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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)

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Study Statistician (IQVIA)

PPD

Date

Study Statistician (AZ)

PPD

Date

Global Product Statistician (AZ)

PPD

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
AESI	AE of Special Interest
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CR	Complete Response
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DCO	data cut-off
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
GI	Gastro-Intestinal
HbsAg	Hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus

Abbreviation or special term	Explanation
IP	Investigational Product
IxRS	Interactive Voice/Web Response System
KM	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
NED	No Evidence of Disease
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Physical Examination
PR	Partial Response
RDI	Relative Dose Intensity
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Stable Disease
Sd	Standard Deviation
SDTM	Study Data Tabulation Model
SoAs	Schedule of Activities
TTR	Time To Response

AMENDMENT HISTORY

Date	Brief description of change
04 Nov 2022	• The characteristics at the baseline have been clarified. • Durvalumab exposure actual treatment duration was updated to better clarify how the variable is derived, adding an additional step. • In the "Violations and deviations" section, a text was added to clarify that despite starting date comes from parent studies, the analyzed data only come from WAVE study. Additionally, the protocol deviations process was updated according to the new standards used to capture subject and site important protocol deviations using the Clinical Trial Management System (CTMS) data. Protocol deviations (2 and 3) wording was improved. • Adverse events definition was updated, clarifying the period time. • In the "Overall Survival" (OS) section, for the single-arm parent studies the calculation wording of OS was improved.

1 STUDY DETAILS

1.1 Study objectives

The study objectives will be assessed among 3 cohorts defined according to treatment status, these cohorts are described in Section 1.2.

The objectives of this study as well as corresponding endpoints are as follows:

Table 1. Study objectives and endpoints

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)	**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/date of first dose [a] in the parent clinical study until the date of death by any cause

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

[a] For randomized parent studies, the randomization date will be used in the calculation of OS. For single-arm parent studies, the date of first dose will be used in the calculation of OS.

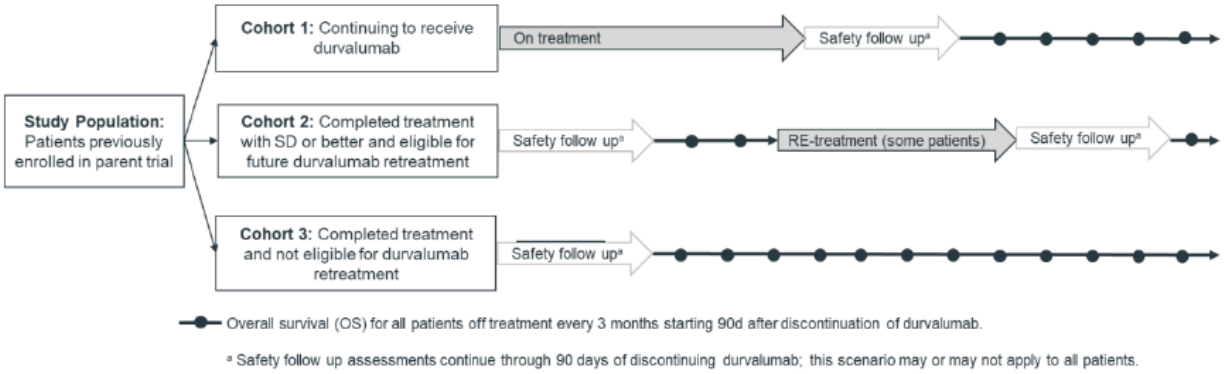
1.2 Study design

This is a multi-center, 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 general study design for this study is summarized in Figure 1. 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 progressive disease (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.

Figure 1: Study design



1.3 Number of subjects

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 in any parent clinical study at any global site. The study will initially enroll approximately 600 patients.

2 ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full Analysis Set (FAS)

The FAS will include all patients enrolled in the study, regardless of the treatment received. OS analysis will be performed on the FAS. In addition, demographic and patient characteristics will be summarized amongst the FAS population.

2.1.2 Response evaluable analysis set

The response evaluable analysis set will consist of patients who are retreated with durvalumab in Cohort 2. This will be the analysis set for ORR and DOR.

