Clinical Study Protocol	
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An Open-Label, Multi-Center, Global Study to Evaluate Long Term Safety and Efficacy in Patients Who are Receiving or Who Previously Received Durvalumab in Other Protocols (WAVE)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s): EudraCT 2019-001402-20; IND 143828

VERSION HISTORY

Changes to the Clinical Study Protocol (Global) Version 4.0 (12 April, 2022) from Global Version 3.0 are summarized below:	
Section	**Summary of change**
1 Protocol summary 4.4 End of study definition	• Revised that the last patient visit will be completed in Q4 2022; removed language that the study will not close if the patient is still receiving durvalumab treatment
1 Protocol summary 4.1 Overall design 9.1 Sample size determination	• Clarification that study sample size is "up to" 600 patients
1 Protocol summary 3 Objectives and Endpoints, Table 4 9.2 Populations for analyses, Table 11 9.3.2 Efficacy analyses	• Clarification that efficacy analysis for patients who are retreated with durvalumab in Cohort 2 will only be performed if there is sufficient sample size
4.4 End of study definition	• Details added pertaining to study completion activities with cohort-specific activities, such as safety data collection and monitoring
6.4 Concomitant therapy, Table 7	• Clarification that drugs with laxative properties and herbal or natural remedies for constipation should be used with caution through 90 days after the last dose of tremelimumab, which is relevant only to patients who received tremelimumab/durvalumab combination in the parent clinical study
6.6 Treatment after the end of the study	• Details added pertaining to recommendations for patient management following study completion for Cohort 1 or 2
8.3.14 Safety data to be collected following the final DCO of the study	• Clarification language pertaining to collection and reporting of safety events after the final DCO, with appropriate cross-referencing throughout document to this revised section
Version 3.0, 25 September, 2019	
Section	**Summary of change**
1 Protocol summary	• Addition of statement clarifying that any assessments which are relevant to the preservation of patient safety, as scheduled in the parent clinical study, will be conducted and followed up as per the WAVE study schedule of activities (SoA)
1 Protocol summary 1.2 Synopsis 4.1 Overall design	• Clarification that patients that have discontinued treatment may receive any subsequent anticancer therapy at the discretion of the Investigator

6.1.3 Duration of treatment and criteria for treatment through progression and for retreatment 7.1 Discontinuation of study treatment	
1.1 Schedule of activities	• Addition of physical examination 30 days (±3 days) after treatment discontinuation • Clarification that pregnancy testing should be conducted at 30 days after last dose of study drug and as clinically indicated thereafter • Language of footnote "a" for Tables 2 and 3 has been corrected to indicate that "follow-up visits" not "procedures" are to be performed based on the duration since the last dose of study drug in either the parent clinical study or current study. • Addition of statement clarifying that any assessments which are relevant to the preservation of patient safety, as scheduled in the parent clinical study, will be conducted and followed up as per the WAVE study SoA
5.2 Exclusion criteria	• Exclusion criteria regarding receipt of live vaccine 30 days after receiving study drug updated to 90 days
5.2 Exclusion criteria 5.3 Lifestyle restrictions	• Clarification that patients randomized to receive SoC treatment in parent protocols are to follow local prescribing information relating to contraception
6.4 Concomitant therapy	• Prohibited concomitant medication (Table 7) updated to correct the time period of prohibition of live (attenuated) vaccines from 30 days to 90 days after the last dose of study drug
6.4.3 Rescue medication	• Correction that rescue medications do not need to be administered by the pharmacist
8.1 Safety assessments	• Addition of statement clarifying that any assessments which are relevant to preservation of patient safety, as scheduled in the parent clinical study, will be conducted and followed up as per the WAVE study SOA
12.5 Patient confidentiality	• Updated regulations to be followed
Version 2.0, 21 June, 2019	
Section	**Summary of change**
5.1 Inclusion criteria	• Inclusion criterion was added to include the minimum age requirement • A header was added for inclusion criteria 6 – 8.

5.2 Exclusion criteria	• Additional exclusion criteria for Cohorts 1 and 2 were combined for clarity.
8 Study Assessments and Procedures; Appendix B	• Reference to central laboratory has been removed, as local laboratories will be used for this study, only.
Appendix D Dosing Modification and Toxicity Management Guidelines For Immune-Mediate, Infusion-Related, and Non-Immune-Mediated Reactions	• Appendix D was removed and will now be Annex 1. • Appendix E (Abbreviations) has been changed to Appendix D.
Version 1.0, 29 April, 2019	
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

This is a multicenter, open-label study that will enroll patients who are currently receiving durvalumab or have previously received durvalumab as monotherapy or in combination with other agents in an eligible AstraZeneca/MedImmune-sponsored clinical study (herein referred to as a parent clinical study). The aims of the study are to monitor the long-term safety of durvalumab, to provide continued treatment or retreatment with durvalumab to eligible patients, and to collect overall survival (OS) information.

Patients in this study will be enrolled into one of 3 Cohorts:

Cohort 1 includes patients who received durvalumab monotherapy or durvalumab combination therapy under the parent clinical study (including those undergoing retreatment per the parent study) who have not clinically progressed and who are eligible to continue durvalumab treatment after completing dosing of all other anticancer agents, including other investigational agents, which are a formal component of the parent study. If a patient was already retreated with durvalumab in the parent clinical study and has not progressed while on treatment, then they would be potentially eligible to enter Cohort 1; a combination treatment course initiated in the parent clinical study must be completed prior to study entry. All treatment cycle assessments will occur every 4 weeks (±3 days) until confirmed progressive disease (PD), unless unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Treatment beyond disease progression is allowed at the Investigator's discretion, if it is in the patient's best interest. The baseline imaging results from start of the parent clinical study will be used for baseline tumor assessments for Cohort 1. Follow-up tumor assessments will be performed according to the Investigator's standard practice using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; at least every 12 weeks) (Table 1). Upon discontinuation of durvalumab, patients may receive any subsequent anticancer therapy at the discretion of the Investigator and will follow the schedule of activities (SoA) detailed for Cohort 3 for safety and survival follow-up (Table 3).

Cohort 2 includes patients who completed durvalumab monotherapy or in combination with any other approved or investigational anticancer agents in a parent study, without confirmed PD during the period of treatment, and who are potentially eligible for retreatment with durvalumab. The patient should not have received any other approved or investigational anticancer agents since completion of durvalumab treatment. Patients who completed the prespecified duration of treatment with durvalumab in a parent clinical study, who received clinical benefit and then subsequently experienced confirmed PD after completion of planned treatment, will be permitted to restart durvalumab treatment provided they meet the eligibility criteria. If a patient was already retreated with durvalumab in the parent clinical study and retreatment has ended, they are no longer eligible for retreatment in this study. In addition, intervening chemotherapy treatment will not be allowed before retreatment with durvalumab. Cohort 2 patients who will be eligible for future retreatment with durvalumab must agree to reconsenting to start retreatment and meet the eligibility criteria detailed in Sections 5.1 and 5.2. Patients who undergo retreatment will follow assessments as per the SoA for Cohort 1 until confirmed PD, unless unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (Table 2). Only 1 course of retreatment is allowed (inclusive of any retreatment in the parent

clinical study). Treatment beyond disease progression is allowed at the Investigator's discretion, if it is in the patient's best interest. The baseline imaging results for Cohort 2 must be available within 28 days of retreatment. While on retreatment, follow-up tumor assessments will be performed according to the Investigator's standard practice (at least every 12 weeks) using RECIST v1.1 (Table 1). Upon discontinuation of durvalumab, patients may receive any subsequent anticancer therapy at the discretion of the Investigator and will follow the SoA detailed for Cohort 3 for safety and survival follow-up (Table 3).

Cohort 3 includes survival follow-up only for patients previously treated with durvalumab monotherapy or durvalumab in combination with any other approved or investigational anticancer agents who are no longer receiving durvalumab and are not eligible to receive retreatment. Safety assessments will be collected among the patients who are within 90 days since last dose of study drug in the parent study. The patients would undergo OS assessments as per the SoA (Table 3) and may receive any subsequent anticancer therapy at the discretion of the Investigator.

For all cohorts, any assessments which are relevant to preservation of patient safety, as scheduled in the parent clinical study, will be conducted and followed up as per the SoA for this study.

1.1 Schedule of activities

The SoA are based on Cohort entry type as part of the study design (Table 1 to Table 3).

Patients in Cohort 1 and those going onto durvalumab retreatment in Cohort 2 will receive durvalumab monotherapy by infusion every 4 weeks on Day 1 of each cycle. For all patients treated with durvalumab, cycle assessments will be completed every 4 weeks (±3 days) until confirmed PD, unless unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (Table 1 and Table 2). For the purposes of this study, "confirmed" PD is determined by the Investigator using RECIST v1.1 at least every 12 weeks while the patient remains on treatment according to standard clinical practice. There are no mandated confirmatory scans, unless the Investigator plans to treat the patient beyond PD. All assessments on treatment days are to be performed prior to durvalumab infusion, unless otherwise indicated. Prior to commencing infusion with durvalumab (within 3 days), the results for liver function tests, electrolytes, full blood count, and creatinine must be available and reviewed by the treating physician or Investigator. Patients will undergo various assessments for vital signs (including temperature, respiratory rate, blood pressure, body weight, and pulse), concomitant medication, laboratory, safety, adverse event/serious adverse event, and tumor assessments. Safety assessments will be performed according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Any assessments which are relevant to preservation of patient safety, as scheduled in the parent clinical study, will be conducted and followed up as per the SoA for this study.

Upon discontinuation of durvalumab, for both Cohort 1 and among the patients who undergo retreatment in Cohort 2, follow-up will continue as per the SoA for Cohort 3 (Table 3). Only one course of retreatment is allowed (inclusive of any retreatment in the parent clinical study).

For patients receiving durvalumab monotherapy

- Patients may delay dosing under certain circumstances:
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, due to either an immune or a non-immune-related AE (Annex 1).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-lives of durvalumab (see current Investigator's Brochure for durvalumab).

