adult dose).

Furthermore, based on emerging PK, safety and tolerability data, intermediate DLs may also be tested.

De-escalation for toxicity may occur for durvalumab or tremelimumab to DL -1 with reduced doses of 15 mg/kg and 0.75 mg/kg, respectively (See Figure 3).

Figure 3 Dose-finding: de-escalation schema



DL Dose level

Assessments

During Cycle 1 and until Cycle 2 (Day 1), safety, tolerability, PK, and activity will be assessed as follows:

1. Encountered AEs will be reported and DLTs (defined in Section 4.1.2) will be identified
2. Four durvalumab PK samples (taken predose and end-of -infusion on Day 1 and on Day 8 and Day 15) will be obtained and
3. Three samples will be taken on Day 1 (pre- and postdose) and Day 8 to determine CCI [redacted].

During Cycle 2, safety, tolerability, PK, and activity will be assessed as follows:

1. Encountered AEs will be reported and DLTs will be identified
2. Two durvalumab PK samples (taken predose and at the end of infusion on Day 1) will be obtained
3. Four tremelimumab PK samples (taken predose and end-of -infusion on Day 1 and on Day 8 and Day 15) will be obtained and
4. One sample will be taken on Day 1 prior to dosing of tremelimumab to determine CCI [redacted].

4.1.2 Definition of dose-limiting toxicities and stopping criteria

Dose-limiting toxicities will be determined during Cycles 1 and 2 of the dose-finding phase using CTCAE version 5. Toxicities that occur during the first 28 day cycle and meet the criteria below will be assessed for attribution to durvalumab monotherapy. Any of the below listed AEs encountered between Cycle 1 Day 1 and Cycle 2 Day 28 (ie, 56 day DLT monitoring period for combination therapy) and in the opinion of the Investigator is thought to be attributable to durvalumab or/and tremelimumab, given a reasonable possibility based on temporal exposure to IP and for which an alternate etiology does not exist or cannot be identified, will be classified as DLTs:

- Grade 5 toxicity
- Hematological toxicity: Any Grade ≥3 (including febrile neutropenia Grade ≥3) except for the following:
    - Grade 3 thrombocytopenia that does not result in a bleeding event or does not require platelet transfusion
    - Grade 3 neutropenia that resolves to Grade ≤2 within 7 days.
- Non-hematological toxicity:
    - Any Grade 4 imAE
    - Any ≥ Grade 3 colitis
    - Any Grade 3 or 4 noninfectious pneumonitis
    - Any Grade 2 pneumonitis that does not resolve within 5 days to ≤ Grade 1 after initiation of maximal supportive care (including use of steroids)
    - Any Grade 3 imAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids and does not downgrade to ≤ Grade 1 or baseline within 14 days of onset
    - Liver transaminase elevation >5 × upper limit of normal (ULN) or total bilirubin (TBL) >3 × ULN. For patients with liver metastases at baseline, transaminase elevation >8 × ULN will constitute a DLT
    - Grade 4 vomiting, diarrhea, electrolyte abnormality, or systemic reaction
    - Grade 3 toxicity lasting >7 days despite optimal supportive care
    - Any ≥ Grade 3 non-imAE, except for the exclusions listed below
    - Any Grade 3 immune-mediated peripheral neuropathy or other immune-mediated neurotoxicity
    - Grade ≥3 inflammatory reactions.

The definition of DLTs excludes the following conditions:

- Grade 3 fatigue lasting ≤7 days.
- Grade 3 endocrine disorder (pituitary and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic.
- Grade 3 hypothyroidism adequately treated with hormone replacement therapy.
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).
- Concurrent vitiligo or alopecia of any AE grade.
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
- Grade 3 fever (fever greater than 40ºC [>104ºF] for ≤24h in duration).
- Any grade lymphopenia.
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention (including supplementation) within 7 days of initiating supplementation.

Immune-related adverse events are defined as AEs of immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing must be conducted to confirm significant laboratory findings prior to designation as a DLT.

Guiding principles:

1. While the rules outlined above dictate the classification of AEs as DLTs, any other AEs that are observed during the observation period may be defined as a DLT in consultation with the DRC; after having taken into consideration the emerging safety profile of durvalumab and tremelimumab.
2. The NCI CTCAE (version 5.0) will be used for AEs reporting and its severity will be graded on a scale from 1 to 5 provided for each AE term.
3. An immune-mediated AE is defined as an AE that is associated with exposure to durvalumab or/and tremelimumab and is consistent with an immune-mediated mechanism of action after alternate etiologies have been considered and excluded.

4. In the absence of clinical findings, repeat laboratory testing must be conducted to confirm the clinical significance of abnormal laboratory test result before it is classified as a DLT.

Patient dosing or study enrollment may be halted in the dose-finding phase until the toxicity data can be further studied. If DLTs occur in ≥2/6 patients on a given cohort, enrollment will be placed on hold and the DRC will be required to fully evaluate the available information prior to further patient enrollment. Upon review, a decision will be made to resume, stop or modify the study. If ≥2 DLTs occur at DL -1, the study may be prematurely stopped.

In the dose-expansion phase, enrollment in a disease-specific cohort will be halted and the DRC will be required to fully evaluate the available information prior to further patient enrollment if ≥3/9 patients have an AE or SAE that would be considered a DLT based on criteria established in the dose-finding phase. Upon review, a decision will be made to resume, stop or modify the study.

4.1.3 Determining a recommended Phase II dose

A DRC will be established prior to the initiation of the study to review all the data, with a primary emphasis on safety and PK, to establish RP2D to be further explored in the dose-expansion phase of the study. Dose escalation decisions and determination of RP2D will mainly consider safety assessments from at least 3 patients followed up for 4 cycles, to include a single cycle of durvalumab and 3 cycles of the combination of durvalumab and tremelimumab (for a total of 120 days). More details on the DRC constitution are described in Section 9.6.1.

The key considerations to be followed by the DRC during the dose-finding phase of the study are outlined in Table .

Table 8 Key considerations for dose escalation decisions

#DLTs	Pharmacokinetics	Decision/Outcome
0 out of 3-5	Equivalent to adult exposure (5 out of 6 patients)	Declare tolerated and observe for 4 cycles, and if <2 patients with DLTs are observed during the first 4 cycles of study drug, enter dose-expansion stage
OR		
1 out of 6	Less than 80% of adult exposure (≤2 patients)	Declare tolerated and move to next DL
1 out of 3		Increase number of patients to 6
≥2		Declare not tolerated; if observed on DL 1, move to DL -1

DL Dose level; DLT Dose-limiting toxicity.

4.1.4 Dose-expansion phase

During dose-expansion, patients will be monitored for safety according to the same criteria employed during the dose-finding phase (although events will not be considered DLTs during dose-expansion). Additionally, 4 cycles of safety information are required prior to opening the initial dose-expansion cohorts. See Section 4.1.2 for stopping criteria.

The dose-expansion phase will be conducted using a Simon 2-stage optimal design with an additional provision to include 1 mixed disease cohort (other malignant solid tumors).

Once the RP2D has been established, patients will be recruited to each of the following cohorts:

1. SARCOMA (bone sarcomas: osteosarcoma and Ewing sarcoma; soft-tissue sarcomas [≥ 40% of enrollment]: rhabdomyosarcoma, non-rhabdomyosarcoma, and other sarcomas)

2. STO (other solid tumors).

For the SARCOMA cohort, the initial stage will allow 11 evaluable patients, to be dosed in this disease-specific cohorts. If 2 or more responses in either of these cohorts are observed, additional patients will be accrued, as part of the second stage, into the corresponding expansion cohort; 15 patients will be accrued into the SARCOMA expansion cohort for a total of 26 evaluable patients. If there has been ≤1 objective response in either cohort, at the time that evaluable patients (11 patients) dosed in the initial stage who have been followed for at least 3 cycles have been assessed, the cohort will be discontinued for lack of benefit.

For the STO cohort, 10 evaluable patients will be enrolled into this mixed-disease cohort; Simon rules are not applicable for this cohort.

4.1.5 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 clinical study protocol (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 Good Clinical Practice (GCP), and minimize 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 option:

- Obtaining consent for the mitigation procedures (note, in the case of verbal consent, 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 medical monitor.
- 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 K.

4.2 Scientific rationale for study design

The dose-finding phase of the study will be conducted to determine whether adult PK exposure levels can be achieved by the administration of the adult recommended dose of both durvalumab and tremelimumab to pediatric patients. Furthermore, simulations and preliminary PK results from the ongoing CCI [redacted] study show that children weighing ≥35 kg are predicted to have exposure levels consistent with adult patients, whereas children with a body weight <35 kg are predicted to have approximately 2-fold lower exposure than those observed in adults (Section 4.3.1.1). Overall, 3 DLs may be explored in this study, with 2 arms separated by a cutoff body weight of 35 kg, based on these PK findings.

4.3 Justification for dose

4.3.1 Durvalumab and tremelimumab dose and treatment regimen justification

4.3.1.1 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 CCI [redacted] demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetics/Pharmacodynamics data

Durvalumab:

Study patients will initially receive the recommended adult weight-adjusted dose of 20 mg/kg IV durvalumab q4w (maximum durvalumab dose to be explored is 40 mg/kg). Based on the simulations and preliminary PK results from study CCI [redacted], children ≥35 kg are predicted to have exposure levels consistent with adult patients. However, simulations also indicated that patients <35 kg in weight are expected to have approximately 2 to 10-fold lower exposure than those observed in adults depending on weight. The minimum acceptable AUC_{0-28} for this

pediatric population is 50% of the adult AUC (3233-day × µg/mL). The systemic exposure in children will be considered adequate if the lower 80% confidence bound on estimated AUC_{0-28} at the current DL is higher than 3233-day × µg/mL. If lower exposures are confirmed, escalations defined in Section 4.1.1 will take place, and PK assessments will take place to confirm that exposure levels similar to adults are achieved.

Tremelimumab:

Children and young adults will initially receive the recommended adult weight-adjusted dose of 1 mg/kg IV tremelimumab q4w. Based on the simulations, children ≥35 kg are predicted to have exposure levels consistent with adult patients. However, simulations also indicated that patients <35 kg in weight are expected to have approximately 2 to 4-fold lower exposure than those observed in adults. AUC_{0-28} will be used to determine adequacy of systemic exposure. The minimum acceptable AUC_{0-28} for this pediatric population is 50% of the adult AUC, or 137-day × µg/mL. The systemic exposure will be considered adequate if the lower 80% confidence bound on estimated AUC_{0-28} at the current DL is greater than 137-day × µg/mL. If lower exposures are confirmed, escalations defined in Section 4.1.1 will take place, and new assessments will take place to confirm that exposure levels similar to adults are achieved.

Clinical data

The durvalumab and tremelimumab combination has not yet been studied in the pediatric population.

4.3.1.2 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, pre-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I study performed in Japanese patients with advanced solid tumor CCI [redacted]

PK/Pharmacodynamic data

Study patients will initially receive the recommended adult weight-adjusted dose of 20 mg/kg IV durvalumab q4w. Preliminary PK results from study CCI [redacted] and applicable to the durvalumab doses selected are described in Section 4.3.1.1. If lower exposures are confirmed, escalations defined in Section 4.1.1 will take place, and new assessments will take place to confirm that exposure levels similar to adults are achieved.