2.1.3 Safety Analysis Set (SAS)

The SAS will consist of 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. The primary objective analysis will be assessed in the SAS.

2.2 Violations and deviations

The following general categories will be considered important protocol deviations; such protocol deviations will be reviewed and categorized by the medical team, and the Epidemiology team based on data from the Clinical Trial Management System (CTMS) data, and finally confirmed with the site management team. Subject and site level protocol deviations are collected from the CTMS. Subject-level protocol deviations will be listed and discussed in the clinical study report (CSR) as appropriate:

- **Deviation 1:** Patients who deviate from key entry criteria per the Clinical Study Protocol (CSP). Key entry criteria are the following (please refer to the CSP for more details):
  - 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.
  - 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).

    [Additional inclusion criteria for patients entering Cohort 1]
  - 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]
  - Adequate organ function (see detailed definition in the CSP)
  - Evidence of postmenopausal status or negative urinary or serum pregnancy test for female premenopausal patients.
  - World Health Organization / Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2 at enrolment

    [Additional inclusion criteria for retreatment patients in Cohort 2]
  - Received durvalumab in a parent clinical study that is approved to enroll into this study
  - Completed the defined treatment duration with durvalumab monotherapy or durvalumab combination therapy in the parent clinical study (see more details in the CSP)
  - 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 or magnetic resonance imaging), and that is suitable for accurate repeated measurements as per RECIST v1.1 guidelines.

In addition, patients are considered as with deviation if any of the exclusion criteria are met:

- 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]

- 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).
- 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.
- With 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
- 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
- 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.
- History of allogenic organ transplantation
- 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 interstitial lung disease, serious chronic Gastro Intestinal (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.

- Documented active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination(PE) 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
- 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
- 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.
- 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 (NED).
- 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
- Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients

- **Deviation 2**: Baseline RECIST scan date is greater than 28 days before the date of starting Cycle 1 of retreatment for Cohort 2, during the WAVE study period.
- **Deviation 3**: No baseline RECIST 1.1 assessment on or before the date of starting Cycle 1 of retreatment (Cohort 2), during the WAVE study period.
- **Deviation 4**: Received prohibited concomitant medications (including other anticancer agents). Please refer to the CSP Section 6.4 for those medications that are detailed as being ‘excluded’ from permitted use during the study. This will be used as a guiding principle for the medical data reviewer of all medications prior to database lock.

All the violations and deviations considered only come from WAVE without taking into account data from parent studies. The important subject-level protocol deviations will be listed and summarized by treatment group (study cohort) in the main part of the CSR. All

participants with important protocol deviations will be listed by center, as an appendix. Site level protocol deviations are collected from the CTMS. The important site level protocol deviations will be listed, as an appendix of the CSR.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy variables

3.1.1 Objective response rate (ORR)

ORR is defined as the percentage of patients with a confirmed investigator-assessed response of complete response (CR) or partial response (PR) from the date of re-initiation of treatment with durvalumab monotherapy. ORR will be assessed in the response evaluable analysis set (patients who are retreated with durvalumab in Cohort 2).

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit. Data obtained up until progression, or last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Patients who discontinue treatment without progression, receive a subsequent anticancer therapy (note that for this analysis radiotherapy is not considered a subsequent anticancer therapy) and then respond will not be included as responders in the ORR (i.e., both visits contributing to a response must be prior to subsequent therapy for the patient to be considered as a responder).

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR- Not evaluable (NE), CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

CR and PR can be assessed using the following Electronic Case Report Form (eCRF) modules:

- **Overall Exam Assessment (OVERALL):**

  Overall Assessment of Target and Non-Target Lesions

  - Assess Target Lesions as a Whole (CR; PR; PD; Stable Disease [SD]/ Not Evaluable)
  - Assess Non-Target Lesions as a Whole (CR/PD/ Non-CR/Non-PD; Not Evaluable)
  - Overall Tumor Response Assessment (CR; PR; PD; SD; NED); Not Evaluable
  - Latest Scan Date for the Timepoint
  - Progression Scan Date

- **Tumor Evaluation: New Lesions and Investigator Assessment of Response (RECIST2)**

  Overall visit response

  - RECIST response (CR; PR; PD; SD(Non-CR/Non-PD); Not evaluable)
  - Investigator's opinion agrees with RECIST response (yes/no)
  - Investigator's opinion of patient status (Responding; Stable; Progressing)

3.1.2 Duration of response (DOR)

DOR will be assessed in the response evaluable analysis set (patients who are retreated with durvalumab in Cohort 2). To be consistent with RECIST 1.1 guidelines, the starting point for DOR is the first time at which the visit response is PR or CR.