Table 1 Schedule of assessments for patients currently receiving treatment with durvalumab monotherapy (Cohort 1)

		C1	C2	C3	C4	C5 onwards[a]
Week	**Baseline[b]/ Enrollment**	**0**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**			
Day		**1**	**Q28days ±3 days unless dosing needs to be held for toxicity reasons**			
Informed consent						
Informed consent[c]	X					
Eligibility criteria[d]	X					
Study procedures						
Vital signs[e]	X	X	X	X	X	X
Physical examination[f]	X	X	X	X	X	X
WHO/ECOG performance status	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Laboratory safety assessments						
Clinical chemistry[g]	X	X	X	X	X	X
Hematology[g]	X	X	X	X	X	X
TSH (reflex free T3 or free T4)[h]	X	X	X	X	X	X
Pregnancy test[i]	X	X	X	X	X	X
Monitoring						
AE/SAE assessment[j]	X	X	X	X	X	X
Study drug administration[k]						
Durvalumab (monotherapy)[l]		X	X	X	X	X

		C1	C2	C3	C4	C5 onwards[a]
Week	**Baseline[b]/ Enrollment**	**0**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**			
Day		**1**	**Q28days ±3 days unless dosing needs to be held for toxicity reasons**			
Tumor assessment						
Tumor assessment[m]	X[n]	Assessment performed according to RECIST v1.1 as determined by the Investigator (at least every 12 weeks) until withdrawal of consent, progression or death.				

a. Patients will continue their assigned treatment and all assessments Q4W (±3 days) until confirmed PD, unless unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Upon discontinuation of study drug, patients will follow the study assessments detailed in the follow-up module (Section 7.1.1,Table 3).
b. Baseline assessments may be performed over more than 1 visit if necessary. If laboratory or imaging procedures were performed for alternate reasons prior to signing the consent, these can be used for baseline assessment purposes with consent of the patient. However, all baseline laboratory assessments must be obtained within 3 days prior to Day 1 (first treatment visit). Baseline laboratory assessments performed within 3 days prior to Day 1 do not need to be repeated at Day 1.
c. Informed consent of study procedures may be obtained prior to enrollment, if necessary. Patients in Cohort 1 will sign the treatment ICF.
d. Patient eligibility criteria specific to Cohort 1 that may require additional baseline assessments to be documented and/or performed are described in Sections 5.1 and 5.2.
e. Vital signs include temperature, respiratory rate, BP, and pulse. Body weight is measured along with vital signs. Vital signs should be measured, collected/recorded in eCRF prior to the start of the 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.
f. Physical examination 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. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. A physical examination should be performed 30 days (±3 days) after treatment discontinuation (Table 3). Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.
g. Serum or plasma chemistry, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated. Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion.
h. Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
i. For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1 of each cycle, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion. A pregnancy test should also be performed 30 days (±3 days) after treatment discontinuation (Table 3). Further pregnancy testing after 30 days of treatment discontinuation should be conducted as clinically indicated.
j. For AEs and SAEs reported during the study, additional information such as concomitant medications will be needed. Medical history previously recorded in the parent clinical study will be made available in the present study and does not need to be collected. AE/SAE assessment will be performed according to CTCAE v5.0.

k. Patients will receive durvalumab monotherapy until confirmed PD. Section 6.6 details recommendations for patient management after the end of the study.

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

m. Disease progression during treatment should be confirmed by the Investigator according to RECIST v1.1 modified for confirmation of progression, as described in Appendix C.

n. The baseline imaging results from the parent clinical study will be used for baseline tumor assessments for Cohort 1.

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

Cohort 1 will move to SoA for Cohort 3 after durvalumab treatment ends.

AE adverse event; BP blood pressure; C Cycle; CTCAE v5.0 Common Terminology Criteria for Adverse Events version 5.0; ECOG Eastern Cooperative Oncology Group; eCRF electronic case report form; GI gastrointestinal; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; ICF informed consent form; LFT liver function test; PD progressive disease; Q28days every 28 days; Q4W every 4 weeks; RECIST v1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE serious adverse event; SoA schedule of activities; SoC standard of care; T3 triiodothyronine; T4 thyroxine; TSH thyroid-stimulating hormone; WHO World Health Organization.

Table 2 Schedule of assessments for patients who completed treatment with durvalumab monotherapy or durvalumab in combination with any other approved or investigational anticancer agents, and are eligible for future retreatment (Cohort 2)

	Follow-up before retreatment					**Retreatment**				
	Time since the last dose of study drug[a]				**Long-term follow-up**	**Baseline[b]/ C1**	**C2**	**C3**	**C4**	**C5 onwards[c]**
Week	**Baseline/ Enrollment[a]**	**Day (±3 days)**	**Day (±7 days)**		**Every 3 months (±2 weeks)**	**0**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**			
Day		**30**	**60**	**90**		**1**	**Q28days ±3 days unless dosing needs to be held for toxicity reasons**			
Informed consent										
Informed consent	X[d]					X[e]				
Eligibility criteria	X[d]					X[e]				
Study procedures										
Vital signs[f]		X	X	X		X	X	X	X	X
Physical examination[g]		X				X	X	X	X	X
WHO/ECOG performance status						X	X	X	X	X
Concomitant medications		X	X	X		X	X	X	X	X
Laboratory safety assessments										
Clinical chemistry[h]		X	X	X		X	X	X	X	X
Hematology[h]		X	X	X		X	X	X	X	X
TSH (reflex free T3 or free T4)[i]		X	X	X		X	X	X	X	X
Pregnancy test[j]		X				X	X	X	X	X

	Follow-up before retreatment					**Retreatment**				
	Time since the last dose of study drug[a]				**Long-term follow-up**	**Baseline[b]/ C1**	**C2**	**C3**	**C4**	**C5 onwards[c]**
Week	**Baseline/ Enrollment[a]**	**Day (±3 days)**	**Day (±7 days)**		**Every 3 months (±2 weeks)**	**0**	**Q4W ±3 days unless dosing needs to be held for toxicity reasons**			
Day		**30**	**60**	**90**		**1**	**Q28days ±3 days unless dosing needs to be held for toxicity reasons**			
Monitoring										
AE/SAE assessment[k]		X	X	X		Throughout				
Survival status[l]					X					
Study drug administration										
Durvalumab (monotherapy)[m]						X	X	X	X	X
Tumor assessment										
Tumor assessment[n]	Assessment performed according to the Investigator's standard practice until withdrawal of consent, progression or death.					X[o]	Assessment performed according to RECIST v1.1 as determined by the Investigator (at least every 12 weeks) until withdrawal of consent, progression or death.			

a. Follow-up visits are performed based on the duration since the last dose of study drug in either the parent clinical study or current study (whichever most recently administered the study drug). Patients who are more than 90 days beyond the last dose of study drug, will not undergo follow-up for AEs/ SAEs, vital signs, concomitant medications, or laboratory safety assessments; these patients will be followed for survival and undergo tumor assessment per Investigator's standard practice.

b. Baseline assessments may be performed over more than 1 visit if necessary. If laboratory or imaging procedures were performed for alternate reasons prior to signing the consent, these can be used for baseline assessment purposes with consent of the patient. However, all baseline laboratory assessments must be obtained within 3 days prior to Day 1 (first retreatment visit), and baseline imaging results must be obtained within 28 days prior to Day 1 of retreatment. Baseline laboratory assessments performed within 3 days prior to Day 1 do not need to be repeated at Day 1. Patients with documented HIV test results from the parent clinical study do not need to undergo a repeat test, but HBV and HCV must be retested within the 28-day period.

c. Patients will continue their assigned treatment and all C5 assessments Q4W until confirmed PD, unless unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Upon discontinuation of study drug, patients will follow the study assessments detailed in the follow-up module (Section 7.1.1, Table 3). Section 6.6 details recommendations for patient management after the end of the study.

d. Informed consent of study procedures may be obtained prior to enrollment, if necessary. Patients in Cohort 2 will sign the follow-up ICF while off treatment, and must meet the eligibility criteria detailed in Sections 5.1 and 5.2.

e. Patients must agree to reconsenting (treatment ICF) to start retreatment and must meet the eligibility criteria detailed in Sections 5.1 and 5.2 prior to starting retreatment.

f. Vital signs include temperature, respiratory rate, BP, and pulse. Body weight is measured along with vital signs. Vital signs should be measured, collected/recorded in eCRF prior to the start of the 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.
g. Physical examination 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. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. A physical examination should be performed 30 days (±3 days) after last dose of study drug and discontinuation of retreatment (Table 3). Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.
h. Serum or plasma chemistry, hematology, and/or LFT monitoring may be performed more frequently if clinically indicated. Results for urea and electrolytes, full blood count, and liver function tests must be available before commencing an infusion.
i. Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
j. For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1 of each cycle, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion. A pregnancy test should also be performed 30 days (±3 days) after last dose of study drug and discontinuation of retreatment (Table 3). Further pregnancy testing after 30 days of treatment discontinuation should be conducted as clinically indicated.
k. For AEs and SAEs reported during the study, additional information such as concomitant medications will be needed. Medical history previously recorded in the parent clinical study will be made available in the study and does not need to be collected. AE/SAE assessment will be performed according to CTCAE v5.0.
l. Upon completing the 90-day follow-up for AEs and SAEs, patients will be followed for survival. Survival follow-up will be performed by telephone call (or a prespecified preferred method of contact, as an alternative). Patients will be contacted by telephone in the week following data cut-offs to confirm survival status. No additional retreatment with durvalumab will be allowed.
m. Results for LFTs, electrolytes, full blood count, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.
n. Disease progression during treatment should be confirmed by the Investigator according to RECIST 1.1 modified for confirmation of progression, as described in Appendix C.
o. The most recent imaging results from the parent clinical study may be used as the baseline assessment, provided it was obtained within 28 days prior to Day 1.

Note: Cohort 2 will move to SoA for Cohort 3 after retreatment with durvalumab ends.

AE adverse event; BP blood pressure; C Cycle; CTCAE v5.0 Common Terminology Criteria for Adverse Events version 5.0; ECOG Eastern Cooperative Oncology Group; eCRF electronic case report form; GI gastrointestinal; HBV hepatitis B virus; HCV hepatitis C virus; HIV human immunodeficiency virus; ICF informed consent form; LFT liver function test; PD progressive disease; Q28days every 28 days; Q4W every 4 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors version 1.1; SAE serious adverse event; SoA schedule of activities; SoC standard of care; T3 triiodothyronine; T4 thyroxine; TSH thyroid-stimulating hormone; WHO World Health Organization.