Clinical data

There is an ongoing study evaluating durvalumab monotherapy in pediatrics (CCI [redacted]
This is a Phase I, open-label, single institution study to assess the safety, tolerability, and PK of durvalumab in pediatric patients (aged ≥12 months to ≤18 years at the time of enrollment) with relapsed or refractory solid tumors, lymphoma, and central nervous system tumors. As of July 2019, 3 patients have been treated at DL 1 (10 mg/kg every 14 days) and 10 patients at DL 2 (15 mg/kg every 14 days); 1 patient at DL 2 discontinued treatment due to disease progression.

Of 11 patients evaluable for safety assessment, no DLTs have been reported. The safety and tolerability for the 11 patients evaluated so far are similiar to that seen in the adult population in terms of imAEs.

The starting dose of 10 mg/kg was selected based on the manageable safety and tolerability profile seen in adults (in which no maximum tolerated dose [MTD] was identified) and mathematical PK modeling.

4.3.1.3 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 q3w for 4 doses and then discontinued), shows that adult patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow-up (Schadendorf et al 2013). Following the data obtained from adults, the same treatment schedule will be applied in this study for the pediatric population.

The durvalumab + tremelimumab combination regimen will be administered for 4 doses q4w followed by durvalumab monotherapy q4w until PD or unless other specific discontinuation criteria are met.

4.4 End of study definition

Without regard to the present study, the primary completion date of the study for the purpose of the primary analysis, will occur approximately 6 months following enrollment of the last patient (See Section 9.5.1). End of study is defined as the completion of the 90-day safety follow-up period for the last patient who is no longer receiving study treatment (i.e., last subject, last visit [LSLV]. .

A patient is considered to have completed the study when the 90-day safety follow-up period has been completed following their last dose of study treatment.

Patients may be withdrawn from the study if the study itself is stopped. The study will be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned to a study intervention. Under no circumstances can there be

exceptions to this rule. Patients who do not meet the entry requirements are screen failures, refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who sign informed consent.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3 and Section 6.2.2, respectively.

5.1 Inclusion criteria

5.1.1 Solid malignant tumors (except primary central nervous system malignant tumors)

Patients with solid tumors are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Provision of signed and dated, 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), from each patient or patient's legally acceptable representative, parent(s) or legal guardian in accordance with regional laws or regulations and the patient's assent, when applicable, before any study-specific activity, including screening evaluation, is performed. For patients who reach the age of legal consent during the clinical study, notification may be required and a new consent form may need to be signed by the patient.

The ICF process is described in Appendix A 3.

Age

2. Age from birth to <18 years of age at the time of screening.

Type of patient and disease characteristics

3. Patients must have a histopathologic confirmation of malignancy. Patients must have progressed or are refractory to standard therapies (see Appendix A 10), and for whom no standard of care treatments exist.

4. If a patient has a diagnostic [redacted], provision of this sample is mandatory for study entry [redacted] and is preferred in formalin-fixed paraffin-embedded blocks (FFPE). If no tissue is available or the [redacted] Tumor lesions used for [redacted] should not be the same lesions used as RECIST 1.1 or International Neuroblastoma Response Criteria (INRC)

target lesions (TLs), unless there are no other lesions suitable for biopsy (reassessment after biopsy may be required).

5. Lansky play performance scale ≥50 (Appendix J) for patients ≥1 and <16 years of age and Karnofsky performance status score ≥50 (Appendix I) for patients ≥16 years of age (patients <1 year of age are exempt from this criterion).

6. At least 1 lesion, not previously irradiated, that can be accurately evaluated or measured by RECIST 1.1 (Appendix E), INRC for NB (Appendix F). Tumor radiological assessments must be performed within 21 days prior to first dose. Lesions in a previously irradiated field can be used as measurable disease, provided that there has been demonstrated progression in the lesion

   Or

   Have evaluable disease following methods used in common clinical practice.

7. No prior exposure to immune checkpoint inhibitors or genetically engineered cellular therapies including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2 antibodies and chimeric antigen receptor T-cell therapy (CAR-T) or other cell therapies, excluding therapeutic anticancer vaccines. Exposure to other investigational agents may be permitted after discussion with the Sponsor or designee.

8. Adequate organ and marrow function, independent of transfusion for at least 7 days prior to screening and independent of growth factor support for at least 14 days prior to screening, as defined below:

   - Hemoglobin ≥9.0 g/dL
   - Absolute neutrophil count ≥1.0 × 10^9/L
   - Platelet count ≥75 × 10^9/L
     - For patients with marrow involvement, criteria established for the hematology malignancies will apply, including a provision for platelet count ≥50 × 10^9/L
   - Serum bilirubin ≤1.5 × the ULN. In case of patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician, the upper limit will be ≤3.0 × ULN
   - Alanine transaminase (ALT) and aspartate transaminase (AST) ≤3 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN
   - Inclusion of patients with concomitant transaminases + bilirubin elevations should be discussed with the Sponsor or designee

- Creatinine for age within local laboratory ranges. If abnormal creatinine for age based on local laboratory ranges, inclusion can be based on a calculated creatinine clearance using the Schwartz pediatric equation, radioisotope measured glomerular filtration rate (GFR) of ≥70 mL/min/1.73m^2, or by 24-hour urine collection.

9. Must have a life expectancy of at least 3 months.

Sex

10. Male or female.

5.2 Exclusion criteria (All Patients)

Medical conditions

1. History of allogeneic organ transplantation. Patients who have previously received an autologous bone marrow transplant are eligible (eg, after discussion with Sponsor or designee).

2. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of a prior resolved episode of diverticulosis], celiac disease or other serious GI chronic conditions associated with diarrhea, systemic lupus erythematosus, Wegener syndrome [granulomatosis with polyangiitis]; myasthenia gravis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc), autoimmune myocarditis, and autoimmune pneumonitis. The following are exceptions to this criterion:

   - Patients with vitiligo or alopecia
   - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
   - Psoriasis that does not require systemic therapy
   - Patients with celiac disease controlled by diet alone.

3. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, cardiac arrhythmia, ILD, or psychiatric illness or social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs from IP, or compromise the ability of the patient to give written informed consent.

4. History of primary immunodeficiency.

5. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive hepatitis B virus [HBV] surface

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

6. Any unresolved toxicity NCI CTCAE version 5.0 Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, lymphopenia and the laboratory values defined in the inclusion criteria

   – Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis and may be included after consultation with the Study Physician.

   – Persistent toxicities (CTCAE Grade ≥2) caused by previous anticancer therapy, excluding alopecia. Patients with toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab in the opinion of the Investigator (eg, hearing loss, gastrostomy tube), may be included

7. Patients with clinically active brain metastases (known or suspected), spinal cord compression, and choloromas are excluded, unless these conditions have been previously treated and are considered stable. Stable brain metastases are defined as no change on computed tomography (CT) scan or magnetic resonance imaging (MRI) scan for a minimum of 2 months AND no clinical requirement for steroids above physiologic replacement dose.

8. History of leptomeningeal carcinomatosis, or involvement of any other anatomic area that, in the opinion of the Investigator, may cause significant symptoms if an inflammatory reaction occurs.

9. Known allergy or hypersensitivity to any of the IPs or any of the IP excipients.

10. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the IP or interpretation of patient safety or study results.

Prior/concomitant therapy

11. Receipt of the last dose of an anticancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, or mAbs) ≤28 days or 5 half-lives of the drug and a minimum of 7 days, whichever is shorter, prior to the first dose of IP. If sufficient washout time has not occurred due to the schedule or PK properties of an agent, a longer washout period will be required, as agreed by AstraZeneca and the Investigator.

12. 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.

13. Receipt of any radiotherapy or hormonal therapy for cancer treatment within 30 days prior to first dose of IP.

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

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

16. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:

    – Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection).

    – Systemic corticosteroids at physiologic doses as replacement therapy, not to exceed 10 mg/m^2/day of prednisone or its equivalent.

    – Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

Prior/concurrent clinical study experience

18. Previous IP assignment in the present study.

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

Other exclusions

20. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ highly effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy. A patient is considered to be of childbearing potential if, in the opinion of the Investigator, she is biologically capable of having children and is sexually active.

21. Non-sterilized male patients who are sexually active with a female partner of childbearing potential who are not willing to employ male condom plus spermicide from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy.

22. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

5.3 Lifestyle restrictions

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

1. Female patient of childbearing potential

   – If in the opinion of the Investigator, the patient is biologically capable of having children and is sexually active, they will be considered of childbearing potential.

   – Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner, and in accordance with local regulations, must use at least 1 highly effective method of contraception (Table) from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use a 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 contraception. Female patients should refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

   – Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). 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).

   – If a patient's partner becomes pregnant during or within 90 days after the last dose of durvalumab/180 days after the last dose of durvalumab in combination with tremelimumab, the partner or partner's parent/guardian is asked to sign the "Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

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

Table 9 Highly effective methods of contraception (<1% failure rate)

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

[a] This is also considered a hormonal method.

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 6.4.

5.4 Screen failures

Screen failures are patients who have provided informed consent to participate in the study but on screening are found not to fulfill the eligibility criteria for the study, and therefore must not be assigned to study treatment. These patients should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures. Patients may be rescreened a single time, if the screening failure was due to a temporary condition. Any rescreening of patients must be done in consultation of the Sponsor’s Study Physician and any decision must be captured in the patient’s medical notes.

If a patient who has failed screening is rescreened, a new E-code must not be assigned. Patients will reconfirm their consent to participate in the study by resigning and dating their original consent form(s), next to their original signature and date. All assessments CCI [redacted] must be repeated for rescreening, unless they are within 28 days of initial dose.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

6. STUDY TREATMENTS

Study treatment is defined as any IP(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study patient according to the study protocol. Study treatment in this study refers to durvalumab and tremelimumab.

6.1 Treatments administered

6.1.1 Dose and treatment regimens

6.1.1.1 Dose-finding phase

The patient's weight at baseline is to be used for subsequent treatment cycle dose calculations unless there is a ≥10% change in the measured weight at the beginning of a new treatment cycle.

Study treatment will consist of the combination of durvalumab and tremelimumab, administered at 3 planned DLs as described in Table , Table 11, and Table 12 (de-escalation doses to DL -1 are found in Table 13). Treatment will be administered on 28-day (4 week) cycles. For the dose-finding phase, Cycle 1 will always start with administration of durvalumab ***only***; subsequently, during Cycles 2 to 5 (for a total of 4 cycles), tremelimumab will be co-administered with durvalumab. Starting with Cycle 6, treatment consists of durvalumab monotherapy only and continues until clinical or radiological progression or until evidence of unacceptable toxicity, withdrawal of consent or another discontinuation criterion is met.

However, if in the opinion of the Investigator, a patient received clinical benefit from treatment with the combination of durvalumab and tremelimumab and subsequently progressed whilst on durvalumab maintenance monotherapy, such patients may restart treatment with the combination of durvalumab and tremelimumab for 4 cycles. A patient who meets these criteria should be reconsented and receive another 4 cycles of tremelimumab while continuing durvalumab treatment. Retreatment with an additional combination regimen may only occur once (for a single time).

From Cycle 2 onwards, a treatment delay of up to 14 days is permitted between consecutive cycles to manage any side-effects. If a treatment delay of more than 14 days is required, the start of the cycle that had to be delayed must be skipped until the planned Day 1 of the next cycle. No dose reductions are permitted throughout the study period.