DOR will be defined as the time from the date of first documented (which is subsequently confirmed) CR or PR until date of documented progression or death in the absence of disease progression (i.e. date of documented disease progression or death in the absence of disease progression, or censoring – date of first response + 1). DOR will be expressed in months.

The time of the initial response will be defined as the latest of the dates contributing towards the first visit that was CR or PR that was subsequently confirmed.

If a patient does not progress or die following a response, then their DOR analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient progresses or dies immediately after two or more consecutive missed visits, the patient will be censored at the time of the latest evaluable RECIST 1.1 assessment prior to the two missed visits. The minimum elapsed time from the previous RECIST 1.1 assessment defined as two missed visits is calculated as 2 * (the protocolled time between scans + the protocol allowed visit window): 2 * 12 = 24 weeks. Note: NE visit is not considered as missed visit.

Same eCRF modules described in Section 3.1.1 will be used to retrieve the date of first documented CR or PR, the date of the latest evaluable RECIST 1.1 assessment, as well as the date of progression (if any). The date of death will be retrieved from "DEATH" module of the e-CRF.

3.1.2.1 Time to response (TTR)

TTR will be used in support to the DOR endpoint and will be assessed in the response evaluable analysis set (patients who are retreated with durvalumab in Cohort 2).

TTR is defined as the time from the date of first retreatment dose until the date of first documented response (CR or PR), which is subsequently confirmed.

TTR will be calculated as follows: date of documented response (CR or PR) – date of first retreatment dose +1. The date of first documented response will coincide with that used for the DOR endpoint. TTR will be expressed in months.

TTR will not be defined for those patients who do not have a documented response (CR/PR) that is subsequently confirmed.

3.1.3 Overall survival (OS)

OS will be assessed in the FAS.

OS is defined as the time from the date of randomization/date of first dose in the parent clinical study until death due to any cause. For randomized parent studies, the randomization date will be used in the calculation of OS. For single-arm parent studies (durvalumab monotherapy) and combination parent studies, the date of first dose (durvalumab or combination treatment) will be used in the calculation of OS.

Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (Date subject confirmed to be alive (SUR_DAT), recorded within the SURVIVE module of the eCRF).

Patient contact calls to determine survival will be made within 7 days following the date of DCO for the OS analysis, and if patients are confirmed to be alive or if the death date is after the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and “lost to follow-up” patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient’s notes, hospital records, contacting the patient’s general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

Note that when a survival sweep is performed the SURVIVE module should be completed for every patient.

Note, for any OS analysis performed prior to the final OS analysis, in the absence of survival calls being made, it may be necessary to use all relevant case report forms (CRF) fields to determine the last recorded date on which the patient was known to be alive for those patients still on treatment (since the SURVIVE module is only completed for patients off treatment if a survival sweep is not performed). The last date for each individual patient is defined as the latest among the following dates recorded on the CRFs:

- AE start and stop dates
- Admission and discharge dates of hospitalization

- Study treatment date
- End of treatment date
- Laboratory test dates
- Date of vital signs
- Disease assessment dates on RECIST CRF
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF
- End of study date

Note that for the final analysis, the SUR_DAT date defined earlier in this section should be used as censoring date for every patient. For the final analysis, the list of above CRF dates should not be used to determine the censoring date.

If a patient is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive +1 from the database and the death date using the available information provided and the rules for imputing AE start dates (section 3.2.1).

If there is evidence of death but the date is entirely missing, it will be treated as missing, i.e., censored at the last known alive date +1.