Table 3 Schedule of assessments for patients who previously received treatment with durvalumab monotherapy or durvalumab in combination with any other approved or investigational anticancer agents, and are not eligible for any future treatment (Cohort 3)

		Time since the last dose of study drug[a]			Long-term follow-up
Evaluation	**Baseline/ Enrollment**	**Day (±3 days)**	**Day (±7 days)**		**Every 3 months (±2 weeks)**
		30	**60**	**90**	
Informed consent					
Informed consent[b]	X				
Eligibility criteria[b]	X				
Study procedures					
Vital signs[c]		X	X	X	
Physical examination[d]		X			
Concomitant medications		X	X	X	
Subsequent anticancer therapy[e]	X	X	X	X	X
Laboratory safety assessments					
Clinical chemistry		X	X	X	
Hematology		X	X	X	
TSH (reflex free T3 or free T4)[f]		X	X	X	
Pregnancy test[g]		X			
Monitoring					
AE/SAE assessment[h]		X	X	X	
Survival status[i]					X
Tumor Assessments					
Tumor assessment[j]	Assessment performed according to the Investigator's standard practice until withdrawal of consent, progression or death.				

a. Follow-up visits are performed based on the duration since the last dose of study drug in either the parent clinical study or current study (whichever most recently administered the study drug). Patients who are more than 90 days beyond the last dose of study drug will not undergo follow-up for AEs/ SAEs, vital signs, concomitant medications or laboratory safety assessments; these patients will be followed for survival.
b. Informed consent of study procedures may be obtained prior to enrollment, if necessary. Patients in Cohort 3 will sign the follow-up ICF, and must meet the eligibility criteria detailed in Sections 5.1 and 5.2.
c. Vital signs include temperature, respiratory rate, BP, and pulse. Body weight is measured along with vital signs.
d. Physical examination should be performed 30 days (±3 days) after treatment discontinuation. A physical examination 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. 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.
e. Only the first subsequent anticancer therapy regimen used after durvalumab discontinuation will be collected.
f. Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
g. Pregnancy test should be performed 30 days (±3 days) after treatment discontinuation. Further pregnancy testing after 30 days of treatment discontinuation should be conducted as clinically indicated.
h. For AEs and SAEs reported during the study, additional information such as concomitant medications will be needed. Medical history previously recorded in the parent clinical study will be made available in the study and does not need to be collected. AE/SAE assessment will be performed according to CTCAE v5.0.
i. Upon completing the 90-day follow-up for AEs and SAEs, patients will be followed for survival. Survival follow-up will be performed by telephone call (or a prespecified preferred method of contact, as an alternative). Patients will be contacted by telephone in the week following data cut-offs to confirm survival status.
j. Tumor assessment of best overall response to the first subsequent treatment after durvalumab, only (where evaluable). After that, tumor assessments will no longer be required for long-term follow-up.

Note: Following discontinuation of study drug, patients who decline to return to the site for evaluations should be contacted by telephone, or their prespecified preferred method of contact, as an alternative.

AE adverse event; BP blood pressure; CTCAE v5.0 Common Terminology Criteria for Adverse Events version 5.0; PD progressive disease; SAE serious adverse event; SoC standard of care; T3 triiodothyronine; T4 thyroxine; TSH thyroid-stimulating hormone.

1.2 Synopsis

International Co-ordinating Investigator: PPD
Chapel Hill, NC, USA 27514

Protocol Title: An Open-Label, Multi-Center, Global Study to Evaluate Long Term Safety and Efficacy in Patients Who are Receiving or Who Previously Received Durvalumab in Other Protocols (WAVE)

Short Title: Durvalumab Long-Term Safety and Efficacy Study

Rationale: Durvalumab administered either as a single agent or in combination, continues to be evaluated in multiple oncology clinical studies. Durvalumab has been administered intravenously (IV) in multiple clinical studies for up to 12 months or until progressive disease (PD), dependent on the specific protocol. The primary aim of this study is to evaluate the long-term safety and tolerability of durvalumab.

Study Objectives:

The objectives of this study are as follows:

- To monitor long-term safety of durvalumab (all cohorts)
- To assess the efficacy of durvalumab in terms of overall response rate (ORR) and duration of response (DOR) in patients who undergo retreatment with durvalumab (Cohort 2 only)
- To assess the overall survival (OS) of patients (all cohorts)

Overall design: This is a multicenter, open-label, global study that will enroll patients who are currently receiving durvalumab monotherapy, or have previously received durvalumab as monotherapy or in combination with any other approved or investigational anticancer agents, in an eligible AstraZeneca/MedImmune-sponsored clinical study (herein referred to as a parent clinical study).

Patients may enroll under one of three cohorts described as follows:

- Cohort 1: includes patients who received durvalumab monotherapy or durvalumab combination therapy under the parent clinical study (including those undergoing retreatment per the parent study) who have not clinically progressed and who are eligible to continue durvalumab treatment after completing dosing of all other anticancer agents, including other investigational agents, which are a formal component of the parent study. If a patient was already retreated with durvalumab in the parent clinical study and has not progressed while on treatment, then they would be potentially eligible to enter Cohort 1; a combination treatment course initiated in the parent clinical study must be completed prior to study entry.

- Cohort 2: includes patients who completed durvalumab monotherapy or in combination with any other approved or investigational anticancer agents in a parent study, without confirmed PD during the period of treatment, and who are potentially eligible for retreatment with durvalumab. The patient should not have received any other approved or investigational anticancer agents since completion of durvalumab treatment. Patients who completed the prespecified duration of treatment with durvalumab in a parent clinical study, who received clinical benefit and then subsequently experienced confirmed PD after completion of planned treatment, will be permitted to restart durvalumab treatment provided they meet the eligibility criteria. If a patient was already retreated with durvalumab in the parent clinical study and retreatment has ended, they are no longer eligible for retreatment in this study.

- Cohort 3: includes patients previously treated with durvalumab monotherapy or in combination with any other approved or investigational anticancer agents who are no longer receiving durvalumab and are not eligible to receive retreatment.

In addition to providing continued treatment to eligible patients, the study will monitor long-term safety of durvalumab and OS (Cohorts 1 to 3).

Study Period:

Estimated date of first patient enrolled: Q3 2019

Estimated date of last patient visit completed is Q4 2022.

Number of patients: This study will enroll patients who have been previously treated with durvalumab and/or durvalumab in combination with any other approved or investigational anticancer agents at any global site. The study will enroll up to 600 patients. The number of patients is subject to change as new parent studies are included into this long-term safety and efficacy study.

Treatment and treatment duration

Patients in Cohort 1 and those going onto durvalumab retreatment in Cohort 2 will receive durvalumab monotherapy. Patients in Cohort 3 will not receive any study drug.

Durvalumab monotherapy

- Durvalumab 1500 mg via intravenous (IV) infusion every 4 weeks until confirmed PD, unless unacceptable toxicity, withdrawal of consent, death, or another discontinuation criterion is met. Please note, if a patient's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between Investigator and Study Physician, until the weight improves to above 30 kg (>30 kg).

Duration of treatment

Patients in Cohort 1 will continue to receive treatment with durvalumab until confirmed PD. This includes patients who received durvalumab monotherapy or combination therapy under the parent clinical study, and who are eligible to continue durvalumab treatment after completing dosing of any other approved or investigational anticancer agents, which are a formal component of the parent study.

Continuation with durvalumab monotherapy (Cohort 1) and retreatment with durvalumab monotherapy (Cohort 2) will continue until confirmed PD, unless unacceptable toxicity, withdrawal of consent, death, or another discontinuation criterion is met. Patients will only be eligible for 1 course of retreatment (inclusive of any retreatment in the parent clinical study and this study). Patients will not be eligible to receive retreatment with any other approved or investigational anticancer agents administered in the parent clinical study. Disease progression will be determined by the Investigator following Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).

Cohort 3 includes patients who have previously received durvalumab treatment or durvalumab combination therapy and are not eligible for future treatment. These patients will be followed for OS.

Progression during treatment

Patients receiving the study drug who experience disease progression and, in the Investigator's opinion, continue to receive benefits from their assigned treatment; may continue to receive the study drug for as long as they meet specific clinical criteria, and are deriving clinical benefit in the opinion of the Investigator.

For all patients who are treated through progression, the Investigator should ensure that patients still meet all the inclusion criteria and none of the exclusion criteria for this study, and obtain additional informed consent for continuation of treatment. This consent addendum document will be part of the treatment informed consent form (ICF); it will specify that treatment beyond initial evidence of PD is not the standard of care and that alternative treatment options, either locally licensed treatments or other clinical trials, are potentially available for this patient population. Patients with rapid tumor progression or with symptomatic progression that require medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression) will not be eligible for continuing durvalumab.

Follow up of patients post discontinuation of study drug

Treatment is given until progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. Patients in Cohort 1 who discontinue durvalumab for any reason will not be eligible for further retreatment and will be followed subsequently for safety and survival. All patients in the study will be followed for safety for 90 days after the last dose of durvalumab and for OS and may receive any subsequent anticancer therapy at the discretion of the Investigator. The details of first subsequent anticancer therapy

and overall best response after discontinuation of durvalumab treatment will be collected from the Investigator.

Survival

All patients in the study are followed up for survival every 3 months (±2 weeks) beginning 90 days after the last dose of the study drug. Patients who enter Cohort 3 are in survival follow-up from the time of enrollment since no study drug is being administered to that cohort. Survival information may be obtained via telephone contact (or a prespecified preferred method of contact, as an alternative) with the patient or the patient's family, or by contact with the patient's current physician.

Statistical methods and endpoints

The primary objective is to monitor long-term safety of durvalumab. The safety analysis set will be used to summarize safety data according to the treatment received for all patients who received at least one dose of durvalumab. This analysis set would include patients continuing study treatment or retreatment, and those who enrolled in this study within 90 days of the last dose of durvalumab or durvalumab combination on the respective parent clinical study. Adverse events (AEs), vital signs and laboratory safety assessments (clinical chemistry, hematology and Thyroid-stimulating hormone [reflex free triiodothyronine or free thyroxine]) will be listed individually by patient. The number of patients experiencing each AE will be summarized by cohort and the National Cancer Institute Common Terminology Criteria for Adverse Events grade (v5.0) (Annex 1).

The analysis set for assessment of efficacy will be based on patients who are retreated with durvalumab in Cohort 2. Efficacy analysis will be performed only if there is sufficient sample size; if so, data may be summarized by tumor type in each tumor type, otherwise, only listings will be provided as descriptive results.

One secondary objective is to assess the efficacy of durvalumab in terms of ORR and DOR for durvalumab retreatment patients. ORR is defined as the number (%) of patients with at a confirmed response of complete response (CR) or partial response (PR). DOR is defined as the time from first documented of CR or PR until the time of first documented disease progression or death in the absence of disease progression since re-initiation of durvalumab treatment. Tumor assessments will be performed by computed tomography scans per standard practice (at least every 12 weeks). Tumor assessments will be performed by the Investigator according to RECIST v1.1; only the response outcomes will be collected in the case report form.

The OS is defined as the time from date of randomization/enrollment in the parent clinical study until the date of death by any cause. A listing of OS data will be provided for all study patients.

In addition, OS and tumor efficacy data in this study may be combined with the parent study data for integrated analysis.

No statistical methods will be employed to test a specific hypothesis in this study. In addition to the 5 planned interim analyses, ad hoc analyses may be performed at various time points in order

to support publications, internal decision making by AstraZeneca, and/or regulatory submissions as appropriate.