Table 10 Planned dose level 1

Dose Level 1			
Drug	**Cycle 1**	**Cycles 2-5**	**Cycle 6 onwards**
Durvalumab	20 mg/kg	20 mg/kg	20 mg/kg
Tremelimumab	NA	1 mg/kg	NA

NA Not applicable.

Table 11 Planned dose level 2

Dose Level 2			
Drug	**Cycle 1**	**Cycles 2-5**	**Cycle 6 onwards**
Durvalumab	40 mg/kg	40 mg/kg	40 mg/kg
Tremelimumab	NA	1 mg/kg	NA

Dose level 2 may be skipped with progression directly to dose level 3 (see details in the dose level 2 description in Section 6.1.1.1).
NA Not applicable.

Table 12 Planned dose level 3

Dose Level 3			
Drug	**Cycle 1**	**Cycles 2-5**	**Cycle 6 onwards**
Durvalumab	40 mg/kg	40 mg/kg	40 mg/kg
Tremelimumab	NA	2 mg/kg	NA

NA Not applicable.

Table 13 Planned dose level -1

Dose Level -1			
Drug	**Cycle 1**	**Cycles 2-5**	**Cycle 6 onwards**
Durvalumab	15 mg/kg	15 mg/kg	15 mg/kg
Tremelimumab	NA	0.75 mg/kg	NA

NA Not applicable.

- **Dose Level 1:** Patients will receive the equivalent adult weight-based dose of both durvalumab and tremelimumab, as listed in Table .

- **Dose Level 2:** Patients will receive a tremelimumab dose that remains constant to that of DL 1 (1 mg/kg). However, there will be a planned dose escalation for durvalumab to increase the dose to a maximum of 40 mg/kg (reflecting a 100% increase from the starting dose). If data from the PK modeling obtained from patients treated at DL 1 suggests that adequate exposure levels will require less than a doubling of the dose, then an appropriate dose between 24 mg/kg and 40 mg/kg may be evaluated instead of 40 mg/kg. If data from the PK modeling obtained from patients treated at DL 1 suggests that adequate exposure level have not been obtained and a higher dose may be needed to achieve such an exposure, the dose escalation plan may be adjusted to incorporate subsequent dose increases.

    - If at DL 1 durvalumab exposure is adequate and tremelimumab exposure is too low, DL 2 can be skipped and tremelimumab alone will be escalated to DL 3 with durvalumab dosing remaining at the initial dose of 20 mg/kg.

- **Dose Level 3:** Patients will receive adjusted doses of both durvalumab and tremelimumab; the dose of durvalumab will be determined from PK modeling data obtained from DL 2. There will be a planned dose escalation for tremelimumab to increase the dose to 2 mg/kg (reflecting a 100% increase from the starting dose). If data from the PK modeling obtained from patients treated at DL 1 suggests that adequate exposure level will require less than a doubling of the dose, then an appropriate dose between 1.2 mg/kg and 2 mg/kg may be evaluated instead of 2 mg/kg. If data from the PK modeling obtained from patients treated at DL 1 suggests that adequate exposure level have not been obtained and a higher dose may be needed to achieve such an exposure, the dose escalation plan may be adjusted to incorporate subsequent dose increases.

- **Dose Level -1:** In the event of toxicity, patients will be treated at a reduced dose of both durvalumab and tremelimumab at doses of 15 mg/kg (durvalumab) and 0.75 mg/kg (tremelimumab) to reflect 25% reduction from the starting dose.

6.1.1.2 Dose-expansion phase

Patients will be treated with the combination of durvalumab and tremelimumab using the RP2D of each agent, based on data obtained from the dose-finding phase. Durvalumab and tremelimumab will be administered concurrently on an every 28-day (4 weeks) cycle for a total of 4 cycles (Cycles 1 to 4); subsequently, durvalumab is continued on an every 28-day cycle as monotherapy until clinical or confirmed PD, or other discontinuation criteria is met, whichever comes first.

However, if in the opinion of the Investigator, a patient received clinical benefit from treatment with the combination of durvalumab and tremelimumab and subsequently progressed whilst on durvalumab maintenance monotherapy, such patients may restart treatment with the combination of durvalumab and tremelimumab for 4 cycles. A patient who meets these criteria should be reconsented and receive another 4 cycles of tremelimumab while continuing durvalumab treatment. Retreatment with an additional combination regimen may only occur once (for a single time).

6.1.2 Study Drug Administration

During Cycles 1 and 2 of the dose-finding phase, durvalumab is infused over 120 minutes (2 hours). Starting with Cycle 3, if tolerated, the durvalumab infusion time may be reduced to 60 minutes (1 hour). Tremelimumab infusions will be administered over 60 minutes (1 hour) during all treatment cycles.

- During the dose-expansion phase, all durvalumab infusions will be administered over 60 minutes (1 hour)

On days when both durvalumab and tremelimumab are scheduled (Cycles 2 to 5 in dose-finding phase and Cycles 1 to 4 in dose-expansion phase), the tremelimumab infusion is to be administered ***first*** followed by a 1-hour interval (maximum 2 hours) before the start of the durvalumab infusion.

- Refer to Section 8.2.3 (Vital signs) for details on required vital signs and observation periods

Both durvalumab and tremelimumab infusions are to be administered using a 0.2 or 0.22 µm low-protein binding in-line filter.

No other drugs are to be infused through the same line or port while study infusions are being administered.

The IV tubing is flushed with a volume of saline equal to the priming volume of the administration set used after the contents of the IV bag or IV syringe are fully administered, according to institutional policy to ensure the full dose is administered.

The study infusion may be interrupted for an infusion reaction and when permitted, is restarted at a slower (ie, 50%) infusion rate. In instances where the total dose cannot be completed using an 8 hour hang time, a new infusion bag must be prepared to complete the study infusion.

6.1.3 Study Drug Preparation

AstraZeneca will supply durvalumab (MEDI4736) and tremelimumab to be used according to Table 14.

Table 14 Study treatments

	Treatment 1	Treatment 2
Study treatment name	Durvalumab (MEDI4736)	Tremelimumab
Dosage formulation:	500- or 120-mg vial solution (50 mg/mL)	400- or 25-mg vial solution (20 mg/mL)
Route of administration	IV	IV
Dosing instructions:	Section 6.1.1.1 (dose-finding). Section 6.1.1.2 (dose-expansion).	Section 6.1.1.1 (dose-finding). Section 6.1.1.2 (dose-expansion).
Packaging and labeling	Study treatment will be provided in 500- or 120-mg vials. Each vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.[a]	Study treatment will be provided in 400- or 25-mg vials. Each vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirement.[a]
Provider	AstraZeneca	AstraZeneca

[a] Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.
GMP Good Manufacturing Practice, IV intravenous.

For patients >20 kg, both durvalumab and tremelimumab doses can be prepared and administered either by an infusion bag or as a syringe, according to local practices. For patients ≤20 kg, doses should be prepared in a syringe with suggested final volumes based on weight ranges, as listed in Table 15, and administered via a syringe pump.

Table 15 Syringe administration volumes for patients ≤20 kg

Weight (kg)	Total syringe volume range (mL)
2.4–5.0	15
5–10	15–20
10–15	20–30
15–20	30–50

6.1.3.1 Durvalumab (MEDI4736)

Durvalumab is supplied by AstraZeneca as a 500- or 120–mg vial formulated as solution containing 50 mg/mL durvalumab, 26 mM histidine/histidine–hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; the final pH of the solution is 6.0. The nominal fill volume is 10.0 mL for the 500–mg vial and 2.4 mL for the 120–mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in the original packaging until use to prevent prolonged exposure to light.

The starting DL, using a weight-based approach, will be 20 mg/kg; during the dose-finding phase, 2 additional DLs of durvalumab will be evaluated (Table , Table 11, and Table 12). The patient's weight at baseline is to be used for subsequent treatment dosing calculations unless there is a ≥10% change in the measured weight. The dose will be prepared using an IV bag (polyvinyl chloride [PVC] or non-PVC) or a syringe, according to local practices, and administered via a standard infusion or syringe pump.

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

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

The durvalumab vial size (120 mg or 500 mg) should be selected based on: 1) availability and 2) calculated durvalumab dose volume. It is recommended that for small durvalumab volumes (2.4 mL or less), the 120–mg vial size may be used; and for larger volumes (greater than 2.4 mL), the 500-mg vial size may be used. A combination of vial sizes may be used depending on the dose volume in order to minimize drug wastage (eg, for a dose volume of 11.0 mL, one 500 mg and one 120 mg vial may be used).

Durvalumab will be diluted in 0.9% sodium chloride (normal saline [NS]) to a final concentration between 1 and 20 mg/mL, and administered with IV tubing containing a 0.2 µm or 0.22 µm low-protein binding in-line filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

Preparation of durvalumab doses for administration with an IV bag

Intravenous bag preparation

Dose calculation

The volume (in mL) of durvalumab to be added to an IV bag containing 0.9% sodium chloride is calculated as follows:

Dose level (mg/kg) × patient weight (kg) / 50 (mg/mL of durvalumab)

Example:

- Dose: 20 mg/kg
- Patient weight: 80 kg
- Dose for patient: 20 (mg/kg) × 80 (kg) = 1600 (mg)
- Dose volume: 1600 (mg) / 50 (mg/mL) = 32.0 mL
- Add the durvalumab dose volume into an infusion bag (PVC or non-PVC) containing 0.9% sodium chloride (NS); mix the solution using gentle inversion. Do not shake.
- Final products are prepared at a concentration between 1 and 20 mg/mL.
- Infusions should be administered immediately after preparation; however, once prepared, infusions can be stored for up to 24 hours under refrigeration and 4 hours at room temperature. Once the infusion has started, the hang-time of the infusion should not exceed 8 hours.
- Sites are to follow local practices for final IV bag preparation, including attachment of IV tubing (PVC or non-PVC) and priming (if applicable), and to ensure the IV infusion set connected to the IV infusion bag contains a 0.2 or 0.22 μm low-protein binding in-line filter.

Preparation of durvalumab doses for administration with an IV syringe

Intravenous syringe preparation

The volume (in mL) of durvalumab to be added to an IV syringe containing 0.9% sodium chloride is calculated as follows:

Dose level (mg/kg) × patient weight (kg) / 50 (mg/mL of durvalumab)

Example:

- Dose: 20 mg/kg
- Patient weight: 10 kg
- Dose for patient: 20 (mg/kg) × 10 (kg) = 200 (mg)
- Dose: 200 (mg) / 50 (mg/mL) = 4.0 mL
- Withdraw the durvalumab dose volume into a suitable size syringe. Prepare a separate syringe containing required amount of sodium chloride 0.9% (NS) to achieve the total syringe volume.

- Transfer the durvalumab solution into the NS syringe; once capped (or secured with an attached needle), mix the solution using a gentle inversion. Do not shake.
- Final products are prepared at a concentration between 1 and 20 mg/mL.
- Infusions should be administered immediately after preparation; however, once prepared, infusions can be stored for up to 24 hours (refrigeration) and 4 hours (room temperature. Once the infusion has started, the hang-time of the infusion should not exceed 8 hours.
- Sites are to follow local practices for final preparation, including attachment of IV tubing (PVC or non-PVC) and priming (if applicable), and to ensure the IV administration set connected to the IV syringe contains a 0.2 or 0.22 µm low-protein binding in-line filter.