Survival status will be assessed using "SURVIVE" module of the eCRF, where the following information will be collected:

- Subject status:
  - Dead
  - Alive
  - Lost to follow-up
  - Unknown
- Date subject confirmed to be alive
- Contact date

If death occurs, the following details on death will be recorded in "DEATH" module of the eCRF:

- Date of death
- Autopsy performed (yes/no)
- Cause of death (primary and secondary)

3.2 Safety variables

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, and exposure (i.e., durvalumab monotherapy or combination therapy). These will be collected for all patients. The following safety variables will be assessed:

- 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 (e.g., heart, liver, kidney, lungs, central nervous system)
- 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

3.2.1 Adverse events

"On treatment" will be defined as assessments between date of start dose and 90 days following discontinuation of Investigational Product (IP) (i.e., 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. The Medical Dictionary for Regulatory Activities (MedDRA) (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (using the CTCAE version 5).

AEs will be assessed using the following eCRF modules:

Adverse Events (AE)

- Adverse Event (y/n)
- AE medical code
- Date AE started
- Date AE stopped
- Serious AE (y/n)
- Action taken with durvalumab (Dose not changed; Drug Interrupted; Drug permanently discontinued; Not applicable)
- AE outcome (Recovered/resolved; Recovering/resolving; Recovered/resolved with; sequelae, Not recovered/not resolved; Fatal)
- Reasonable Possibility AE Caused by durvalumab (y/n)

- CTCAE Grade (Mild AE; Moderate AE; Severe AE; Life-threatening or disabling AE; Death related to AE)
- Dose Limiting Toxicity (y/n)
- Immune-mediated AE (y/n)
- Infusion Reaction AE (y/n)

Serious Adverse Event Report (SERAE)

- AE medical code
- Date AE met criteria for serious AE
- Date investigator aware of serious AE
- AE is serious due to (medical code)
- Death (y/n)
- Inpatient hospitalization or prolongation of existing inpatient hospitalization (y/n)
- Congenital anomaly or birth defect (y/n)
- Life-threatening (y/n)
- Persistent or significant disability/incapacity (y/n)
- Important medical event (y/n)
- Date of hospitalization
- Date of discharge
- SAE caused by other medication (y/n)
- SAE caused by study procedure(s) (y/n)
- Description of AE

AE of Special Interest (AESI)

- AE medical code
- AE SI (full list of AESI is reported in the Appendix section)
- Current Bowel Movements CTCAE Grade (Mild AE, Moderate AE, Severe AE, Life-threatening or Disabling AE, Death Related to AE)
- Body Surface Area Covered (<10%, 10-30%, >30%)
- Anatomical Site [up to 6 sites] (Lower Leg, Other, Abdominal Cavity, Inguinal Region, Back, Neck, Face, Chest, Arm, Foot, Hand, Buttock, Scalp)
- Signs and Symptoms (Abdominal Pain, Paresthesia, Loss of Deep Tendon Reflexes, Rapid Progressive Weakness, Respiratory Insufficiency, etc.)

- Specialist Consulted or Additional Inv (y/n)
- Services and Result Description
- Any Additional Laboratory Investigations (y/n)
- Any Significant Medic or Surgical History (y/n)
- Event Triggered by Disease Progression (y/n)
- Event Attributed to Disease/Metastasis (y/n)
- Anatomic Location
- Potential Alternate Etiology (y/n)

In addition to the above modules, AEs can be detected based on examinations and tests (physical examinations, vital signs and laboratory tests; these are described in Sections 3.2.2, 3.2.3, and 3.2.4 respectively). Situations in which examinations and tests results should be reported as AEs are described in Section 8.3.7 of the CSP.

AE imputation rules

For missing AE start dates, the following imputation rules will be applied

- If the day is missing, the 1st day of the month will be used unless month is the same as month of the first dose of study drug then the first dose date will be used.
- If the day and month are missing, 1st January will be used unless year is the same as first dose date then the first dose date will be used.
- Completely missing-impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st January of the same year as the end date.