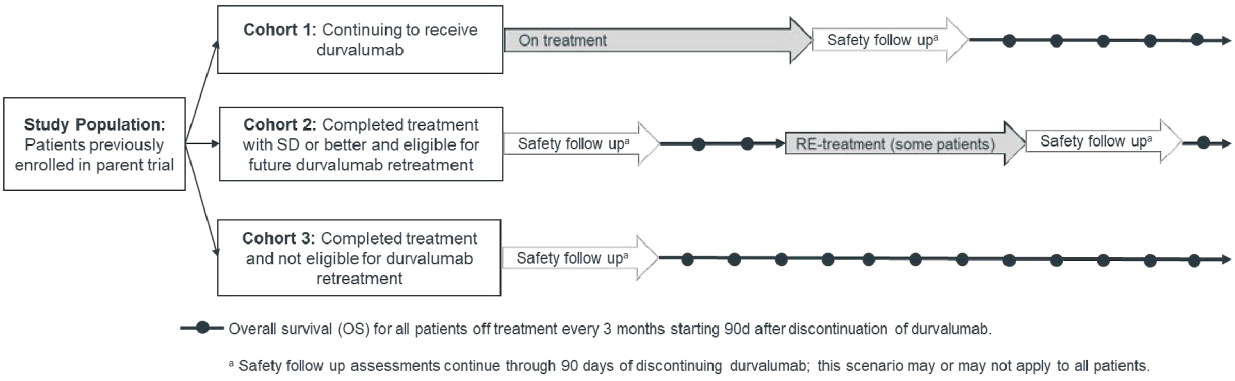
Sample size estimate

The number of patients enrolled in this study will be determined by the number of patients who received durvalumab and/or durvalumab in combination with any other approved or investigational anticancer agents in original trials, and who wish to participate, and who meet the eligibility criteria. The study will enroll up to 600 patients and the number of patients may change as new parent studies are included into this long-term safety and efficacy study.

1.3 Schema

The general study design for this study is summarized in Figure 1.

Figure 1 Study design



SD stable disease.

2. INTRODUCTION

2.1 Study rationale

This is a multicenter, open-label, global study that will enroll patients who are currently receiving durvalumab monotherapy, or have previously received durvalumab as monotherapy or in combination with any other approved or investigational anticancer agents, in an eligible AstraZeneca/MedImmune-sponsored clinical study (herein referred to as a parent clinical study).

The aims of the study are the following:

- To collect long-term safety and survival data from patients who received durvalumab monotherapy and/or durvalumab in combination with any other approved or investigational anticancer agents.
- To provide continued access to durvalumab monotherapy until confirmed progressive disease (PD) to patients currently receiving treatment.
- To allow for future retreatment with durvalumab monotherapy upon disease progression in patients who previously benefited from treatment with durvalumab as monotherapy, and/or durvalumab in combination with any other approved or investigational anticancer agents and experienced disease progression after completion of planned treatment.

The primary aim of this study is to monitor the long-term safety of durvalumab. Extensive safety-related data are being collected throughout the course of drug development, and knowledge about a drug's safety profile continually evolves as safety data accumulate. This study is aligned with the growing interest in larger, simpler trials to obtain outcome data, including long-term effects of drugs and comparative effectiveness and safety.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the Investigator's Brochure (IB).

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 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 protein 1 (PD-1) receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). 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 (IC). This activity overcomes PD-L1-mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T cell reactivation, this mechanism of action (MOA) is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of preclinical 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.

Preclinical data has now been added to a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as cytotoxic T-lymphocyte-associated antigen-4 (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, including metastatic melanoma, squamous and non-squamous cell non-small cell lung cancer (NSCLC), 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.

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on IC. 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 propose MOA for durvalumab

is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon gamma (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 by shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies, either as monotherapy or in combination with any other approved or investigational anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1.1 and Section 8.3.13. Refer to the current durvalumab IB for a complete summary of preclinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

Durvalumab administered either as a single agent or in combination continues to be evaluated in multiple immuno-oncology clinical studies. To date, several different doses and schedules have been evaluated in multiple indications, including administration for a fixed duration. Durvalumab has been administered intravenously (IV) in multiple clinical studies for up to 12 months or until PD, whichever occurs earlier. After the completion of therapy in these ongoing clinical studies, patients are followed with regular tumor assessments to continue monitoring the clinical activity of durvalumab. Emerging data from these ongoing studies suggest that some patients lose clinical benefit after completing 12 months of therapy, eg, HAWK (NCT02207530) and ATLANTIC (NCT02087423) studies.

Patients treated with chemotherapy alone are generally unlikely to respond to re-challenge with the same agent upon progression. In contrast, responses have been observed upon retreatment with immunotherapies (Santini 2018). Several potential mechanisms of resistance to immunotherapy exist, including loss of T cell "memory" or recurrence of immune escape, which suggest that retreatment for patients who initially respond or demonstrate stable disease (SD) merits further study. Preliminary data in patients previously treated with immunotherapies suggest that responses are similar to those observed following initial treatment (Forde et al 2014, Hodi et al 2010).

Therefore, AstraZeneca has modified the durvalumab treatment regimen in specific indications, to allow patients to continue treatment until confirmed PD, rather than requiring treatment discontinuation at 12 months. Treatment until progression is consistent with the approved agents with a similar MOA to durvalumab, such as PD-1 targeting antibodies nivolumab and pembrolizumab, which are used to treat patients in a number of indications, including but not limited to melanoma, NSCLC, urothelial cancer, and renal cell carcinoma.

2.3 Benefit/risk assessment

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

2.3.1 Overall benefits

As is commonly the case for clinical trials with a fixed treatment or study duration, long-term safety and efficacy endpoints often lack feasibility within the time frame permitted by design. The benefit of this study, which identifies potentially eligible patients from parent clinical studies, allows for the continued access of durvalumab and observation of patients treated with durvalumab. Durvalumab will be provided to eligible, treatment-experienced patients who have been treated for months under parent clinical studies and have demonstrated a response and tolerability to treatment. They will be treated as long as they continue to receive benefit for treatment with durvalumab.

Conducting this study serves the important purpose to better understand the long-term patient safety and survival outcomes across a diverse group of patient population exposed to durvalumab.

2.3.1.1 Benefits of durvalumab as monotherapy

The majority of the safety and efficacy data currently available for durvalumab are based on 5 monotherapy studies (CD-ON-MEDI47361108, ATLANTIC, HAWK, PACIFIC, and D4190C00007) for which efficacy data are available. Data from these studies have demonstrated clinical activity of durvalumab therapy in patients with NSCLC. PACIFIC has shown significant improvements in median progression-free survival with durvalumab treatment compared with placebo for patients with NSCLC (16.8 months [95% confidence interval {CI}: 13.0, 18.1] versus 5.6 months [95% CI: 4.6, 7.8]; stratified hazard ratio for disease progression or death, 0.52; 95% CI: 0.42, 0.65; $p<0.001$). Similar findings in favor of durvalumab compared with placebo were found for duration of response (DOR; 72.8% versus 46.8% of patients had ongoing response at 18 months, respectively) and median time to death or distant metastasis (23.2 months versus 14.6 months, respectively; $p<0.001$).

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 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 hyperthyroidism.

2.3.2.1 Potential risks of durvalumab monotherapy

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, and type I diabetes mellitus [DM]), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neuromuscular toxicities, 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 an incidence of ≥20%, this included events such as fatigue, cough, decreased appetite, dyspnea, and nausea. A total of 5% to 10% of patients discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, serious adverse events (SAEs), and Common Terminology Criteria 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 8.4.4).

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

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints for this study are listed in Table 4.

Table 4 Study objectives

Primary Objective:	**Endpoints/Variables:**
To monitor long-term safety of durvalumab (all cohorts)	• All SAEs • Non-serious AEs that lead to dose modification, drug discontinuation, or withdrawal from the study • All Grade 3 and Grade 4 AEs • Grade 2 AEs that affect vital organs (eg, heart, liver) • Immune-mediated AEs • Laboratory findings qualifying as an SAE/AE (endpoints defined above) up until 90 days after the last dose of durvalumab in all patients
Secondary Objectives:	**Endpoints/Variables:**
To assess the efficacy of durvalumab in terms of ORR and DOR in patients who undergo retreatment with durvalumab (Cohort 2 only)[a]	• **ORR:** Number (%) of patients with a confirmed response of CR or PR. • **DOR:** Time from first documented CR or PR to time of first documented disease progression or death in the absence of disease progression
To assess the OS of patients (all cohorts)	• **OS**: Time from date of randomization/enrollment in the parent clinical study until the date of death by any cause

AE adverse event; CR complete response; DOR duration of response; ORR overall response rate; OS overall survival; PR partial response; SAE serious adverse event.

[a.] To be performed only if there is sufficient sample size in retreated Cohort 2 patients to evaluate efficacy; otherwise, only listings will be provided for this objective (Section 6.6)

4. STUDY DESIGN

4.1 Overall design

This is a multicenter, open-label, global study that will enroll patients who are currently receiving durvalumab monotherapy, or have previously received durvalumab as monotherapy or in combination with any other approved or investigational anticancer agents, in an eligible parent clinical study. The study aims to enroll up to 600 patients; study size may increase as new parent clinical studies are incorporated into this study. Some of these patients will no longer be eligible to receive treatment or retreatment with durvalumab, and will be followed for overall survival

(OS). For patients who are eligible to continue treatment or restart durvalumab, treatment will be administered every 4 weeks (q4w; ±3 days) until PD, unless there is unacceptable toxicity, withdrawal of consent, death, or another discontinuation criterion is met. All patients in the study will be followed for safety for 90 days after the last dose of durvalumab, and every 3 months (±2 weeks) beginning 90 days after the last dose of study drug for OS. For an overview of the study design, see Section 1.3. For details on treatments given during the study, see Section 6.1. Upon discontinuation of durvalumab, patients may receive any subsequent anticancer therapy at the discretion of the Investigator (Section 7.1).

4.2 Scientific rationale for study design

4.2.1 Rationale for retreatment option

In contrast to patients treated with chemotherapy, who are unlikely to respond to re-challenge with the same agent upon progression, responses have been observed upon retreatment with immunotherapies. Several potential mechanisms of resistance to immunotherapy exist, including loss of T cell "memory" or recurrence of immune escape, which suggests that retreatment for patients who initially respond or demonstrate SD is reasonable. Preliminary data in patients previously treated with immunotherapies suggest that responses are similar to those observed following initial treatment (Forde et al 2014, Hodi et al 2010).

Durvalumab has been administered IV in multiple clinical studies up to 12 months. After the completion of therapy in these ongoing clinical studies, patients are followed with regular tumor assessments to continue monitoring the clinical activity of durvalumab. Emerging data from these ongoing studies suggest that some patients lose clinical benefit after completing 12 months of therapy.