6.1.3.2 Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400- or 25–mg vial solution containing 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; the final pH of the solution is 5.5. The nominal fill volume is 20.0 mL for the 400-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged exposure to light.

The starting dose, using a weight-based approach, is 1 mg/kg; during the dose-finding phase, 1 additional DL will be evaluated (Table , Table 11, and Table 12). The patient's weight at baseline is to be used for subsequent dosing calculations unless there is a ≥10% change in the measured weight. The dose will be prepared using an IV bag (PVC or non-PVC) or as a syringe and administered via a standard infusion pump. Tremelimumab will be diluted in 0.9% sodium chloride (NS) to a final concentration between 0.10 and 10 mg/mL, and administered through an IV infusion line containing a 0.2 µm or 0.22 µm low-protein binding in-line filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

The dose of tremelimumab for administration must be prepared by the Investigator's or site's pharmacist (or designee) using aseptic technique. Once a vial has been punctured (ie, at time of preparation) the final (diluted) preparation is to be stored as follows:

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

The tremelimumab vial size (25 mg or 400 mg) should be selected based on: 1) availability and 2) calculated tremelimumab dose volume. It is recommended that for small tremelimumab volumes (1.25 mL or less), the 25–mg vial size may be used; and for larger volumes (greater than 1.25 mL), a combination of 25–mg and the 400–mg vial sizes may be used.

Preparation of tremelimumab doses for administration with an IV bag

IV bag preparation

Dose calculation

The volume (in mL) of tremelimumab to add is calculated as follows:

Dose level (mg/kg) × patient weight (kg) / 20 (mg/mL tremelimumab)

Example:

- Dose: 1 mg/kg
- Patient weight: 80 kg
- Dose for patient: 1 (mg/kg) × 80 (kg) = 80 (mg)
- Dose to be added into infusion bag: 80 (mg) / 20 (mg/mL) = 4.0 mL
- Add tremelimumab dose volume into an infusion bag (PVC or non-PVC) containing 0.9% sodium chloride (NS); mix the solution using gentle inversion. Do not shake.
- Final products are prepared at a concentration between 0.1 and10 mg/mL.
- Infusions should be administered immediately after preparation; however, infusions once prepared, can be stored for up to 24 hours (refrigeration) and 4 hours (room temperature). Once the infusion has started, the hang-time of the infusion should not exceed 8 hours.
- Sites are to follow local practices for final preparation, including attachment of IV tubing (PVC or non-PVC) and priming (if applicable), and to ensure the IV set connected to the IV infusion bag contains a 0.2 or 0.22 µm low-protein binding in-line filter.

Preparation of tremelimumab doses for administration with an IV syringe

IV syringe preparation

Dose calculation

The volume (in mL) of tremelimumab to add is calculated as follows:

Dose level (mg/kg) × patient weight (kg) / 20 (mg/mL tremelimumab)

Example:

- Dose: 1 mg/kg
- Patient weight: 10 kg
- Dose for patient: 1 (mg/kg) × 10 (kg) = 10 (mg)
- Dose: 10 (mg) / 20 (mg/mL) = 0.5 mL
- Withdraw tremelimumab dose volume into a suitable size syringe. Prepare a separate syringe containing required amount of 0.9% sodium chloride (NS) to achieve the total syringe volume.
- Transfer the tremelimumab solution into the NS syringe; once capped (or secured with an attached needle), mix the solution using gentle inversion. Do not shake.
- Final products are prepared at a concentration between 0.1 and 10 mg/mL.
- Infusions should be administered immediately after preparation; however, infusions once prepared, can be stored for up to 24 hours under refrigeration and 4 hours at room temperature. Once the infusion has started, the hang-time of the infusion should not exceed 8 hours.
- Sites are to follow local practices for final preparation, including attachment of IV tubing (PVC or non-PVC) and priming (if applicable), to ensure the IV set connected to the IV syringe contains a 0.2 or 0.22 µm low-protein binding in-line filter.

6.1.4 Duration of treatment and criteria for restarting treatment with durvalumab in combination with tremelimumab

All treatment will be administered beginning on Day 1 until clinical progression or confirmed radiological progression (refer to Appendix E for solid tumors, Appendix F for NB, other malignancies will be analyzed based on the best response assessed by the Investigator) unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

If during the durvalumab monotherapy component of the treatment (after the 4 cycles of durvalumab + tremelimumab, where applicable), a patient's disease progresses, re-administration of durvalumab in combination with tremelimumab for another 4 cycles may be considered, following the conditions below:

- Patients who complete the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of defined PD, with or without confirmation, during the durvalumab monotherapy portion of the combination regimen may restart treatment with the combination once (4 cycles only). After this, durvalumab monotherapy will resume, if the Investigator judges there is clinical benefit to the patient.

6.1.5 Storage

The Investigator, or an approved representative (eg, pharmacist), will ensure that both durvalumab and tremelimumab are stored in a secured area, under refrigerated temperature (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 study product storage requirements reflected on the product label.

In the situation where the site is required to maintain a study supply of protocol-specified rescue medications (eg, infliximab, mycophenolate), proper storage requirements must be maintained in accordance with published information provided on the product packaging. Additionally, sites will be required to maintain temperature logs for such medications, when provided by the Sponsor.

6.2 Measures to minimize bias: randomization and blinding

6.2.1 Patient enrollment and randomization

This study will not be randomized. Patients will be assigned to a treatment regimen based on study phase and disease type (see Section 4.1). Interactive Response Technology (IRT)/Randomization and Trial Supply Management (RTSM) will only be used for the dose-expansion phase. The dose-finding phase will be manually supplied/managed.

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

1. Obtain signed informed consent from the potential patient's parent(s)/legally authorized representative(s) before any study-specific procedures are performed. When applicable and as per local regulations, assent will be provided by patients.

2. Assign potential patient a unique 7-digit enrollment code (E-code) beginning with 'E#' after written informed consent has been obtained. The E-code (EWWXXYZZ) will consist of a 2-digit country number (WW), a 2-digit site number (XX), a 1-digit study number (Y) and a 2-digit patient number (ZZ, starting with 01) issued by the study center in order of informed consent taken.

3. Determine patient eligibility. See Sections 5.1 and 5.2 for inclusion and exclusion criteria, respectively.

Patients may be enrolled but not treated. If the patient is not treated or withdraws from participation in the study, then his/her enrollment code cannot be reused and they cannot re-enter into the study. Refer to Section 5.4 (Screen failures) for conditions for rescreening.

Patients must not be treated unless all eligibility criteria have been met (Sections 5.1 and 5.2).

The IRT/RTSM will be used to track drug supply, patient assignment and kit assignment in the dose-expansion phase. The dose-finding phase will be manually supplied/managed (management procedures will be provided in a separate document).

6.2.2 Procedures for handling incorrectly enrolled patients

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

Where a patient does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca Study Physician immediately, and a discussion should occur between the AstraZeneca Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca Study Physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the patient.

6.2.3 Methods for ensuring blinding

This is an open-label study, no blinding methods will be applied.

6.3 Treatment compliance

Any change from the dosing schedule, dose delays/interruptions, and dose discontinuations must be recorded in the case report form (CRF).

The IP Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP.

6.4 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including 90 days since the last dose of IP.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, unit and frequency.

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 16 and Table 17. Refer also to the TMGs (see Section 8.4.5).

Table 16 Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage:**
Any investigational anticancer therapy other than those under investigation in this study.	Should not be given concomitantly whilst the patient is on study treatment.
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study.	Should not be given concomitantly whilst the patient is on study treatment.
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study.	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding TLs, for palliative intent is acceptable [eg, by local surgery or radiotherapy]).
Live attenuated vaccines.	Should not be given from 30 days prior to the first dose of IP until 30 days after the last dose of IP.
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/m^2/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers.	Should not be given concomitantly, or used for premedication prior to the immune-oncology infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs • Use in patients with contrast allergies • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).
Drugs with laxative properties and herbal or natural remedies for constipation.	Should be used with caution through to 90 days after the last dose of tremelimumab during the study.
Sunitinib.	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib).

Prohibited medication/class of drug:	Usage:
Tyrosine-kinase inhibitors (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 concomitantly unless agreed by the Sponsor or designee.

AE Adverse event; CTLA-4 Cytotoxic T-lymphocyte-associated antigen 4; EGFR Epidermal growth factor receptor; IP Investigational product; IT intrathecal; mAb Monoclonal antibody; PD-1 Programmed cell death 1; PD-L1 Programmed cell death ligand 1; TL target lesion; TKI Tyrosine-kinase inhibitor.

Table 17 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-TLs, etc]).	Should be used, when necessary, for all patients.
Inactivated viral vaccine preparations, such as the influenza vaccine.	Permitted.

TL target lesion.

6.4.1 Background medication

Not applicable.

6.4.2 Other concomitant treatment

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

6.4.3 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 CL. 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 PK 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.

6.4.4 Tremelimumab drug-drug interactions

No formal drug-drug interaction studies have been conducted with tremelimumab. However, in renal cell carcinoma studies, acute renal failure has been reported with the combination of tremelimumab and sunitinib. It is unknown whether a similar reaction will be observed when tremelimumab is combined with other tyrosine kinase inhibitors. More information is available in the product IB.

6.4.5 Rescue medication

As a result of imAEs that could potentially be experienced by patients on durvalumab, steroids and other immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into the category of immunosuppressants are infliximab (eg, for colitis) and mycophenolate (eg, for hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy related toxicities. These rescue medications must be receipted, controlled, and administered by the pharmacist and stored according to the labeled storage conditions, with temperature excursions reported accordingly by the pharmacist.

6.5 Dose modification

Dose delays are permitted for IO therapy (see TMGs).

6.6 Continued Access to Study Intervention After the Final DCO: Patient Management

After the final DCO for this study, AstraZeneca will continue to supply durvalumab to patients who are receiving treatment with clinical benefit; treatment will continue until evidence of PD as judged by the investigator or until the patients meets any other discontinuation criteria, as defined in Section 7.1. Patients will continue to receive durvalumab infusions, administered on an every 28-day schedule. Routine safety monitoring (i.e., labs, vital signs) will be performed as standard of care procedures, per the site's local practices. Patients will be continued to be monitored for treatment-related immune mediated toxicity, specifically attributed to study treatment. In the event of a treatment-related immune adverse event, Investigators should continue to consult the toxicity management guidelines (TMGs) in place for Durvalumab. (see Section 8.4.5.)

Tumor assessments will be performed according to the sites local imaging schedule.

See section 8.3.14 for SAE and AESI reporting requirements for patients remaining on treatment after DCO.

The schedule of activities for patients receiving ongoing treatment after the final DCO is reflected in Table 4.

Research studies/activities intended for collection at the time of progression, as an end-of-treatment visit, or during the follow-up period (currently reflected in tables 1, 2 and 3) **are no longer required**; therefore, the following studies/activities are now waived: blood sample for vaccine antibody titer, Durvalumab PK sample, Tremelimumab PK sample, Durvalumab ADA sample, Tremelimumab ADA sample, recording of concomitant medications, and non-serious/non-imAE assessments.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the participant(s) to alternative supply, where possible.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

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

- Withdrawal of consent from further treatment with IP. The patient or parent(s)/legal guardian(s)/legally authorized representative 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 (eg, for safety and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3).
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation as defined in the TMGs (see Section 8.4.5).
- Pregnancy or intent to become pregnant.