For missing AE end dates, the following imputation rules will be applied:

- If the day is missing, the last day of the month will be used unless month is the same as month of study discontinuation, then impute as study discontinuation date.
- If the day and month is missing, the 31st December will be used unless year is the same as year of study discontinuation then impute study discontinuation date.

3.2.2 Physical examinations

Physical examinations (PE) will be performed according to the assessment schedules (see the Schedule of Activities (SoAs) in CSP). Full PE 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 PE are to be utilized by the Investigator on the basis of clinical observations and symptomatology.

As reported in the CSP, any new or aggravated clinically relevant abnormal medical finding at a PE as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Sections 8.3.9 and 8.3.10 of CSP.

Height will be retrieved from parent clinical studies. PE are assessed under "Physical Examination (PE)" eCRF module, the following information are reported:

- Was the PE performed? (y/n)
- What was the PE date?

3.2.3 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. Situations in which vital sign results should be reported as AEs are described in Section 8.3.7 for the CSP.

Vital signs are assessed under "Vital Signs Pre-Infusion (VS)", "Vital Signs During Infusion (VS1)", and "Vital Signs Post Infusion (VS2)" eCRF modules. The following information are reported in these modules:

- Date of assessment
- Test name (Temperature, Weight, Systolic blood pressure, Diastolic blood pressure, Pulse Rate, Respiratory rate)
- Assessment result and unit

3.2.4 Laboratory safety assessments

Laboratory safety assessments consist of blood and urine samples for determination of clinical chemistry, hematology, TSH, and pregnancy. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.7 of the CSP.

Laboratory safety assessments are assessed under the following eCRF modules:

- Non-central Laboratory Test Results (LB) - Clinical Chemistry:
  - lab specimen collection date
  - name of the laboratory used
  - test results (including but not limited to: Blood Urea Nitrogen, Bicarbonate, Amylase, Chloride, Lipase, etc.)
- Non-central Laboratory Test Results (LB2) – Hematology

  - lab specimen collection date
  - name of the laboratory used
  - test results (including but not limited to: Hemoglobin, Platelets, Neutrophils Absolute Count, Lymphocytes %/Ratio, Neutrophils %/Ratio, Lymphocytes, Absolute Count, White Blood Cells, etc.)
- Non-central Laboratory Test Results (LB3) - Thyroid Function Tests
  - lab specimen collection date
  - name of the laboratory used
  - test results (T3, Free; T4, Free; Thyroid Stimulating Hormone; Time field for Lab CFs)
- Pregnancy Test (PREG)
  - Sampling date
  - Pregnancy test results (positive/negative)
- Pregnancy Report (PREGREP)
  - Last menstrual period
  - Expected delivery date
  - Subject using hormonal contraception (oral or implant) or an IUD at time of conception (y/n)
  - Previous pregnancies details:
    - Overall number
    - Number of normal deliveries
    - Number of spontaneous miscarriages
    - Number of other previous pregnancies
  - Relevant pregnancy risk factor (smoking, alcohol, etc)
  - Relevant family history

3.2.5 Durvalumab exposure

Exposure (i.e. duration of treatment) will be defined as follows:

Total exposure of study treatment:

Total (or intended) exposure= min (last dose date where dose > 0 [units] + 27 (where 27 is the number of days between dosing – 1), date of death, date of DCO) – first dose date +1.

Total (or intended) exposure will be expressed in months.

Actual exposure of study treatment

Actual exposure = intended exposure – total duration of dose interruptions, where intended exposure will be calculated as above and a dose interruption is defined as any length of time where the patient has not taken any of the planned daily dose; hence, the total duration of dose interruptions in days is calculated as the cumulated lengths between the interruption dose date and the resuming dose day + 1.

Actual exposure and total duration of dose interruptions will be expressed in months. The actual exposure calculation will make no adjustment for any dose reductions that may have occurred.

3.2.6 Relative Dose Intensity (RDI)

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. RDI will be defined as follows:

RDI = 100% * d/D, where:

- d is the actual cumulative dose delivered up to the actual last day of dosing. Actual dose (in mg) is reported in "Exposure - durvalumab (EX)" eCRF form as "**Study drug dose per administration**" Actual cumulative dose will be calculated by summing all doses for each day, across all treatment cycles.
- D is the intended cumulative dose up to and including the actual last day of dosing. D is the total dose that would be delivered, if there were no modification to dose or schedule. Intended dose (in mg) is reported in "Exposure - durvalumab (EX)" eCRF form as "**Planned study drug dose per administration**".