4.3 Justification for dose

4.3.1 Durvalumab dose and treatment regimen justification

4.3.1.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, preclinical 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 (D4190C00002).

Pharmacokinetic/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with dose ranging from 0.1 to 10 mg/kg every 2 weeks (q2w) or 15 mg/kg every 3 weeks (q3w), durvalumab exhibited nonlinear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and soluble PD-L1), and further showed that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent

suppression in peripheral soluble PD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB.)

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

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

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg q4w regimen. The IB reflects the current regimen that is used across the program when durvalumab monotherapy is dosed q4w.

4.3.1.2 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from Study 1108 (N=292; doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; solid tumors). Population PK analysis indicated only a minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight (WT)-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5^{th}, median, and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40 to 120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body weight-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and

peptides, and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community, due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to 20 mg/kg q4w) is included in the current study.

4.3.1.3 Rationale for duration of treatment

In this study, the duration of treatment was selected to allow eligible patients to continue treatment with durvalumab monotherapy until confirmed PD. Additionally, patients who completed the defined duration of treatment with durvalumab or durvalumab plus any other approved or investigational anticancer agents in a parent clinical study and subsequently experienced confirmed PD, will be permitted to start retreatment with durvalumab monotherapy, if they meet eligibility criteria.

4.4 End of study definition

The end of study is expected to occur in Q4 2022 and is defined as the date of the last scheduled visit of the last participant in the study at the time of the final data cut-off (DCO).

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled visit shown in the SoA at the end of study.

Any patients in Cohort 2 or Cohort 3 not receiving treatment will discontinue further follow-up at the end of study.

For patients receiving treatment in Cohort 1 or 2, refer to Section 6.6 & 8.3.14 which details recommendations for patient management following study completion.

5. STUDY POPULATION

The study population will consist of patients who are currently receiving or have previously received durvalumab monotherapy or durvalumab in combination with any other approved or investigational anticancer agents, in a parent clinical study. Patients enrolled on a control arm in a parent study are not eligible.

At enrollment, informed consent to participate in the study will be obtained from all patients, and eligible patients will be enrolled in Cohorts 1, 2 or 3, according to their treatment status. There are 2 consent forms that will be signed by the patient based on whether the patient is on treatment or starting retreatment (treatment informed consent form [ICF]) or off treatment (follow-up ICF). All patients in Cohort 1 must sign the treatment ICF. The follow-up ICF will be used for patients who enroll in Cohort 3. Cohort 2 patients who will be eligible for future retreatment with durvalumab must sign the follow-up ICF at enrollment, then must agree to

reconsenting under the treatment ICF to start retreatment, and must meet the eligibility criteria detailed in Sections 5.1 and 5.2.

- Cohort 1: includes patients who received durvalumab monotherapy or durvalumab combination therapy under the parent clinical study (including those undergoing retreatment per the parent study) who have not clinically progressed and who are eligible to continue durvalumab treatment after completing dosing of all other anticancer agents, including other investigational agents, which are a formal component of the parent study. If a patient was already retreated with durvalumab in the parent clinical study and has not progressed while on treatment, then they would be potentially eligible to enter Cohort 1; a combination treatment course initiated in the parent clinical study must be completed prior to study entry.

- Cohort 2: includes patients who completed durvalumab monotherapy or in combination with any other approved or investigational anticancer agents in a parent study, without confirmed PD during the period of treatment, and who are potentially eligible for retreatment with durvalumab. The patient should not have received any other approved or investigational anticancer agents since completion of durvalumab treatment. Patients who completed the prespecified duration of treatment with durvalumab in a parent clinical study, who received clinical benefit and then subsequently experienced confirmed PD after completion of planned treatment, will be permitted to restart durvalumab treatment provided they meet the eligibility criteria. If a patient was already retreated with durvalumab in the parent clinical study and retreatment has ended, they are no longer eligible for retreatment in this study.

- Cohort 3: includes patients previously treated with durvalumab monotherapy or in combination with any other approved or investigational anticancer agents who are no longer receiving durvalumab and are not eligible to receive retreatment.

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, to be assigned to a study cohort. 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.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

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

General inclusion criteria for all patients:

1. Patient must be 18 years or older, at the time of signing the ICF. For subjects aged <20 years and enrolled in Japan, a written ICF should be obtained from the subject and his

or her legally acceptable representative.

2. Patient received durvalumab monotherapy and/or durvalumab containing combination in an AstraZeneca/MedImmune-sponsored parent clinical study that is approved for enrollment into this study.

3. Patients who received durvalumab in combination with any other approved or investigational anticancer agents in the parent clinical study must have completed or discontinued all other anticancer therapy (beyond durvalumab regimen).

4. Patient must be willing and able to provide written informed consent and to comply with scheduled visits and other study procedures.

Additional inclusion criteria for patients entering Cohort 1:

5. Currently receiving durvalumab monotherapy (this includes patients enrolled in durvalumab combinations who have completed or discontinued all other anticancer therapy combined with durvalumab in the parent clinical study, and are now receiving durvalumab monotherapy), and is currently benefiting from treatment with durvalumab therapy, as determined by the Investigator.

Additional inclusion criteria for patients entering Cohort 1 and Cohort 2:

6. Adequate organ function as defined below:

   (a) Serum bilirubin ≤1.5 × the upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.
   (b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN.
   (c) Measured creatinine clearance (CL) >40 mL/min or calculated CL >40 mL/min as determined by Cockcroft-Gault (using actual body WT)

   Males:

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

   Females:

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

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

(a) Women <50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range for the institution.
(b) Women ≥50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.
(c) Women who are surgically sterile (eg, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

8. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2 at enrollment

Additional inclusion criteria for retreatment patients in Cohort 2

9. Received durvalumab in a parent clinical study that is approved to enroll into this study.

10. Completed the defined treatment duration with durvalumab monotherapy or durvalumab combination therapy in the parent clinical study, as defined below:

(a) Previously benefited from treatment with durvalumab monotherapy or durvalumab combination therapy, as determined by the Investigator.
(b) Has not previously received retreatment with durvalumab monotherapy.
(c) Maintained SD or better (Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) throughout the period of defined treatment duration, and has not received any subsequent anticancer therapy.

11. At least 1 lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have a short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI), and that is suitable for accurate repeated measurements as per RECIST v1.1 guidelines.

5.2 Exclusion criteria

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

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

Additional exclusion criteria for Cohort 1 and Cohort 2:

2. Currently receiving treatment in another interventional clinical study other than a parent clinical study, or received treatment during the follow-up period before retreatment (Cohort 2 only).

3. Experienced an immune-mediated or non-immune-mediated (hematologic and non-hematologic) toxicity that led to permanent discontinuation of durvalumab in the parent clinical study.

4. Any unresolved toxicity National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

5. Prior treatment with immunotherapy other than durvalumab, or any other approved or investigational anticancer agents other than MedImmune/AstraZeneca's investigational immunotherapy molecules administered in the parent clinical study.

6. Any concurrent chemotherapy, investigational product (IP), biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

7. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

   (a) Patients with vitiligo or alopecia.
   (b) Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
   (c) Any chronic skin condition that does not require systemic therapy.
   (d) Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician.
   (e) Patients with celiac disease controlled by diet alone.

8. History of allogenic organ transplantation.

9. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active ILD, serious chronic GI conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

10. Documented 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 virus (HBV) (known positive HBV surface antigen [HbsAg] result), hepatitis C virus (HCV), or human immunodeficiency virus (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 HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Prior HIV and HBV/HCV testing from the parent

clinical study is acceptable documentation and patients will not need to undergo an additional testing prior to Cohort 1 enrollment in this study. For Cohort 2 patients, prior HIV testing from the parent clinical study is acceptable documentation and patients will not need to undergo an additional test prior to retreatment. However, patients will require retesting for HbsAg and HCV within the 28-day window prior to retreatment.

11. Receipt of live attenuated vaccine within 30 days prior to the first dose of study drug in the present study. Note: Patients, if enrolled, should not receive live vaccine while receiving study drug and up to 90 days after the last dose of study drug.

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

    – Highly effective methods of contraception are defined as one that results in a low failure rate (eg, less than 1% per year) when used consistently and correctly. 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).

    – For patients randomized to receive SoC treatment in parent protocols, follow the local prescribing information relating to contraception, the time limit for such precautions, and any additional restrictions for agents in the SoC treatment regimen.

13. Diagnosis of a new primary malignancy since enrollment into the parent clinical study, with the exception of adequately treated non-melanomatous skin cancer and carcinoma in situ with no evidence of disease.

14. Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE >Grade 1, have not experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of >10 mg prednisone or equivalent per day.

15. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

5.3 Lifestyle restrictions

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

1. Female patient of childbearing potential

   – Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner, must use at least 1 **highly** effective method of contraception (Table 5) 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.

   – Pregnancy testing will be performed according to the schedule of activities (SoA) (Table 1, Table 2, and Table 3).

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 5).

Please note, females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or postmenopausal.

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

- Women <50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range for the institution.

- Women ≥50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

- Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

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 5. 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 5 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. For patients randomized to receive SoC treatment in parent protocols, follow the local prescribing information relating to contraception, the time limit for such precautions, and any additional restrictions for agents in the SoC treatment regimen.

4. 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 combination therapy or 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

5. Restrictions relating to concomitant medications are described in Section 6.4.

5.4 Screen failures

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

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/non-enrollment details, eligibility criteria, and any SAEs.

6. STUDY TREATMENTS

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

6.1 Treatments administered

6.1.1 Investigational product

AstraZeneca will supply durvalumab (MEDI4736). All patients in Cohort 1 will receive durvalumab monotherapy at the dosing regimen described below (Table 6). While patients in Cohort 2 are all eligible for retreatment with durvalumab, some may never receive treatment. Patients who were previously administered durvalumab at a dose regimen different from the regimen described for the present study will switch to the dose regimen described below. Only 1 course of retreatment is allowed (inclusive of any retreatment in the parent clinical study). Patients enrolled in Cohort 3 will not receive any study drug.

Table 6 Study treatment

	Treatment
Study treatment name:	Durvalumab (MEDI4736)
Dosage formulation:	500-mg vial solution for infusion after dilution, 50 mg/mL
Route of administration:	Intravenous (IV)
Dose:	1500 mg
Dosing instructions:	A dose of 1500 mg will be delivered through an IV administration set with a 0.2 µm or 0.22 µm filter. If a patient's weight falls to 30 kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q4w until weight improves to above 30 kg (>30 kg).
Packaging and labeling:	Study drug will be provided in vials. Each vial will be labeled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement.[a]
Frequency:	Every 4 weeks
Manufacturer:	MedImmune
Provider:	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.