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

- Initiation of alternative anticancer therapy including another investigational agent.

- Clinical progression or confirmed radiological progression (refer to Appendix E for solid tumors, Appendix F for NB; other malignancies will be analyzed based on the best response assessed by the Investigator) and Investigator determination that the patient is no longer benefiting from treatment with IP.

7.1.1 Procedures for discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient or his/her parent(s)/legally authorized representative(s) who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient or his/her parent(s)/legally authorized representative(s) does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient or his/her parent(s)/legally authorized representative(s), a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient or his/her parent(s)/legally authorized representative(s) that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

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

Patients who permanently discontinue drug for reasons other than objective PD should continue to have OR assessments performed every 8 weeks ± 1 week relative to the date of the first dose until PD plus an additional follow-up assessment or death (whichever comes first) as defined the SoAs.

If a patient is discontinued for PD, then the patient should have 1 additional follow-up assessment performed 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.

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

Patients or his/her parents/legally authorized representatives who decline to return to the site for evaluations should be contacted by telephone as indicated in the SoAs as an alternative.

Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IRT/RTSM (Note that IRT/RTSM will only be used for the dose-expansion phase. Dose-finding phase will be manually supplied/managed).

7.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.3.1.3), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis set (FAS) and the safety analysis set (SAS) 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 CRF modules will be updated.)

- In the event that the patient or his/her parents/legally authorized representatives has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

7.3 Withdrawal from the study

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 or his/her parent(s)/legally authorized representative(s) 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 or his/her parent(s)/legally authorized representative(s) 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 or his/her parent(s)/legally authorized representative(s) 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 8.8.7).

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA. The schedule for study procedures for the dose-finding and dose-expansion phases are presented in Table 1 and Table 2 respectively. The schedule of study procedures for patients who have discontinued all study treatments (durvalumab monotherapy or durvalumab and tremelimumab combination therapy) in the dose-finding or the dose-expansion are presented in Table 3.

The Investigator will ensure that data are recorded on the electronic CRF. The Web Based Data Capture system will be used for data collection and query handling.

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

Immediate safety concerns should be discussed with the Sponsor or designee immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count and imaging assessments) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Enrollment/screening period

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The screening procedures (presented in Table 1 and Table 2) will be completed within 28 days of signing the ICF and before durvalumab infusion on Cycle 1 Day 1 (radiological assessments to be completed within 21 days before on Cycle 1 Day 1). The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. At screening, consenting patients are assessed to ensure that they meet eligibility criteria (Sections 5.1 and 5.2). Patients who do not meet these criteria must not be started on treatment. Patients will be considered to be in the screening period until all screening visit assessments are completed and eligibility is confirmed. Patients will be considered to be in the dose-finding period after the first dose of durvalumab has been administered.

Dose-finding phase

Descriptions of the procedures for this period are included in the SoA for the dose-finding phase of the study (Table 1).

Patients will receive durvalumab monotherapy on Cycle 1 Day 1 and will be closely monitored for 28 days for safety and tolerability (DLT observational period 1) attending clinic visits on Days 8 and 15. Starting on Cycle 2, patients will receive durvalumab + tremelimumab in combination on Day 1 and attend clinic visits on Days 8 and 15. Cycle 2 Day 1 to Day 28 is the second DLT observational period; the total DLT observational period is 56 days or 2 cycles. Starting at Cycle 3, patients will have a scheduled visit only on Day 1 of the treatment cycle. From Cycle 6 onwards, patients will receive durvalumab monotherapy until progression.

Dose-expansion phase

Once a RP2D has been confirmed, patients will be recruited to the dose-expansion phase and will follow the procedures for this period in Table 2. All patients will receive durvalumab + tremelimumab in combination on Day 1 of Cycles 1, 2, 3, and 4. From Cycle 5, patients will receive durvalumab monotherapy until progression.

Off-treatment follow-up

Patients should be discontinued from study treatment if any discontinuation criteria are fulfilled, (Section 7.1). The assessments to be carried out during follow-up are detailed in Table 3. Any SAEs and/or non-serious AEs ongoing at the time of treatment discontinuation or which have occurred during the follow-up period must be followed up (in accordance with Section 8.3.3). Appropriate safety evaluations should be repeated and/or additional tests performed at any time when clinically indicated, or at the discretion of the Investigator, until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease. If the patient is lost to follow-up, then this should be noted in the CRF. Survival will be collected every 2 months for all patients (Section 8.1.2).

Volume of blood and prioritization of laboratory sampling

For a patient weighing less than 6 kg, the following parameters for blood volume collection should apply:

- Maximum blood volume in 24 hours: 2 mL/kg.
- Maximum blood volume in 8 weeks: 8 mL/kg.

The total volume of blood that will be drawn as maximum per day (Cycle 1 Day 1) and for the 60-day period encompassing Cycle 1 and Cycle 2 has been carefully assessed across the weight range 6 kg to 55 kg to stay below the World Health Organisation blood limit guidelines (Table 18; Howie 2011). Pediatric tubes/microcontainers should be used, whenever possible, for blood collection. If there is any difficulty obtaining specimens or the local blood volume limits are met at any one time for any patient, the order of sampling priority should be followed as

outlined below. Safety labs, as listed in the prioritization schedule, include chemistry, hematology (see Table 19 and Table 20) and thyroid stimulating hormone.

Sampling and prioritization order for Cycles 1 through 3

Dose-finding phase:

- ≤6 kg: Safety >PK durvalumab/tremelimumab >ADA durvalumab/tremelimumab [redacted].
- >6 kg to ≤20 kg: Safety >PK durvalumab/tremelimumab >ADA durvalumab/tremelimumab [redacted].
- >20 kg: Safety >PK durvalumab/tremelimumab >[redacted] >ADA durvalumab/tremelimumab [redacted]

Dose-expansion phase:

- ≤6 kg: Safety >PK durvalumab/tremelimumab >ADA durvalumab/tremelimumab [redacted].
- >6 kg to ≤20 kg: Safety >PK durvalumab/tremelimumab >ADA durvalumab/tremelimumab [redacted] >vaccine titer.
- >20 kg: Safety >PK durvalumab/tremelimumab >ADA durvalumab/tremelimumab [redacted] >vaccine titer [redacted]

Table 18 Volume of blood to be collected (by weight and including World Health Organisation limits)

Total blood volume (TBV): 80 mL/kg[a]					
Weight (kg)	6	10	20	35	55
TBV (mL)	480	800	1600	2800	4400
WHO limits per 24 hours: **1–5% TBV** Sick kids: **3.8% TBV**			WHO limits per 8 weeks: **up to 10% TBV**		
Dose-finding phase					
Max volume (mL) per 24 hours (% TBV)	12.5 (2.6)	12.5 (1.6)	20.5 (1.3)	20.5 (0.73)	20.5 (0.47)
Volume (mL) per 8 weeks (%TBV)	32 (6.6)	32 (4)	56 (3.5)	56 (2)	56 (1.27)
Volume (mL) from Cycle 3 until progression	Safety labs (chemistry/hematology/TSH) at each cycle: 4 mL				
	Research labs (according to Schedule of Activities): up to 14.5 mL (+3.5 mL for tumor markers with each tumor assessment) between Cycles 3 and 12				
EOT (mL)	4	4	4	4	4
Dose-expansion phase					
Max volume (mL) per 24 hours (% TBV)	20 (2.9)	20 (2.5)	28 (1.7)	28 (1)	28 (0.63)
Volume (mL) per 8 weeks (%TBV)	38 (7.9)	40.5 (5)	64.5 (4)	64.5 (2.3)	64.5 (1.5)
Volume (mL) from Cycle 3 until progression	Safety labs (chemistry/hematology/TSH) at each cycle: 4 mL				
	Research labs (according to Schedule of Activities): up to 6 mL (+3.5 mL for tumor markers with each tumor assessment) between Cycles 3 and 12				
EOT (mL)	4	7.5	7.5	7.5	7.5

[a] WHO range: 75–80 mL/kg (beyond neonatal period); maximum of 105 mL/kg from birth to 1 month.

EOT end of treatment; Max maximum; TBV total blood volume; TSH thyroid-stimulating hormone; WHO World Health Organisation.

8.1 Efficacy assessments

Efficacy assessments of ORR, duration of response (DoR), DCR, and PFS will be derived (by AstraZeneca) using the response criteria defined below. Overall survival will also be assessed for each individual patient.

Tumor assessments will be done in accordance with the type of tumor: NB (Appendix F), other solid tumors (Appendix E).

Radiological assessments will be made following routine clinical practice procedures during screening and then every 8 weeks (relative to the date of Cycle 1 Day 1), until radiological progression. For patients who achieve an objective response (CR, PR) or stable disease and for whom the response is still evident at 12 months, subsequent tumor assessments are to occur every 16 weeks. Unscheduled assessments can be performed at any time during the study, as clinically indicated, based on signs and symptoms. Disease progression requires confirmation, the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment will continue between the initial assessment of progression and confirmation for progression.

Tumor assessments will be made during screening/baseline and at regular (follow-up) intervals during study treatment. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. It is important to follow the tumor assessment schedule as closely as possible (refer to the SoAs). If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent assessments at the next scheduled visit. Treatment continues until clinical progression/deterioration or confirmed radiological progression, and scanning/tumor assessments continue throughout treatment until radiological progression plus an additional follow-up scan (if clinically feasible).

Screening/Baseline imaging should be performed no more than 21 days before start of study treatment, and ideally should be performed as close as possible to and prior to the start of study treatment. Definitions of lesions, methods of assessments and response types are defined in Appendix F for NB, Appendix E for other solid tumors (RECIST 1.1)

8.1.1 Central reading of scans

All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca appointed contract research organization (CRO) for quality control check (QCC). Guidelines for image acquisition, de-identification, 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 radiological assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the radiological assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter, (also referred to as 'Imaging Charter').

8.1.2 Survival assessments

Assessments for survival must be made 30 days, 2 months, 3 months, 4 months, and every 2 months following treatment discontinuation (Table 3). Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

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

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

Full and targeted physical examinations will be performed according to the assessment schedules (see the SoAs) and in unscheduled visits. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height and weight will be measured at screening, and q4w (on dosing days 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 8.3.7.

8.2.2 Clinical safety laboratory 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 the SoAs).

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

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

The laboratory variables to be measured are presented in Table 19 (clinical chemistry), Table 20 (hematology), and Table 21 (urinalysis).

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

The following laboratory variables will be measured:

Table 19 Clinical chemistry

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

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

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

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, magnesium testing are to be performed at baseline, 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 data management using the Schwartz pediatric equation, radioisotope measured GFR, or by 24-hour urine collection.

[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. TSH will be collected every 4 weeks.

[f] Free T4 or free T3 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system. Free T4 can be collected with or without free T3.

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; GFR glomerular filtration rate; T3 Triiodothyronine; T4 Thyroxine; TBL total bilirubin; TSH Thyroid-stimulating hormone.

Table 20 Hematology

Absolute neutrophil count[a]	Absolute lymphocyte count[a]
Hemoglobin	Platelet count
Total white cell count	
Coagulation[b]	

[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.