  The total number of planned doses will be calculated as the following: round ((last dosed date – first dosed date +28)/28)

  When accounting for the calculation of intended cumulative dose 3 days will be added to the date of last dose to reflect the protocol allowed window for dosing.

4 OTHER ASSESSMENTS

In addition to primary and secondary variables that will be collected under this study, other key information will be collected using either directly into Electronic Data Capture (EDC) system or transferred from clinical parent studies (Table 2).

Table 2. Parent study assessments

Study variables	Data source
• Parent study protocol number, study e-CODE • Vital signs (weight, temperature, blood pressure, pulse rate, respiratory rate) • Date and last dose of durvalumab and durvalumab combination treatment administration • Ongoing safety events at the end of parent study	EDC entry

Study variables	Data source
• Ongoing concomitant medications at the end of the parent study • Subsequent anticancer therapy	
• Patient identification or linkage key, including connection to the Interactive Voice/Web Response System (IxRS) and EDC and transfer of old enrolment code (E-code) • Demographics: date of birth	New IxRS system
• Date of randomization from parent study (for randomized parent studies) • Date of first administration of durvalumab and durvalumab combination treatment (for non-randomized parent studies). • Height	Transfer of data from clinical parent study (SDTM data)
• Contact information: (patient, caregiver, physician) as allowed by regulation for each country	Patient contact module

In addition to parent study assessments, the following data will be collected and described:

- Disposition of Subjects, assessed at study termination, under "disposition (DS)" eCRF module. The following information will be collected:
  - Discontinuation date
  - Subject's status at discontinuation: Death, Lost to follow-up, Screen failure, Withdrawal by subject, Withdrawal by parent/guardian, Development of study-specific withdrawal criteria (to be specified), Other (to be specified), Adverse Event, and Pregnancy
- Patient demographic and Other Baseline Characteristics assessed at baseline visit:
  - Age
  - Sex
  - Race
  - Ethnicity
  - Country
- **[Only for Cohort 1 and Cohort 2]** Exposure to durvalumab assessed under "Exposure - durvalumab (EX)" eCRF module. The following information will be collected:
  - Start date and time
  - End date and times
  - Dose per administration

  - Dose units
  - Action taken (dose not changed, drug interrupted, Drug permanently discontinued)
  - Main reason for action taken (AE, other (to be specified)
  - Treatment cycle delayed (y/n)
  - Reason for treatment cycle delayed (Delayed hematological recovery, Adverse event, Disease symptoms, Logistic, Subject decision, Lab abnormality not reported as an AE, Other (to be specified))
- Concomitant and other treatments assessed under "Prior and Concomitant Medications (CM)" eCRF module. The following information will be collected:
  - Medication verbatim name
  - AE number for which medication taken
  - Medical history condition(s) number for which medication taken
  - Medication route of administration
  - Total daily dose
  - Dose unit
  - Medication dosing frequency
  - Treatment start date
  - Treatment stop date
  - Ongoing treatment (y/n)
  - Indication
- Concomitant Procedures assessed under "Concomitant Procedures (CONPRO)" eCRF module:
  - Procedure text
  - Procedure start date
  - Procedure reason
- Current and Concurrent cancer therapy assessed under "Current Cancer Therapy (CAPRX1)" and "Cancer Therapy - Post withdrawal of IP (CAPRX2)" eCRF modules respectively. The following information will be collected:
  - Cancer therapy agent name
  - Route of administration
  - Number of cycles
  - Therapy class (Immunotherapy, Hormonal Therapy, Cytotoxic chemotherapy, Systemic Therapy, Targeted Therapy, Antiangiogenic Therapy, Taxane chemotherapy, Radiopharmaceuticals, Platinum Chemotherapy, PARP Inhibitor, Biologic therapy, Experimental therapy, Other)