6.1.1.1 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

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

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

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

- 4 hours at room temperature

A dose of 1500 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500 mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤30 kg, WT-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

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

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

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

If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives and any unused portion must be discarded.

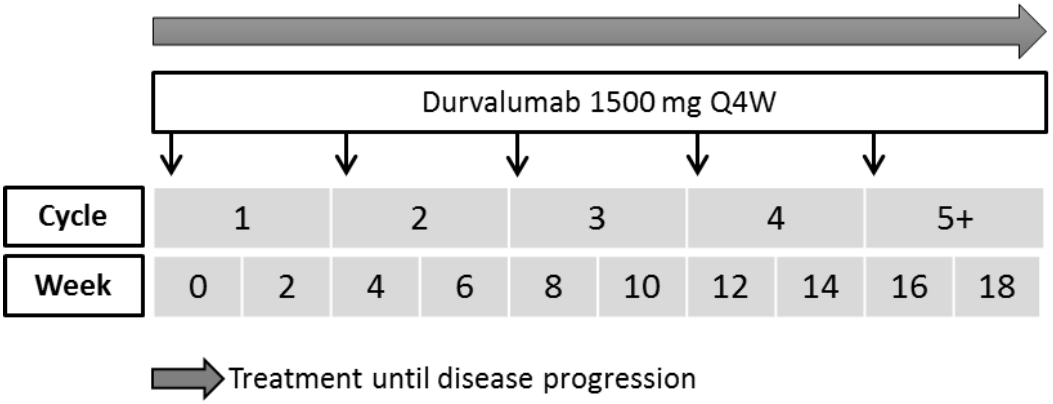
6.1.2 Dose and treatment regimen

6.1.2.1 Durvalumab (MEDI4736) monotherapy

Patients who receive durvalumab monotherapy treatment (Cohort 1) or durvalumab monotherapy retreatment (Cohort 2) will receive 1500 mg durvalumab via IV infusion q4w, until PD is determined by the Investigator following RECIST v1.1, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Figure 2 (Please note, if a patient's weight falls to 30 kg or below, the patient should receive WT-based dosing equivalent to 20 mg/kg of durvalumab q4w after consultation between the Investigator and Study Physician, until the weight improves to >30 kg).

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

Figure 2 Durvalumab monotherapy dosing schedule



Q4W every 4 weeks.

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

All durvalumab treatment will be administered beginning on Day 1 (Cohort 1) or Day 1 retreatment (Cohort 2), until progression as determined by the Investigator using RECIST v1.1 (refer to Appendix C), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Patients receiving durvalumab who experience PD and, in the Investigator's opinion, continue to receive benefit from their assigned treatment may continue to receive durvalumab for as long as they meet specific clinical criteria and are deriving clinical benefit in the opinion of the Investigator. For all patients who are treated through PD, the Investigator should ensure patients still meet all of the inclusion criteria and none of the exclusion criteria for this study and obtain additional informed consent for continuation of treatment. The treatment ICF will specify that treatment beyond initial evidence of PD is not the standard of care and that alternative treatment options, either locally licensed treatments or other clinical trials, are potentially available for this patient population.

Patients with rapid tumor progression or with symptomatic progression, that require urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) will not be eligible for continuing durvalumab (refer to Appendix C).

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

- The patient does not have any significant, unacceptable, or irreversible toxicities, that indicate continuing treatment will not further benefit the patient. The patient may not have experienced a toxicity that required permanent discontinuation of study treatment.

- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline in WHO/ECOG PS to >2
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, central nervous system metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention
- The patient still fulfills the eligibility criteria for this study (see Sections 5.1 and 5.2). Patients must also agree to reconsenting to restart durvalumab monotherapy.
- The patient has not received an intervening systemic anticancer therapy after their assigned treatment discontinuation from the parent study

The patient has had a retreatment baseline tumor assessment within a maximum of 28 days prior to restarting durvalumab (Cohort 2). In Cohort 1, patients will continue with durvalumab monotherapy at 1500 mg q4w until disease progression as confirmed by the Investigator following RECIST v1.1.

During the retreatment period in Cohort 2, eligible patients will resume durvalumab dosing at 1500 mg q4w until disease progression as determined by the Investigator following RECIST v1.1.

Patients who the Investigator determines may not continue treatment after PD will be followed up for OS, and are no longer eligible for retreatment. Patients who have discontinued treatment due to toxicity or symptomatic deterioration, or who have commenced subsequent anticancer therapy, will be followed for OS until withdrawal of consent or death. Upon discontinuation of durvalumab, patients may receive any subsequent anticancer therapy at the discretion of the Investigator.

6.1.4 Storage

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

6.2 Measures to minimize bias: randomization and blinding

Not applicable.

6.3 Treatment compliance

Study measures will be taken to ensure to document durvalumab treatment compliance, with dates of administration, dosing information, and any safety events related to medication administration will be captured in the study database. Collection and reporting of durvalumab overdoses are summarized in Section 8.4.3.

The administration of all IPs should be recorded in the appropriate sections of the electronic case report form (eCRF).

Any change from the dosing schedule, dose delays/interruptions, and dose discontinuations should be recorded in eCRF. Dose reductions are not allowed.

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 enrollment until the end of the durvalumab treatment, including the 90-day follow-up period following the last dose of study drug. This applies only for patients receiving durvalumab through 90 days after the last dose, and does not apply to patients from Cohort 2 who are not retreated and patients in Cohort 3. No restrictions apply to patients off treatment who are over 90 days from their last dose of durvalumab.

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 the following tables. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Annex 1).

Table 7 Prohibited concomitant medications

Prohibited medications/class of drug:	Usage:
Cohort 1 and retreated patients in Cohort 2, only	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
Monoclonal antibodies against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy].)
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly or used for premedication prior to the immuno-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).
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor.
Cohorts 1 to 3	
Live attenuated vaccines	Should not be given within 30 days prior to the first dose of IP in the present study and through 90 days after the last dose of IP.
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through 90 days after the last dose of tremelimumab during the study, if the patient received combination therapy of tremelimumab and durvalumab in the parent clinical 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 medications/class of drug:	Usage:
Epidermal growth factor receptor (EGFR) 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 first generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.

AE adverse event; CTL cytotoxic T-lymphocyte-associated; EGFR epidermal growth factor receptor; IP investigational product; TKI tyrosine kinase inhibitor; PD programmed death

Table 8 Supportive medications

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

6.4.1 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 case report form (CRF).

6.4.2 Durvalumab drug-drug interactions

Currently, there is no information to date on drug-drug interactions with durvalumab either preclinically 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 MOA 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.

6.4.3 Rescue medication

As a result of immune-mediated adverse events (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 and controlled by the pharmacist and stored according to the labeled storage conditions, with temperature excursions reported accordingly by the pharmacist. If required for use as a result of an imAE, then the interactive voice response system (IVRS)/interactive web response system (IWRS) will provide to the pharmacists the kit identification number to be allocated to the patient at the time.

6.5 Dose modification

Dose delays are permitted for immuno-oncology therapy (see Dosing Modification and Toxicity Management Guidelines in Annex 1). However, **dose reduction is not permitted**.

6.6 Treatment after the end of the study

AstraZeneca will continue to supply durvalumab after completion of this study, for as long as the patient is receiving clinical benefit in the opinion of the Investigator, or until the participant meets a discontinuation criteria as defined in Section 7.1.

For patients continuing to receive durvalumab treatment following the final DCO and database closure, the procedures defined in the SoA will be limited. It is recommended that the participants continue the scheduled site visits and Investigators monitor the patient's safety laboratory results periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Annex 1), and as described in Section 8.3.14.

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 patient(s) to alternative supply, where possible.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, patient(s) currently receiving treatment with durvalumab may then be transitioned to such a study, and the current study would reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any patient who would be eligible to move to such a study would be given a new informed consent, as applicable.

7. DISCONTINUATION OF TREATMENT AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

An individual patient will not receive any further durvalumab monotherapy if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to remain in the study for safety and OS 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 Dosing Modification and Toxicity Management Guidelines (see Annex 1) or as defined in the local prescribing information for the agent.
- 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
- Disease progression as determined by the Investigator following RECIST v1.1 (refer to Appendix C) and Investigator determination that the patient is no longer benefiting from treatment with IP.

Upon discontinuation of durvalumab, patients may receive any subsequent anticancer therapy at the discretion of the Investigator and will follow the schedule of activities (SoA) detailed for Cohort 3 for safety and survival follow-up (Table 3).

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 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 (Table 3). If the patient 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 a prespecified preferred method of contact, as an alternative), a contact with a relative or treating physician, or information from medical records. The approach

taken should be recorded in the medical records, and the preferred method of contact will be recorded in the patient contact module for this study. A patient 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 have permanently discontinued treatment will enter follow-up (see Section 1.1).

All patients will be followed for survival with contact approximately every 3 months (±2 weeks) beginning 90 days after the last dose of the study drug until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone (or a prespecified preferred method of contact) 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 IVRS/IWRS.

7.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established after 2 consecutive failed contacts. A "contact" is defined as 3 attempts of the preferred method of contact recorded in the patient contact module, and then 3 attempts of the preferred alternative contact designee ±2 weeks from the targeted date (set by the interval shown in the SoAs). At this time, the patient will be flagged as lost to follow-up in the electronic data capture (EDC; 2 consecutive time points with no patient or alternative contact), whereby the Investigator would be requested to review the patient record and update the patient status, if known. Patients who refuse to continue participation in the study, including telephone contact (or a prespecified preferred method of contact, as an alternative), should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

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

- Lost to follow-up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (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 has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

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

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

- All further participation in the study including any further follow up (eg, survival contact telephone calls)

8. STUDY ASSESSMENTS AND PROCEDURES

Data collection and frequency are summarized by each of the 3 cohorts below:

In Cohort 1, all durvalumab treatment cycle assessments will occur every 4 weeks until confirmed PD, unless unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. The most recent imaging results from the parent clinical study may be used for baseline tumor assessments, provided it was obtained within 28 days prior to Day 1, Cycle 1. Tumor assessments throughout all cycles will be performed according to RECIST v1.1, as determined by the Investigator (at least every 12 weeks) until withdrawal of consent, progression, or death. The patients will continue their durvalumab treatment and all cycle assessments every 4 weeks ±3 days unless dosing needs to be held for toxicity reasons (Table 1).