[b] 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.

Table 21 Urinalysis

Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

Note: Urinalysis should be done at the visits shown in Table 1 (for dose-finding) and Table 2 (for dose-expansion).
Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red and white blood cells.

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

If a patient shows an AST or ALT ≥3 × ULN together with TBL ≥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 test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (±3 days) after permanent discontinuation of IP (see Table 3).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the CRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.7.

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

8.2.3 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the SoAs. Peripheral oxygen saturation will be measured at screening/baseline and at clinic visits, in accordance with the SoA, along with the remaining vital signs.

Patients will be monitored and vital signs collected/recorded in CRF as presented in the bulleted list below:

- Based on a 120-minute infusion (durvalumab):
  - Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
  - Approximately 60 minutes during the infusion (**halfway** through infusion)
  - At the end of the infusion (approximately 120 minutes ± 5 minutes).
- Based on a 60-minute infusion (durvalumab and tremelimumab):
  - Prior to the beginning of the 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 (approximately 60 minutes ± 5 minutes).

If the infusion takes longer than 60 minutes then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

Dose-finding phase

Vital signs will be obtained and documented prior to, mid-infusion, and end of infusion for the following:

- Cycle 1 Day 1: Durvalumab infusion.
- Cycle 2 Day 1: Tremelimumab and durvalumab infusion.

For Cycle 3 onwards, only at the beginning of the first infusion:

- Patients should be carefully monitored, and BP and other vital signs should be measured during and post infusion as per institution standard, and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

For the observation period:

- Cycle 1 Day 1 : 1 hour after completion of durvalumab infusion.
- Cycle 2 Day 1 to Cycle 4 Day 1: 1 hour between tremelimumab and durvalumab.
- Cycle 2 Day 1: 1 hour after completion of tremelimumab and durvalumab infusions.

Dose-expansion phase

Vital signs will be obtained and documented prior to, mid-infusion and end of infusion for the following:

- Cycle 1 Day 1: Tremelimumab and durvalumab infusion.

For Cycle 2 onwards, only at the beginning of first infusion:

- Patients should be carefully monitored, and BP and other vital signs should be measured during and post infusion as per institution standard, and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

For the observation period:

- Cycle 1 Day 1: 1 hour between tremelimumab and durvalumab;
  - For Cycle 2 onwards: if no infusion reaction, observation period may be waived allowing durvalumab to be administered immediately after tremelimumab.
- Cycle 2 Day 1: 1 hour after completion of tremelimumab and durvalumab infusions.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.7. For any AEs of infusion reactions, the vital signs values should be entered into the CRF.

8.2.4 Tanner staging

Tanner staging (Appendix H) will also be assessed at Cycle 1 Day 1 and subsequently at visits where radiological efficacy assessments are made (see Section 8.1).

8.2.5 Electrocardiograms

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

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms calculated using Fridericia's formula, an additional 12-lead ECG 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 8.3.7.

8.2.6 Early patient review for safety

Patients should be attending scheduled visits on Cycle 1 Day 15 and Cycle 2 Day 15. It is also recommended patients are contacted on Cycle 3 Day 15 to ensure early identification and management of toxicities.

8.2.7 Performance status

Karnofsky performance status (Appendix I) will be assessed in patients ≥16 years of age and Lansky play performance scale (Appendix J) will be assessed in patients ≥1 and <16 years of age at the times specified in the assessment schedules in line with the SoA.

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

8.2.8 Other safety assessments

8.2.8.1 Other assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the TMGs (see Section 8.4.5) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc) will be captured in the CRF. 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 TMGs 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.
- Saturation of peripheral oxygen (resting and exertion)
- High-resolution CT
- 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 PD

(iii) Additional clinical chemistry: c-reactive protein, lactate dehydrogenase.

8.3 Collection of adverse events

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

The definitions of an AE or SAE can be found in Appendix B.

Adverse events will be reported by the patient or parent(s)/legally authorized representative(s).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse events and SAEs will be collected from the time of the patient signing the ICF until the follow-up period is completed 90 days after the last dose of durvalumab or durvalumab + tremelimumab. If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to IP then it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the Study treatment or study participation, the Investigator should notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAE/non-serious AEs/AEs of special interest (AESI; as defined

in Section 8.3.13), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

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 (this may be beyond the 90 days after the last dose of durvalumab or durvalumab + tremelimumab), but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

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

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8.3.5
- Description of the SAE.

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

8.3.5 Causality collection

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

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

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

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

8.3.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol mandated laboratory values, vital signs, physical examination findings, or ECG 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 IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the

absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to PD, 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 unless unequivocally related to the disease under study, see Sections 8.3.9 and 8.3.10.

8.3.8 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 TBL ≥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.

8.3.9 Disease under study

Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

8.3.10 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 PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study.

8.3.11 New cancers

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

8.3.12 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 IP, must be reported as follows:

- Death clearly resulting from PD should be reported to the Study Physician at the next monitoring visit and should be documented in the CRF in the Statement of Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the CRF. The

report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the CRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

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

8.3.13 Adverse events of special interest

An AESI is one of scientific and medical interest specific to understanding of the IP and may require close monitoring. 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.

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

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

AESIs observed with durvalumab ± tremelimumab include:

- Diarrhea/colitis and intestinal perforation
- Pneumonitis/ILD
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypo-thyroidism and type I diabetes mellitus)
- Hepatitis/transaminase increases
- Nephritis/blood creatinine increases
- Pancreatitis/serum lipase and amylase increases

- Rash/dermatitis
- Myocarditis
- Myositis/polymyositis
- Neuropathy/neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological, neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis) and rheumatological events.

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

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab IBs. More specific guidelines for their evaluation and treatment are described in detail in the TMGs (see Section 8.4.5). 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 IP/study regimen by the reporting Investigator.

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

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that patients continue their scheduled treatment visits and Investigators continue to monitor the patient's safety laboratory results in accordance with standard of care procedures, reflecting local practices. AE and SAE data will be collected, but only SAEs and AESI data will be reported. All data after the final DCO and database closure will be recorded in the patient's notes, but with the exception of SAEs and AESIs, will not otherwise be reported for the purposes of this study.

All SAEs and AESIs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab or until initiation of subsequent anti-cancer therapy), post the final DCO and database closure) must be reported as detailed in Section 8.4.1.

Additional details will be provided to the investigators with instructions for using an alternative process (eg. a non-electronic data capture mechanism) to report these events

8.4 Safety reporting and medical management

8.4.1 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 CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel 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 Investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

This study will use EDC for SAE submission. If we are talking of back-up method when EDC is down, then it will be using SAE or relevant form to be scanned and emailed to the appropriate AstraZeneca representative or faxed.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

Reporting of serious adverse events and adverse events of special interest for patients receiving treatment following the final DCO.

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The timeframe,for SAE reporting to the AstraZeneca representative remains the same during the post-DCO period

Adverse events of special interest are to be reported at the time of diagnosis of the event.

8.4.2 Pregnancy

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

- If the pregnancy is discovered before the study patient has received any IP.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

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

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

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

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

8.4.2.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab + tremelimumab combination or after the last dose of durvalumab monotherapy.

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

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

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

8.4.3 Overdose

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

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

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

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error, Drug Abuse, and Drug Misuse

If an event of medication error, drug abuse or drug misuse occurs during 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 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error, drug abuse, or misuse (see Section 8.3.2) and within 30 days for all other events.

8.4.4.1 Medication error

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

The full definition and examples of Medication Error can be found in Appendix B.

8.4.4.2 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B.

8.4.4.3 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of Drug Misuse can be found in Appendix B.

8.4.5 Management of IP-related toxicities

The following general guidance should be followed for management of toxicities.

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

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

8.4.5.1 Specific toxicity management and dose modification information – Durvalumab and durvalumab + tremelimumab

Comprehensive TMGs have been developed to assist Investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors, durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these 2 compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also other anti-cancer drugs (ie, antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised, however, to

use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document entitled "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy)", and is maintained within the Site Master File.

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 7.1 of this protocol and the TMGs).

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the TMGs. 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 regimen by the reporting Investigator.

8.5 Pharmacokinetics and anti-drug antibodies

8.5.1 Collection of pharmacokinetic samples and determination of drug concentration

Blood samples will be taken at the time points presented in the SoA (Table 1 and Table 2 for dose-finding and dose-expansion, respectively). It is essential that the actual time and date of collection of each blood sample (whether collected as per protocol or not) will be recorded in the CRF. If a patient is receiving durvalumab + tremelimumab combination therapy, because tremelimumab is infused before durvalumab the following principles will be followed when these samples are scheduled:

- Predose samples for tremelimumab PK will be taken before tremelimumab is infused. Predose samples for durvalumab PK will be taken before durvalumab is infused. During the combination period, predose samples for durvalumab PK should ideally be taken in the interval following tremelimumab administration and before durvalumab is infused. However, sampling prior to tremelimumab infusion is also acceptable, if considered necessary for logistical/operational reasons.

- End of infusion sample for tremelimumab PK will be taken after tremelimumab is infused.

- End of infusion sample for durvalumab PK will be taken after durvalumab is infused.

End of infusion PK samples should be taken within 10 minutes of the completion of IP infusion.

- In the dose-finding phase only, an end of treatment tremelimumab sample is required for patients at the EoT visit who have received only a single dose (cycle) of tremelimumab in combination with durvalumab (i.e treatment discontinuation after cycle 2). Preferably, this sample should be collected approximately 30 days after the final tremelimumab infusion, but can be collected at any time beyond the final (day 15) tremelimumab PK sample collection.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Samples for determination of durvalumab and tremelimumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca.

Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

8.5.2 Collection of samples to measure for the presence of ADAs and ADA-neutralizing antibodies

The presence of ADA will be assessed in serum samples taken according to the SoAs (Table 1 and Table 2 for dose-finding and dose-expansion, respectively).

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

8.5.3 Storage and destruction of pharmacokinetic/anti-drug antibody samples

Durvalumab and tremelimumab PK and ADA samples will be destroyed within 5 years of CSR finalization.

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

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

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

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Germline testing is not evaluated in this study.

8.8 Biomarkers

By participating in this study, the patient's parent(s)/legally authorized representative(s) consents to the collection and use of donated biological samples as described here.

CCI [redacted] will be evaluated in enrolled patients CCI [redacted] tumor requirements are briefly described in Section 8.8.1.

CCI [redacted] in Section 8.8.3. CCI [redacted] are described in this section. Samples will be obtained according to the assessment schedules provided in the SoAs.

Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate 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 CCI [redacted] to immunotherapy.

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

8.8.1 Collection of patient samples for CCI [redacted]

The provision of tumor tissue at screening is mandated where available, for enrollment in this study. If tissue is supplied, it must fulfill the following conditions:

- CCI [redacted] Preferably, the most recent sample available should be used for evaluation. CCI [redacted]
- For patients undergoing biopsy as part of standard clinical care, collection of a minimum of 2 core biopsies is recommended CCI [redacted], if clinically acceptable. Tumor lesions used for newly acquired biopsies should not be the same lesions used as RECIST 1.1 or INRC TLs, unless there are no other lesions suitable for biopsy (reassessment after biopsy may be required).