  - Start and stop dates
  - Best response (CR, PR, SD, Progression, Non-evaluable, Not applicable)
  - Treatment status (line of therapy, adjuvant/non-adjuvant, palliative, maintenance, Definitive, Not applicable)
- Radiotherapy:
  - Timing against withdrawal of IP: previous, current, post
  - Radiotherapy site or region
  - Radiotherapy start and stop dates
  - Dose per fraction (Gy)
  - Number of fraction doses (total)
  - Treatment status (Adjuvant, Neo-adjuvant, Palliative, Definitive, Not applicable)

5 ANALYSIS METHODS

5.1 General principles

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation(Sd), median, upper and lower quartiles minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding analysis set.
- For continuous data, the mean and median will be rounded to 1 additional decimal place compared to the original data. The Sd will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data.
- For categorical data, percentages will be rounded to 1 decimal place.
- There are no statistical methods that will be employed to test a specific hypothesis.
- SAS® version 9.4 or later will be used for all analyses.

For efficacy endpoints (only considered for Cohort 2), the last observed measurement prior to retreatment will be considered the baseline measurement.

For safety endpoints (where all cohorts are considered) the last observation before the first dose of study treatment will be considered the baseline measurement. For assessments on the day of first dose/randomization date where time is not captured, a nominal pre-dose indicator will serve as sufficient evidence that the assessment occurred prior to first dose. Assessments

on the day of the first dose where neither time nor a nominal pre-dose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as (post-baseline value - baseline value) / baseline value x 100.

5.2 Analysis methods

5.2.1 Overall survival (OS)

A listing of the OS data will be provided in the FAS, for each cohort. This listing will contain the following information: patient identifier, cohort, date of randomization, date of first dose, survival status (death or no death), date of death or date last known to be alive; days from randomization to death with a flag indicating if the value is censored, cause of death, autopsy performed (yes/no), and death related to disease under investigation (yes/no).

Note: In addition to listings, survival and tumor efficacy data may be combined with the parent study data for an integrated analysis on a “as needed” basis. The Kaplan Meier (KM) approach, Log-Rank test, Cox Proportional Hazards model, etc., will be used if OS analyses are requested for a parent study.

5.2.2 Objective response rate (ORR)

ORR will be assessed in the response evaluable analysis set (patients who undergo retreatment with durvalumab in Cohort 2). The ORR will be based on the site investigator RECIST 1.1 data and using all tumor assessments, regardless of whether they were scheduled or not. Descriptive statistics will be performed on the ORR and the following data will be presented: the number of observations, 95% (Confidence Interval) CIs estimated using the exact probability method. Data will be summarized by tumor type if there is sufficient sample size in each tumor type.

In case there is no sufficient sample size in retreated Cohort 2, the corresponding tables will be purely informative and only listings will be used for the assessment of this objective.

5.2.3 Duration of response (DOR)

DOR will be assessed in the response evaluable analysis set (patients who undergo retreatment with durvalumab in Cohort 2). KM plots of DOR based on the investigator assessment of RECIST will be presented. Median DOR (with associated 95% CI) will be calculated from the KM curve and summarized. Only patients who have a confirmed response will be included in this summary table. In addition, swimmer plots that show the profile of each patient who responds will also be produced.

Results will be summarized by tumor type if there is sufficient sample size in each tumor type.

In case there is no sufficient sample size in retreated Cohort 2, the corresponding tables and graphs will be purely informative and only listings will be used for the assessment of this objective.

5.2.4 Time to response (TTR)

Descriptive data will be provided for TTR in responding patients. In addition, KM plots of TTR will be produced where patients without a response will be censored at their last RECIST assessment. Median TTR (with associated 95% CI) will be calculated from the KM curve and summarized. Results will be summarized by tumor type if there is sufficient sample size in each tumor type.

In case there is no sufficient sample size in retreated Cohort 2, the corresponding tables and graphs will be purely informative and only listings will be used for the assessment of this objective.