Cohort 2 follow-up prior to retreatment with durvalumab monotherapy follows the SoA for Cohort 3, while patients who undergo retreatment begin the assessment as per the SoA for patients in Cohort 1. During the follow-up of patients before retreatment, they will undergo assessments for vital signs, concomitant medications, laboratory safety and AE/SAE at 30 days (±3 days), 60 days (±7 days), and 90 days (±7 days) since the last dose of study drug. The assessment for concomitant medications will be collected throughout 90 days post durvalumab discontinuation. The survival status for these patients will be collected every 3 months (±2 weeks) beginning 90 days after the last dose of the study drug and tumor assessments will be performed according to the Investigator's standard practice until withdrawal of consent, progression, or death. For those that start retreatment, patients will continue their durvalumab monotherapy and all cycle assessments every 4 weeks ±3 days unless dosing needs to be held for toxicity reasons. While on retreatment, tumor assessments and disease progression will be determined by the Investigator following RECIST v1.1 (Table 2).

Cohort 3 includes safety and survival follow-up only for patients previously treated with durvalumab monotherapy or durvalumab in combination with any other approved or investigational anticancer agents who are no longer receiving durvalumab and are not eligible to receive retreatment. The patients would undergo assessments as per the SoA (Table 3).

The Investigator will obtain informed consent of study procedures at baseline/enrollment from eligible study patients. The Investigator will ensure that data are recorded on the eCRFs. The EDC system will be used for data collection and query handling. The Investigator will ensure the accuracy and completeness of eCRFs, including timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor 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 an enrollment log to record details of all patients screened and to confirm eligibility or record reasons for non-enrollment, 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.

The amount of blood collected from each patient over the duration of the study, including any extra assessments that may be required, will be dependent on the local laboratory requirements. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Safety assessments

Planned time points for all safety assessments are provided in the SoA (see Section 1.1). Any assessments which are relevant to preservation of patient safety, as scheduled in the parent clinical study, will be conducted and followed up as per the SoA for this study.

The safety and tolerability of durvalumab monotherapy up until 90 days after the last dose of study in all patients will be assessed as a primary objective, as described in Section 3. After 90 days of the last dose of durvalumab, Investigators will be instructed to report any AE/SAE according to the standard pharmacovigilance process outside of the remit for this study. Additional safety collection and reporting guidelines for this study will be provided in a Safety Handling Plan.

8.1.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and pregnancy will be taken at the times indicated in the SoA and as clinically indicated (see Section 1.1).

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

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

The laboratory variables to be measured are presented in Table 9 (clinical chemistry) and Table 10 (hematology).

The following laboratory variables will be measured:

Table 9 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 total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome), then 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 is 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 Cockcroft-Gault (using actual body weight).
e. If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

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

ALT alanine aminotransferase; AST aspartate aminotransferase, T3 triiodothyronine; T4 tetraiodothyronine; TSH thyroid-stimulating hormone.

Table 10 Hematology

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

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.

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.

If a patient shows an AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN, refer to Appendix B for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law (HL). These cases should be reported as SAEs if, after evaluation, they meet the criteria for a HL 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), 2 months (±1 week), and 3 months (±1 week) after permanent discontinuation of durvalumab (see the SoAs).

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

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from durvalumab 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.

8.1.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). 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 will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

8.1.3 Vital signs

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

First infusion of the retreatment

On the first infusion day, patients receiving durvalumab monotherapy will be monitored and vital signs collected/recorded in the eCRF prior to, during, and after infusion of durvalumab as presented in the bulleted list below.

Blood pressure and pulse will be collected from patients receiving durvalumab treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

- 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. A 1-hour observation period is recommended after the first infusion of durvalumab.

Subsequent infusions

Blood pressure, pulse, and other vital signs should be measured, collected/recorded in eCRF prior to the start of the 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.

Situations in which vital sign 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.

8.1.4 Early patient review for safety for retreated patients

Among patients starting retreatment in Cohort 2, it is recommended that patients are contacted 2 weeks after receiving the first 3 cycles of durvalumab monotherapy (Cycle 1 Day 14, Cycle 2 Day 14, and Cycle 3 Day 14) of study drug to ensure early identification and management of toxicities.

Review of safety data will be conducted in accordance with AstraZeneca's Pharmacovigilance process.

8.1.5 WHO/ECOG performance status

WHO/ECOG PS will be assessed at the times specified in the assessment schedules (see the SoAs) based on the following:

0. Fully active; able to carry out all usual activities without restrictions

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)

2. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours

3. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4. Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5. Dead

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

8.1.6 Other safety 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 Dosing Modification and Toxicity Management Guidelines (see Annex 1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

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
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - ILD markers (KL-6, SP-D) and β-D-glucan
    - Tumor markers: Particular tumor markers which are related to disease progression.
    - Additional clinical chemistry: C-reactive protein, lactate dehydrogenase

8.2 Efficacy assessments

Efficacy of durvalumab will be assessed in terms of overall response rate (ORR) and DOR in patients who undergo retreatment with durvalumab from Cohort 2 if there is a sufficient sample size of retreated patients, otherwise, only listings will be provided. Disease progression will be determined by the Investigator following RECIST v1.1; only the results of assessments will be entered into the eCRF. The RECIST v1.1 guidelines for Investigator's tumor assessments, including protocol-specific requirements, are summarized in Appendix C.

8.2.1 Parent study assessments

To accurately capture endpoints for this study, the following data elements must be transferred from the parent studies for analysis purposes. Minimal mandatory data elements will be entered into the EDC (eg, patient identification); the remainder will be retained in a separate database. This list may be updated or modified depending on the availability and required elements determined for the study endpoints and will be fully captured in the statistical analysis plan (SAP).

- Parent study name, study code, site name, and site number
- Patient identification or linkage key, including connection to the IVRS of the parent study and transfer of old enrollment code (E-code)
- Date of randomization
- Demographics: including date of birth and sex
- HIV status

- Baseline disease information: date of cancer diagnosis, indication, and stage of disease
- All tumor assessment information, including: dates of scans (including baseline comparison scan), results of each assessment (response, SD, progression)
- Study drug administration, including:
  - Date of first administration of durvalumab and durvalumab combination treatment
  - Date and last dose of durvalumab and durvalumab combination treatment administration
- Ongoing safety events at the end of parent study, including SAEs or adverse events of special interest (AESIs) while on treatment with durvalumab and/or durvalumab combination therapy.
- Ongoing concomitant medications at the end of the parent study
- First subsequent anticancer therapy after durvalumab discontinuation (Cohort 3 only)
- Last date of patient contact
- Contact information (patient, caregiver, physician) as allowed by regulation for each country

8.2.2 Survival assessments

Assessments for survival must be made every 3 months (±2 weeks) beginning 90 days after the last dose of study drug. Survival information may be obtained via telephone contact with the patient or the patient's family (or a prespecified preferred method of contact, as an alternative), or by contact with the patient's current physician. The details of first subsequent anticancer therapy and overall best response after discontinuation of durvalumab treatment will be collected from the Investigator.

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

8.2.3 Clinical endpoint assessments

Data for the following endpoints will be collected and may be evaluated as part of the analysis in the parent clinical studies from which the patients originated. Survival data will be collected in terms of OS in all patients. Efficacy variables will be collected in terms of ORR and DOR for patients in Cohort 2 who start retreatment according to clinical practice (so long as they satisfy eligibility criteria in Section 5.1). These endpoints are defined below:

- OS is defined as the time from date of randomization/enrollment in the parent clinical study until the date of death by any cause (all cohorts).

- ORR is defined as the number (%) of patients with a confirmed response of complete response (CR) or partial response (PR) from the re-initiation of treatment with durvalumab monotherapy (Cohort 2).

- DOR is defined as the time from first documented CR or PR until the time of first documented disease progression or death in the absence of disease progression (Cohort 2).

Tumor assessments, performed by the Investigator according to standard practice, to determine ORR and DOR will be collected for patients in Cohorts 1 and 2 at least every 12 weeks while the patient is receiving treatment. Assessments should be performed as deemed medically appropriate by the Investigator, for the purpose of maintaining the safety and wellbeing of the patient. Investigator reported response will be collected and summarized.

8.3 Collection of adverse events

The Principal Investigator 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 A.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

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

AEs 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). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study drug, then it should be reported as an AE or SAE as applicable. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.14.

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

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 A.

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 SAEs/non-serious AEs/AESIs (as defined in Section 8.3.13 and Appendix A) 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 AE assessment or other assessment/visit as appropriate 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), 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:

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

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 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 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 IP?'

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

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

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider 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 and/or vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, e.g. dose adjustment or drug interruption). Clinically relevant deteriorations in non-mandated parameters should also be reported as AE(s).

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).

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study (DUS), 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 total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix B for further instruction on cases of increases in liver biochemistry and evaluation of HL or Potential Hy's law.

8.3.9 Disease under study

Symptoms of DUS are those which might be expected to occur as a direct result of the patient's primary malignancy. Events which are unequivocally due to DUS 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 DUS and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not

an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

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 study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the DUS, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.

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

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

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.

AESIs for durvalumab 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 MOA and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

AESIs observed with durvalumab include:

- Diarrhea/colitis and intestinal perforation
- Pneumonitis/ILD
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I DM)
- 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, 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 IB. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Annex 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

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, AEs and SAEs will continue to be collected, but only SAEs will be reported. In addition, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dosing Modification and Toxicity Management Guidelines (see Annex 1). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs (which will be reported on paper), will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (and within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs must 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. Collection and reporting of SAEs after the final DCO is described in Section 8.3.14.

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).

The following e-mail address should be used for all other clinical study case reports, and for reporting of SAEs after the final DCO; PPD

As a back-up, in the event of a secure e-mail link is unavailable e.g. due to network issues, the following fax numbers should be used.

Fax numbers:

- PPD

PPD

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

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 study drug

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 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 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.

8.4.2.2 Paternal exposure

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

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

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

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

Use of durvalumab 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 an overdose of durvalumab, 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 study drug 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 an SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Management of durvalumab-related toxicities

The following general guidance should be followed for the 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 continue 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 (see Annex 1).

8.4.4.1 Specific toxicity management and dose modification information – Durvalumab

Comprehensive toxicity management guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune checkpoint inhibitors. 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 anticancer 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 anticancer treatment.

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document entitled, “Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy),” and is maintained within the Site Master File. In addition, a current version of TMGs is available through the following link: https://tmg.azirae.com. Please contact the clinical study associate for information on how to gain access to this website.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune-related. In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 of this protocol and the TMGs). Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines (see Annex 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab combination regimen by the reporting Investigator.

8.5 Pharmacokinetics

Not applicable.

8.6 Pharmacodynamics

Not applicable.

8.7 Genetics

Not applicable.

8.8 Biomarkers

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1 Sample size determination

The number of patients enrolled in this study will be determined by the number of patients who received durvalumab and/or durvalumab in combination with any other approved or investigational anticancer agents in original trials, and who wish to participate and who meet the eligibility criteria. The study will enroll up to 600 patients and the number of patients may increase as new parent studies are included into this long-term safety and efficacy study.