- When tissue is newly-obtained by biopsy at screening for this study, effort should be made to [redacted]. Two cores, using an 18-gauge or larger needle, are recommended [redacted]. These should be placed in formalin and processed to a single paraffin-embedded block, as described in the Laboratory Manual.

- ***If no tissue is available or [redacted] the patient will be exempt from this criterion.***

- Tumor block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. Please refer to the Laboratory Manual for specific instructions and guidelines regarding sections. The tumor specimen submitted should be of [redacted] (refer to the Laboratory Manual). [redacted]

- Confirmation required in clinical notes regarding [redacted] during screening period; however, the sample will only be submitted to AstraZeneca once the patient has been confirmed to be eligible for the study.

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, and in this instance only core needle (not excisional/incisional) biopsy is allowed. For patients with a single TL, if screening biopsy is collected prior to screening imaging for baseline tumor assessment, allow approximately 2 weeks before imaging scans are acquired.

- See the Laboratory Manual for further details of requirements including sample quality control and shipping.

A brief description of [redacted] is provided in Section 8.8.3.

[redacted]

8.8.2 [redacted]

[redacted]

Dose-finding phase

Blood will be collected from all patients in the dose-finding phase [redacted], in accordance with Table 1.

Dose-expansion phase

Blood samples for [redacted] will be collected [redacted] in line with the schedule in Table 2.

8.8.3 Exploratory biomarkers

[redacted]

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

The exploratory biomarker plan is described by sample type below.

[redacted]

[redacted]

CCI

[redacted]

Management of biomarker data

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

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

8.8.4 Storage, re-use and destruction of biomarker samples

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

8.8.5 Labeling and shipment of biological samples

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

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

8.8.6 Chain of custody of biological samples

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

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

AstraZeneca will keep oversight of the following: life cycle through internal procedures, monitoring of study sites, auditing and process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be registered in the AstraZeneca-assigned Biobank and will be registered with the AstraZeneca Biobank Team during the entire life cycle.

8.8.7 Withdrawal of informed consent for donated biological samples

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

The PI will:

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

8.9 Effect of immune checkpoint inhibition in response to routine immunizations

Samples for vaccine titers will be omitted in the smallest patients to ensure that appropriate blood volume limits are adhered to (see Section 8; Volume of blood and prioritization of laboratory sampling).

Blood samples for vaccine antibody titer measurement will be taken during the dose-expansion phase only (Table 2). CCI [redacted]

CCI [redacted]

9. STATISTICAL CONSIDERATIONS

The primary aim of the dose-finding phase of the study is to determine the adult equivalent exposure/MTD and safety profile of durvalumab and durvalumab in combination with tremelimumab, in children and young adults using a q4w dosing schedule.

The primary aim of the dose-expansion phase is to determine the preliminary antitumor activity of those recommended doses.

Analyses will be performed by AstraZeneca or its representatives.

A statistical analysis plan (SAP) containing details of all planned statistical analyses will be produced prior to first-patient-in and the mock output shells within 3 months of the first patient enrolled.

9.1 Statistical hypotheses

There is no formal statistical testing for the dose-finding phase of the study.

The dose-expansion phase of the study will formally test the following hypothesis:

- H0: ORR $\leq$10%
- H1: ORR >10%.

The test will be performed for the SARCOMA cohort and it will be done at the 1-sided 5% level. No formal statistical testing will be performed for the STO cohort.

9.2 Sample size determination

Dose-finding phase

The final sample size in the dose-finding phase will depend on the number of DLTs and on the number of DLs to be explored. In addition, any patients not evaluable (NE) will be replaced in order to have the required number of patients evaluable at each DL. A minimum of 12 patients is anticipated to be dosed, to enable exploration of 1 DL in both patients weighing 35 kg and greater, and patients weighing under 35 kg. If all 3 DLs are used at both weight-based arms, then 36 evaluable patients would be necessary to complete the dose-finding phase. If approximately 20% of patients need to be replaced due to non-evaluability, then a maximum of 45 patients will be enrolled on the dose-finding cohorts.

Dose-expansion phase

For the dose-expansion phase, the SARCOMA cohort mentioned in Section 4.1.4 will follow a Simon 2-stage optimal design. An ORR ≤10% will not be considered clinically meaningful.

In the SARCOMA cohort, the Simon 2-stage design will have a type I error rate set at 0.1 (1-sided) and power of at least 85%. Based on the assumption that the ORR for the null hypothesis is 10% and the true ORR for the SARCOMA cohort is 30%, then the SARCOMA cohort will require a total of 26 evaluable patients (with the requirement that ≥ 40% of the patients enrolled must have soft-tissue sarcomas), with 11 evaluable patients required in the first stage. If fewer than 2 responses are observed in the first 11 evaluable patients, then the cohort will be closed for lack of benefit. If 2 or more responses are observed out of the first 11 evaluable patients, then an additional 15 evaluable patients will be enrolled, for a total of 26 evaluable patients.

For a cohort that enrolls the maximum total of evaluable patients for that particular cohort (26 patients in the SARCOMAcohort), if fewer than 5 responses are observed out of the maximum total of evaluable patients, then no further investigation of this cohort will be done; if 5 or more responses are observed out of the maximum total of evaluable patients, then the null hypothesis will be rejected for this cohort and further investigation will be warranted.

The STO cohort is planned to recruit 10 evaluable patients. This sample size is based on practical, rather than formal considerations, as no formal hypothesis testing is planned for this cohort.

With the above considerations, the sample size for evaluable patients in the dose-expansion phase is expected to range from21 to 36. Assuming that about 20% of patients may not be evaluable for ORR, the total number of patients dosed in the dose-expansion phase may range from approximately 25 to 43.

9.3 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 22.

Table 22 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy Data	
ORR (primary for dose-expansion phase)	Evaluable for response analysis set (Sensitivity analysis on FAS)
PFS, OS, BoR, APF12, APF18, OS12, OS24	FAS (ITT population)
DoR	Evaluable for response analysis set (restricted to responders only)
DCR	Evaluable for response analysis set (Sensitivity analysis on FAS)
Demography	FAS (ITT population)
PK data	PK analysis set
Safety Data	
Exposure	SAS
AEs	SAS
Laboratory measurements	SAS
Vital Signs	SAS
DLTs (primary for dose-finding phase)	DLT evaluable analysis set

AE Adverse event; APF12 / APF18 Proportion of patients alive and progression-free at 12 / 18 months from first dose of IP; BoR Best objective response; DCR Disease control rate; DLT Dose-limiting toxicity; DoR Duration of response; FAS Full analysis set; ITT Intention-to-treat; OS Overall survival; OS12 / OS24 Proportion of patients alive at 12 / 24 months from first dose of IP; PFS Progression-free survival; PK Pharmacokinetics; SAS Safety analysis set.

9.3.1 Full analysis set

The FAS will include all patients who were assigned to treatment and received at least 1 dose of study treatment. The FAS (or subset of the FAS specified below) will be used for all efficacy analyses.

9.3.2 Evaluable for response analysis set

The subset of patients in the FAS who had measurable disease at baseline.

9.3.3 Safety analysis set

The SAS will consist of all patients who received at any amount of study treatment. Safety data will be summarized using the SAS according to the treatment received.

9.3.4 Dose-limiting toxicity evaluable analysis set

The DLT evaluable analysis set is a subset of the Safety analysis set for the dose-finding phase of the study. It includes all patients enrolled in the dose-finding phase of the study who receive the protocol-assigned treatment with durvalumab + tremelimumab and complete the safety follow-up through the DLT evaluation period (Cycle 1 + Cycle 2) or experience a DLT during the DLT evaluation period.

9.3.5 Pharmacokinetic analysis set

All patients who receive at least 1 dose of IP per the protocol for whom any postdose 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.

9.3.6 Other analysis sets

Other analysis sets, such as CCI [redacted], may be defined if deemed necessary. These will be subsets of the SAS and will include patients who provided sufficient data for inclusion in the corresponding analyses. More details will be provided in the SAP.

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of efficacy variables

9.4.1.1 RECIST 1.1 and INRC-based endpoints

The analysis of the primary endpoint, ORR, and the analyses of the secondary endpoints, PFS, DoR, and DCR, will be based on the site Investigator assessments using RECIST 1.1 for solid tumors (Appendix E)and INRC for NB (Appendix F). In addition, OS, another secondary endpoint, will also be evaluated.

Investigator RECIST 1.1and INRC-based assessments

All RECIST 1.1 (or INRC) 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 (Appendix E) visit response of complete response (CR), PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments. Baseline will be assessed within the 21 days prior to first dose. 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 corresponding criteria for Appendix F for NB.

Progression-free survival and ORR by irRECIST criteria will also be performed for exploratory purposes only.

9.4.1.2 Primary endpoint: Objective response rate

Objective response rate (per RECIST 1.1or INRC, using Investigator assessments) is defined as the percentage of patients with at least 1 visit response of CR or PR that is subsequently confirmed on another scan not less than 4 weeks after visit observed response. 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.

9.4.1.3 Progression-free survival

Progression-free survival (per RECIST 1.1or INRC, as assessed by the site Investigator) will be defined as the time from the date of first dose of IP until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to progression (ie, date of event or censoring – date of first dose of IP + 1). 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 (or INRC) 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 (or INRC) assessment prior to the 2 missed visits. If the patient has no evaluable visits or does not have baseline data, they will be censored at Day 1 unless they die within 2 visits of baseline, then they will be treated as an event with date of death as the event date.

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

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

- For Investigator assessments, the date of progression will be determined based on the earliest of the RECIST 1.1 (or lymphoma criteria or INRC) 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 assessment/scan dates contributing to a particular overall visit assessment.

Additionally, PFS will also be assessed using irRECIST data for exploratory purposes only.

9.4.1.4 Overall survival

Overall survival is defined as the time from the date of first dose of IP 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 DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If patients are confirmed to be alive or if the death date is post the DCO date, these patients will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

9.4.1.5 Duration of response

Duration of response (per RECIST 1.1,or INRC, using Investigator assessment) will be defined as the time from the date of first documented response (which is subsequently confirmed) until the first date of documented progression or death in the absence of disease progression (ie, date of PFS event or censoring - date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the RECIST 1.1 (or INRC) 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. Duration of response will not be defined for those patients who do not have documented response.

9.4.1.6 Best objective response

Best objective response (BoR) is calculated based on the overall visit responses from each RECIST 1.1 (or INRC) assessment. It is the best response a patient has had during their time in the study up until RECIST 1.1 (or INRC) progression or the last evaluable assessment in the absence of RECIST 1.1 (or lymphoma criteria or INRC) progression.

Categorization of BoR for solid tumors will be based on RECIST 1.1 (Appendix E) using the following response categories: CR, PR, SD, PD, and NE.

For NB, the categories will be based on INRC (Appendix F) and they are CR, PR, minor response (MR), SD, PD, and NE (applicable for the dose-finding phase only).

Complete response or PR must be confirmed. Best objective response will be determined programmatically based on RECIST 1.1 (or lymphoma criteria or INRC) using all Investigator 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 (or INRC) assessments prior to death.

For patients who die with no evaluable RECIST 1.1 (or INRC) assessments, if the death occurs ≤119 days (ie, 2 × 8 weeks + 7 days) after first dose of IP, then BoR will be assigned to the progression (PD) category. For patients who die with no evaluable RECIST 1.1 (or INRC) assessments, if the death occurs >119 days (ie, 2 × 8 weeks + 7 days) after the date of first dose of IP, then BoR will be assigned to the NE category.