5.2.5 Safety

Safety data will be summarized according to the treatment received for the SAS (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, dose at time of AE, 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). Each patient will be represented with the maximum reported CTCAE grade for each system organ class / preferred term. Number (%) of patients with AEs, will be sorted by international System Organ Classes (SOC) order and alphabetical PT and then maximum grade. Event rate per 100 patient-years will also be calculated for each AE.

Individual laboratory measurements and vital signs data will be presented in listing format.

For laboratory measurements, the following data will be listed:

- Subject identifier and cohort
- Age/sex/race
- Analysis visit
- Category of lab test
- Lab test examination name

- Result/finding
- Units
- Reference range indicator

For vital signs, the following data will be listed:

- Subject identifier and cohort
- Vital signs test name
- Analysis visit
- Result
- Unit
- Result clinically significant (yes/no)
- Reference ranges (upper and lower limits).

For vital signs, the following reference ranges and units will be used:

- For Diastolic blood pressure: Range = 40-110, Unit = mmHg
- For Heart rate/Pulse: Range = 50-120, Unit = beats/min
- For Respiratory rate: Range = 12-35, Unit = breaths/min
- For Systolic blood pressure: Range = 60-160, Unit = mmHg
- For Temperature: Range = 35-39, Unit = °C / Range = 95-102.3, Unit = °F
- For Weight: Range = 30-140, Unit = Kg / Range = 66-308, Unit = LB
- Oxygen saturation: 95-100%, unit-free.

Note: Based on an "as needed" request from parent clinical studies, safety data from WAVE may be combined with parent study data in order to update safety summaries.

5.2.6 Demographics and baseline characteristics

The following will be summarized for all patients in the FAS by treatment group (cohort 1, cohort 2, cohort 3). Continuous variables will be summarized by the number of observations, mean, Sd, median, upper and lower quartiles minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category:

- Patient disposition (including screening failures) and inclusion in analysis sets
- Demographics (age, age group [<50, ≥ 50 - < 65, ≥ 65 - < 75 and ≥ 75 years], sex, race, ethnicity, and country)
- Subject recruitment by clinical parent study (for each parent study; the study design, code, total number of patients in parent study and in WAVE study)
- Patient recruitment by country and by center

- Patient characteristics at baseline (height, weight, BMI)
- Disease characteristics at baseline (ECOG performance status, primary tumor location)
- Extent of disease at baseline: locally advanced/metastatic, site of disease

5.2.7 Concomitant and other treatments, and concomitant procedures

All concomitant and other treatment, and concomitant procedures data will be listed in the FAS, using Anatomical Therapeutic Chemical (ATC) classification and ATC coding. Missing coding terms will be listed and summarized as "Uncoded".

5.2.8 Exposure

Exposure to durvalumab treatment will be summarized for the SAS, only in Cohort 1 and Cohort 2 (retreatment). Mean, Sd, median and ranges will be produced for the following summaries:

- Summary of duration of exposure of study treatment (total treatment duration (months), actual treatment duration (months)),
- Summary of delays in study treatment cycles as well as reasons of delays,
- Summary of dose intensity:
  - RDI defined as the percentage of the actual dose delivered relative to the intended dose through treatment discontinuation
  - Percent intended dose defined as the percentage of the actual dose delivered relative to the intended dose through progression.
- Cumulative exposure over time.

5.2.9 Subsequent therapy

Cancer therapy post-discontinuation of durvalumab will be summarized in the FAS. For each cohort, the number (%) of patients will be summarized by tumor location and anticancer regimen.

6 INTERIM ANALYSES

No interim analysis has been planned for this study.

7 CHANGES OF ANALYSIS FROM PROTOCOL

There are no changes to the analyses specified in the version of protocol that this SAP is based on.

8 REFERENCES

There are no references listed in this document.

9 APPENDIX

9.1 List of AESI

The following AESI are listed in the current version of eCRF:

- Potential Endocrinopathies
- Potential Hepatic Events
- Potential Nephritis or Renal Dysfunction
- Potential Neuropathy/Neuro-muscular Toxicity
- Potential Pancreatitis
- Potential Rash or Dermatitis
- Potential GI Toxicity
- Potential Myositis/Polymyositis
- Potential Myocarditis
- Other (to be specified in EDC)

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