9.2 Populations for analyses

The study population used for statistical analyses in this study is described in Table 11. Full details will be provided in the SAP.

Table 11 Population for statistical analyses

Analysis sets	Description
Full analysis set	Patients enrolled in the study.
Safety analysis set	Patients who received at least 1 dose of durvalumab on this study or enrolled on this study within 90 days of the last dose of durvalumab or durvalumab combination on the respective parent clinical study.
Response evaluable analysis set[a]	Patients who are retreated with durvalumab in Cohort 2.

[a.] To be performed if there is a sufficient sample size of retreated patients; otherwise, only listings will be provided.

9.3 Statistical analyses

There are no statistical methods that will be employed to test a specific hypothesis. 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.

9.3.1 Safety analyses

Safety data will be summarized according to the treatment received for the safety analysis set (all patients who received at least 1 dose of durvalumab either as continuation of study treatment or retreatment in this study, and inclusive of patients who received the last dose of durvalumab or durvalumab combination from the parent clinical study within 90 days of enrollment [all cohorts]). AEs, vital signs, and laboratory safety assessments (clinical chemistry, hematology and thyroid-stimulating hormone [reflex free triiodothyronine or free thyroxine]) will be listed individually by patient. The number of patients experiencing each AE will be summarized by study cohort and CTCAE grade (v5.0) (see Annex 1).

9.3.2 Efficacy analyses

One secondary objective is to assess the efficacy of durvalumab in terms of ORR and DOR for retreated patients. The analysis set for ORR and DOR will be based on the patients who undergo retreatment with durvalumab in Cohort 2. Data will be summarized by tumor type if there is sufficient sample size in each tumor type. ORR will be estimated with a 95% CI using the exact probability method. The median DOR and its 95% CI will be estimated using the Kaplan-Meier method. ORR and DOR will be assessed in the response evaluable analysis set. If there are not sufficient counts of retreated patients to conduct the efficacy analysis, then only listings will be provided. Further detail will be provided in the SAP.

A listing of OS data will be provided for full analysis set.

In addition, survival and tumor efficacy data in this study may be combined with the parent study data for integrated analysis. In the integrated analysis, OS will be described using the Kaplan-Meier method.

Efficacy of durvalumab will be assessed in terms of ORR, DOR, and OS as defined in Section 9.3.3.

9.3.3 Endpoint measures for analyses

9.3.3.1 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, and exposure (ie, durvalumab monotherapy or combination therapy). These will be collected for all patients. “On treatment” will be defined as assessments between date of start dose and 90 days following discontinuation of IP (ie, the last dose of durvalumab in combination

with any other approved or investigational anticancer agents or durvalumab monotherapy). 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. For the change from baseline summaries for vital signs, laboratory data, and physical examinations, the baseline value will be the latest result obtained prior to the start of study treatment, or the date of enrollment if the patient is not to receive study treatment (Cohort 3). The denominator in vital signs data should include only those patients with recorded data.

AEs observed up until 90 days following discontinuation of durvalumab will be used for the reporting of the AE summary tables. Any AEs in this period that occur after a patient has received subsequent anticancer therapy will be flagged. Reporting and collection of late onset toxicity after the 90-day period is described in Section 8.3.2.

More details will be provided in the SAP.

9.3.3.2 Investigator RECIST 1.1-based assessments

Tumor assessments will be conducted by the Investigator using RECIST v1.1 (Appendix C).

9.3.3.3 Objective response rate

ORR is defined as the number (%) of patients with a confirmed response of CR or PR. Data obtained up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who go off treatment without progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR.

9.3.3.4 Duration of response

DOR is defined as the time from the date of first documented response (which is subsequently confirmed) until the first date of progression or death in the absence of disease progression. DOR will not be defined for patients who do not have documented response.

9.3.3.5 Overall survival

OS is defined as the time from date of randomization/enrollment in the parent clinical study until the date of death by any cause.

9.4 Interim analyses

There are 5 interim analyses planned for this study, anticipated to occur annually starting 1 year after the first patient is enrolled. No formal statistical adjustments will be made for these interim looks and additional analyses may be performed for the purpose of better characterizing the safety of these patients with long-term follow-up. The SAP will describe the planned interim analyses in greater detail.

9.4.1 Data monitoring committee

Review of safety data will be conducted in accordance with AstraZeneca's Pharmacovigilance process (Section 8.1).

10. REFERENCES

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

Alexandrov et al 2013
Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Blankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.

Brahmer et al 2012
Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26) :2455-65.

Dunn et al 2004
Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

Fairman et al 2014
Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, et al. Pharmacokinetics of durvalumab, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumors. J Clin Oncol, 2014 ASCO Annual Meeting Abstracts;32(5s): (suppl; abstr 2602).

Forde et al 2014
Forde PM, Kelly RJ, Brahmer JR. New strategies in lung cancer: translating immunotherapy into clinical practice. Clin Cancer Res 2014;20(5):1067-73.

Hirano et al 2005
Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089-96.

Hodi et al 2010
Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanan JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma [published erratum appears in N Engl J Med 2010;363(13):1290]. N Engl J Med 2010;363(8):711-23.

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293-7.

Keir et al 2008
Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon alpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet 2013;52:1017-27.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Okazaki and Honjo 2007
PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19(7) :813-24.

Okudaira et al 2009
Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an antitumor effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

Powles et al 2014
Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515(7528):558-62.

Qin et al 2016
Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. Cancer Med 2016;9:2169–70.

Rizvi et al 2015
Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). J Clin Oncol 2015;33:Abstract 8032.

Santini 2018
Fernando C. Santini. Safety and Efficacy of Re-treating with Immunotherapy after Immune-Related Adverse Events in Patients with NSCLC. Cancer Immunology Research 6(9) September 2018.

Segal et al 2015
Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015;33:Abstract 3011.

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015;3(9):1052-62.

Topalian et al 2012
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Zhang et al 2008
Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Antitumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. Cytotherapy 2008;10(7):711-9.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of theraIt peutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18–28.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Study management

This study will be performed by AstraZeneca's representative with the guidance, input, review and approval of AstraZeneca*,* including development of materials, recruitment, training and management of sites, EDC and data management and analysis.

11.1.1 Data entry/electronic data capture

All data will be collected and entered directly into the EDC system. All participating sites will have access to the data entered regarding the individual site its own enrolled patients. All sites will be fully trained on using the on-line data capture system, including eCRF completion guidelines and help files. Sites will be responsible for entering extracted patient data into a secure internet-based EDC registry database via the eCRF. Investigators and site personnel will be able to access their account with a username and password. All eCRFs should be completed by designated, trained personnel or the study coordinator, as appropriate. In most cases, the eCRF should be reviewed, electronically signed, and dated by the Principal Investigator. All changes or corrections to eCRFs are documented in an audit trail and an adequate explanation is required.

11.1.2 Source documents

In most cases, the source documents are contained in the patient's medical record and data collected on the CRFs must match the data in the medical records. In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the Investigator's site and clearly identifying those data that will be recorded in the CRF, and for which the CRF will stand as the source document. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations.

11.1.3 File retention and archiving

To enable evaluations and/or audits from regulatory authorities or AstraZeneca, the Investigator agrees to keep records, including the identity of all participating patients, all original signed ICFs, copies of all CRFs, SAE forms, source documents and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the Investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the registry and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 5 years after the completing participation in the study. Documents to be archived include the patient enrollment log and the signed ICF. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify AstraZeneca.

11.1.4 Quality assurance and monitoring

A study monitoring plan, including for-cause monitoring, that is appropriate for the study design will be developed and implemented.

During the site initiation visit (performed remotely with the exception of sites in Japan), the monitor will provide training on the conduct of the study to the Investigator, co-Investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored. Remote site monitoring will be performed by AstraZeneca's representative to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. The monitor will perform source data verification by review of original patient records.

The monitor will close out each site (performed remotely with the exception of sites in Japan) after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures and frequency of monitoring visits will be described in a monitoring plan. Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of AstraZeneca's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

11.1.5 Data management

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

High data quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

11.1.6 Changes to the protocol

Changes to the protocol will be documented in written protocol amendments. Major (ie, substantial, significant) amendments will usually require submission to the relevant IRB/IECs for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by at each participating site and will be submitted to the relevant IRB/IEC or regulatory authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to continued participation in the study.

11.1.7 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Guiding principles

To ensure the quality and integrity of research, this study will be conducted under the guidelines good pharmacoepidemiology practices issued by the International Society for Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and any applicable national guidelines.

The study will be conducted in compliance with the US FDA Title 21 Code of Federal Regulations Part 50 – Protection of Human Patients and/or Part 56 –IRB; the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) E6(R2) guidelines (15 December 2016) as they apply to non-interventional studies; the Declaration of Helsinki and its amendments; and the Health Insurance Portability and Accountability Act of 1996.

12.2 Required documents

Prior to the enrollment of any patients in the study, the following documents must be provided by the site to the Sponsor (or their designee):

- Copy of the IRB/IEC approval letter for the protocol and informed consent (all written information provided to the patient must be approved by the IRB/IEC)
- Copy of the IRB/IEC-approved informed consent document to be used
- Copy of the protocol sign-off page signed by the Investigator

- Fully executed site agreement

12.3 Financial disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.4 Patient information and informed consent

An ICF must be signed by the patient (or the patient's legally authorized representative) before his or her participation in the study. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICFs, the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

12.5 Patient confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier upon study enrollment. This patient identifier will be used in place of patient name for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database. All parties will ensure protection of patient personal data and will not include patient names on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the registry countries, patients will be informed about data handling procedures and asked for their consent. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality according to the Regulation (EU) 2016/679 (of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)), and refer to the European Commission "Standard Contractual Clauses" with respect to data transfers to Non-EU countries where appropriate.

The database will be housed at the AstraZeneca's representative in a physically and logically secure computer system maintained by AstraZeneca's representative in accordance with a written security policy. The system meets approved established standards for the security of

health information and is validated. The system also meets the standards of the ICH GCP E6 guideline (revision 2) regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

12.6 Independent ethics committee (IEC)/institutional review board (IRB)

Consistent with local regulations and prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (eg, ICF) to the responsible IRB/IEC for its review. Patient enrollment will not start at any site before the Client has obtained written confirmation of a favorable opinion/approval from the relevant central or local IRB/IEC. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given that clearly identifies the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the study in accordance with local regulations and requirements. It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, and ICF, and other relevant documents, if applicable, from their local IRB/IEC and provide documentation of approval to AstraZeneca's representative. All correspondence with the IRB/IEC should be retained in the Investigator file.

Should the study be terminated early for any unanticipated reason, the Investigator will be responsible for informing the IRB/IEC of the early termination.