Progression events that have been censored due to them being >119 days after the last evaluable assessment will not contribute to the BoR derivation.

9.4.1.7 Disease control rate

Disease control rate at 16 or 24 weeks will be defined as the proportion of patients who achieve best response of CR or PR, respectively, or who have SD for at least 16 weeks − 7 days or 24 weeks - 7 days, respectively, after start of treatment.

9.4.1.8 Proportion alive and progression free at 12 and 18 months

Proportion of patients alive and progression-free at 12 months from first dose will be defined as the Kaplan-Meier (KM) estimate of PFS (per RECIST 1.1) at 12 months. Similarly, APF18 will be defined as KM estimate of PFS (per RECIST 1.1) at 18 months.

9.4.1.9 Overall survival at 12 and 24 months

OS12 will be defined as KM estimate of OS at 12 months. Similarly, OS24 will be defined as KM estimate of OS at 24 months.

9.4.2 Calculation or derivation of safety variables

9.4.2.1 Adverse events

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, physical examinations and exposure. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

Adverse events observed up until 90 days following discontinuation of the immunotherapy agents (ie, the last dose of durvalumab, tremelimumab or durvalumab + tremelimumab) or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables. This will more accurately depict AEs attributable to study treatment only as a number of AEs up to 90 days following discontinuation of the immunotherapy agents are likely to be attributable to subsequent therapy. However, to assess the longer term toxicity profile, AE summaries will also be produced containing AEs observed up until 90 days following discontinuation of the immunotherapy agents (ie, without taking subsequent therapy into account). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

The SAS will be used for reporting of safety data.

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

9.4.2.2 Safety assessments

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

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) using the following formula:

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

Corrected calcium product 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, ie, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a NCI CTCAE criterion involves a change from baseline, evaluable patients would have both a predose and at least 1 postdose value recorded.
- If a NCI CTCAE criterion does not consider changes from baseline to be evaluable, the patient only needs to have 1 postdose value recorded.

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

9.4.3 Calculation or derivation of pharmacokinetic variables

9.4.3.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model will be developed using a non-linear mixed-effects modeling approach. The impact of physiologically-relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints will be evaluated, if the data allow. The results of such an analysis will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

9.4.3.2 Pharmacokinetic non-compartmental analysis

The actual sampling times will be used in the PK calculations. Pharmacokinetic concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. Pharmacokinetic parameters will be determined using standard non-compartmental methods. The PK of durvalumab and tremelimumab will be assessed using parameters including maximum serum concentration (C_{max}), minimum serum concentration (C_{min}), time to C_{max}, and AUC after the first dose, if the data allow. Durvalumab and tremelimumab steady-state PK parameters including maximum plasma concentration at steady-state ($C_{max,ss}$) and minimum plasma concentration at steady-state ($C_{min,ss}$) will be estimated. Accumulation ratio to steady-state will be assessed as the ratio of $C_{max,ss}$:C_{max} and $C_{min,ss}$:C_{min}. Samples below the lower limit of quantification will be treated as zero in predose samples and as missing subsequently in the analyses.

9.4.3.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively [redacted]

CCI [redacted]

9.4.4 Calculation or derivation of biomarker variables

Biomarker status, as defined in the exploratory objectives, will be assessed for evaluable patients in each cohort according to pre-specified criteria that will be detailed in the SAP. Descriptive statistics will be the primary method for biomarker analysis. Depending on the nature of the data, geometric mean and other appropriate statistical summaries may be employed.

Vaccine antibody titer measurements CCI [redacted]

CCI [redacted]

9.4.5 Calculation or derivation of pharmacogenetic variables

No genetic data will be analyzed for this study.

9.5 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive SAP will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

The 2 phases of the study will be summarized and analyzed separately. For the dose-finding phase, summaries and analyses will be presented by DL. For the dose-expansion phase, summaries and analyses will be presented by cohort.

All data collected will be listed.

9.5.1 Efficacy analyses

Descriptive statistics will be used for all variables, as appropriate. 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 cohort and DL within cohort where applicable.

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

Efficacy data will be summarized and analyzed based on the FAS and, where appropriate, on the evaluable for response analysis set.

Results of all statistical analyses will be presented using a 90% CI, unless otherwise stated.

The primary analysis cut off will be defined at approximately 6 months after enrollment of the last patient. At this point, data analysis will be performed and the CSR will be written. After this, patients still in the study will continue to be followed and a CSR addendum may be issued for OS and safety data collection.

The following table (Table 23) presents the analyses planned for the efficacy endpoints. All tumor-related endpoints will be analyzed using Investigator RECIST 1.1 assessments.

Table 23 Pre-planned statistical analyses to be conducted

Endpoints analyzed	Notes
Objective response rate	Exact 90% 2-sided CI (Mid-P)
Duration of response	Median estimated from KM curve
Disease control rate	Exact 90% 2-sided CI (Mid-P)
Best objective response	n (%) of patients in each response category
Progression-free survival	Median estimated from KM curve
Overall survival	Median estimated from KM curve
Proportion alive and progression-free at 12 months	90% 2-sided CI estimated from KM curve
Proportion alive and progression-free at 18 months	90% 2-sided CI estimated from KM curve
Proportion alive at 12 months	90% 2-sided CI estimated from KM curve
Proportion alive at 24 months	90% 2-sided CI estimated from KM curve

CI Confidence interval; KM Kaplan-Meier.

9.5.1.1 Primary endpoint: objective response rate

The ORR will be based on the programmatically derived RECIST 1.1 (or INRC) using the Investigator tumor data. The point estimate and 90% CI (2-sided) of the ORR will be presented. The CI will be calculated using an exact Mid-P method. This analysis will be performed on the evaluable for response analysis set.

Summaries will be produced that present the number and percentage of patients with a tumor response (CR/PR).

Sensitivity analysis will be performed for tumor response (CR/PR) on FAS and "unconfirmed CR/PR" on evaluable for response analysis set.

Objective response rate by irRECIST criteria will be presented as described above for exploratory purposes only.

9.5.1.2 Duration of response

Kaplan-Meier plots of DoR based on programmatically derived RECIST 1.1 (or INRC) responses using the Investigator tumor assessments will be presented. The median DoR will also be summarized calculated from the KM curve. Only patients who have a confirmed response will be included in this summary table.

9.5.1.3 Disease control rate

For DCR, the point estimate and 90% CI (2-sided) will be presented. The CI will be calculated using an exact Mid-P method.

Sensitivity analysis will be performed for tumor response (CR/PR) on FAS and "unconfirmed CR/PR" on evaluable for response analysis set.

9.5.1.4 Best objective response

Overall visit response data will be listed for all patients (ie, the FAS). For each cohort (and each DL within cohort in the dose-finding phase), BoR will be summarized by n (%) for each category (CR, PR, SD, PD, and NE or INRC categories). No formal statistical analyses are planned for BoR.

9.5.1.5 Progression-free survival

Progression-free survival will be summarized using the KM curve, from which the median PFS will be estimated. In addition, KM plots will be presented. Summaries of the number of percentage of patients experiencing a PFS event and the type of event (RECIST 1.1 , INRC or death) will also be provided. The analysis will be performed on the FAS.

Progression-free survival by irRECIST criteria will be presented as described above for exploratory purposes only.

9.5.1.6 Overall survival

Kaplan-Meier plots as well as 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 cohort (and DL within cohort where applicable).

9.5.1.7 Proportion alive and progression-free at 12 and 18 months

The proportion of patients alive and progression-free at 12 months, APF12, and its 90% CI will be summarized (using the KM curve) and presented by cohort.

The proportion of patients alive and progression-free at 18 months, APF18, will be summarized as APF12.

9.5.1.8 Overall survival at 12 and 24 months

The proportion of patients alive at 12 months, OS12, and its 90% CI will be summarized (using the KM curve) and presented by cohort.

The proportion of patients alive at 24 months, OS24, will be summarized as OS12.

9.5.2 Safety analyses

Safety and tolerability data will be presented by DL in dose-finding phase and by cohort in dose-expansion phase, using the SAS. The DLT evaluable analysis set will also be used for safety presentations where appropriate.

Data from all cycles of treatment will be combined in the presentation of safety data. Adverse events (both in terms of Medical Dictionary for Regulatory Activities preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by DL in dose escalation phase and by cohort in dose-expansion phase. Additionally, data presentations of the rate of AEs per person-years at risk may be produced. Any safety summaries examining retreatment with durvalumab will be produced separately.

Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. Exposure to durvalumab + tremelimumab combination therapy, and durvalumab monotherapy will be summarized. Time on study, durvalumab + tremelimumab combination therapy, and durvalumab monotherapy dose delays will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.5.3 Pharmacokinetic data

Pharmacokinetic data will be summarized and analyzed based on the PK analysis set (Section 9.3.5).

Pharmacokinetic concentration data will be listed for each patient and each dosing day, and a summary will be provided for all evaluable patients.

9.5.4 Immunogenicity data

Immunogenicity results will be listed by patient, CCI [redacted]

The effect of immunogenicity as well as the effect of its neutralizing properties CCI [redacted] A detailed plan will be written by the AstraZeneca Clinical Pharmacology group or designee.

9.5.5 Pharmacokinetic/pharmacodynamic relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modeling approach.

9.5.6 Biomarker data

Vaccine antibody titer data will be listed by patient.

CCI

[redacted]

9.5.7 Methods for multiplicity control

Not applicable for this study.

9.6 Interim analyses

No formal interim analysis for efficacy is planned for this study. However, ORR will be evaluated on an ongoing basis for the first 11 evaluable patients in the SARCOMA cohort to complete Stage 1 of the Simon 2-stage optimal design (see Section 4.1.4).

9.6.1 Data Review Committee

A DRC will be established prior to the initiation of the study and will review the safety and PK data. The DRC membership will comprise of participating Investigators and representatives from both AstraZeneca (Pharmacovigilance Scientists for durvalumab and tremelimumab, PK Scientist, Study Physician and Biostatistician) and IQVIA (Study Physician, Safety Physician and Biostatistician). On a case-by-case basis, the DRC may also seek advice from pediatric oncologists with the required site specialization expertise.

Working rules, including the timing of planned meetings, will be described in the DRC charter. In summary, recommendations and decisions will be made through consensus of opinion amongst the DRC members with all decisions being documented and distributed to DRC members. Additionally, 'ad-hoc' DRC meetings may be convened, if required, anytime during the conduct of the study.

The key tasks of the DRC members will be to review the data recorded in the clinical database in conjunction with the PK data to:

1. Determine whether DLTs have occurred
2. Decide whether additional patients should be added to a cohort
3. Recommend de-escalating a dose that was poorly tolerated or escalating a dose if PK exposures inferior to those observed in adults, were achieved
4. Declare that dose finding is complete

5. Recommended a RP2D to be explored in the dose-expansion phase of the study

6. Perform a benefit/risk assessment at the completion of safety data analysis for children <1 year old prior to enrolling a patient less than 1 year old; notify local health authority of decision, if applicable, as per local requirements

7. Put enrollment on hold

8. End the study.

During the dose-expansion phase, the DRC will review safety, tolerability, PK, and efficacy data to make consensual decisions on cohort expansion or closure, and end the study, among others.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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