STATISTICAL ANALYSIS PLAN	
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A Phase II, Multicentre, Open-Label Study to Assess the Efficacy and Safety of Olaparib Monotherapy and Olaparib Plus Durvalumab Combination as Neoadjuvant Therapy in Patients with *BRCA* Mutations and Early Stage HER2-Negative Breast Cancer (OlympiaN)

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LIST OF ABBREVIATIONS

List abbreviations and definitions of specialized or unusual terms, measurements, or units.

Abbreviation or Specialized Term	Definition
CCI	
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American joint committee on cancer
ALP	Alkaline phospahtase
ALT	Alanine aminotransferase
CCI	
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
cPD	Clinical progressive disease
CRF	Case report form
CRO	Contract research organisation
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CCI	
DBL	Database lock
DCIS	Ductal Carcinoma In Situ
DCO	Data cut-off
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
FAS	Full analysis set
FDA	Food and drug administration
FSH	Follicle-stimulating hormone
HIV	Human immunodeficiency virus
ICH	International conference on harmonisation
IFNg	Interferon gamma
IMP	Investigational medicinal product
INR	International normalised ratio
IPD	Important Protocol Deviation
IV	Intravenous

Abbreviation or Specialized Term	Definition
LLN	Lower limit of normal
MAX	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIN	Minimum
MoA	Mechanism of action
MRI	Magnetic resonance imaging
N/A	Not applicable
pCR	Pathological complete response
CCI	
PI	Primary investigator
PT	Preferred term
Q1	25% percentile
Q3	75% percentile
RCB	Residual cancer burden
RDI	Relative dose intensity
RFI	Recurence-free interval
CCI	
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	A commercially available integrated system of software products, commonly used for reporting and analysis of Clinical Studies
SD	Standard deviation
SOA	Schedule of assessments
SOC	System Organ Class
CCI	
TEAE	Treatment Emergent Adverse Event
TNM	Tumour classification of Malignant Tumours
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	11/29/2022	Initial approved SAP	N/A	N/A
Choose an item.	Click or tap to enter a date.			
Choose an item.	Click or tap to enter a date.			

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D931CC00001 supporting the clinical study report (CSR). The reader is referred to the clinical study protocol (CSP) and the case report form (CRF) for details of study conduct and data collection. This statistical analysis plan (SAP) is based on the CSP v3.0, dated 10 June 2022.

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

3 DATA ANALYSIS CONSIDERATIONS

3.1 Timing of Analyses

Three analyses will be performed at the following data-cut offs (DCO).

DCO	Analysis	Estimated Timing
1	Interim Assessment*	When the first [redacted] participants in each cohort (A: lower-risk population and B: higher-risk population) have completed neoadjuvant therapy or discontinued study intervention for any reason.
2	Primary pCR analysis**	Approximately 6 months after the last participant is enrolled (i.e., once all participants have been assessed for pCR following surgery or earlier if no surgery is performed).
3	Final Analysis	3 years after last participant dosed or once all participants have had an EFS event, or have withdrawn consent, whichever occurs first.

* Depending on the timing of when the two cohorts are ready for their interim assessment, two DCO/DBLs (1a and 1b) could eventually occur if the [redacted] participants evaluable for interim assessment are obtained in one cohort much earlier than in the other cohort.
**Depending on the timing of when the two cohorts are ready for their assessment of pCR, two DCO/DBLs (2a and 2b) could eventually occur if the 25 participants evaluable for pCR analysis are obtained in one cohort much earlier than in the other cohort.

3.2 Analysis Populations

3.2.1 Enrolled Set

The Enrolled Set will include all participants who sign the informed consent form.

"Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not allocated study intervention (assigned study intervention in Cohort A or Cohort B), are considered "screen failures".

3.2.2 Full Analysis Set

The Full Analysis Set (FAS) will include all enrolled participants who received at least 1 dose of study intervention. Treatment groups will be assessed on the study intervention assigned (olaparib monotherapy in Cohort A or olaparib plus durvalumab combination therapy in Cohort B), regardless of the study intervention received.

3.2.3 pCR Evaluable Set

The pCR evaluable set (pCRES) will include all participants in the FAS from Cohorts A and B that underwent surgery and had an evaluable pCR assessment. Analyses on the pCRES will be performed according to the study intervention assigned (olaparib monotherapy in Cohort A or olaparib plus durvalumab combination therapy in Cohort B), regardless of the study intervention received.

3.2.4 Safety Analysis Set

The Safety Analysis Set will consist of all enrolled participants who have received at least 1 dose of study intervention. Safety Analysis Set participants are analysed according to the actual study intervention received. Patients who receive at least one dose of olapirib and one dose of durvalumab will be summarized in the combination cohort and patients who receive olapirib only will be summarized in the monotherapy cohort.

Adjuvant intervention period: Number of patients in the Safety Analysis Set who enter the adjuvant intervention period (defined as receiving at least one dose of olaparib after surgery) will be summarised and additional summaries of safety by period (i.e., neo-adjuvant intervention period/adjuvant period) may also be generated, as required.

3.2.5 CCI

CCI [redacted]

Table 1 provides a summary of outcome variables and corresponding analysis sets.

Table 1 Summary of Outcome Variables and Analysis Sets

Outcome Variable	Analysis Sets
Efficacy Data	
Pathological Complete Response (pCR)	FAS + pCRES
Residual Cancer Burden (RCB)	FAS + pCRES
Change in tumour volume from baseline	FAS
Event-Free Survival (EFS)	FAS
Recurrence-Free Interval (RFI)	FAS patients who achieved pCR
Demographic Data/Baseline Characteristics	
Demography	FAS
Baseline and disease characteristics	FAS
Protocol deviations (protocol deviations and important protocol deviations)	FAS
Medical/surgical history	FAS
Previous anticancer therapy	FAS
Concomitant/previous medications/procedures	FAS
Subsequent anticancer therapy	FAS
CCI [redacted]	
Safety Data	
Exposure	Safety Analysis Set
Adverse events	Safety Analysis Set
Laboratory measurements	Safety Analysis Set
Vital signs	Safety Analysis Set
Physical examination	Safety Analysis Set
Electrocardiogram (ECG; durvalumab only)	Safety Analysis Set
ECOG Performance Status	Safety Analysis Set

3.3 General Considerations

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

- All analyses and reporting will be by study intervention arms: olaparib monotherapy lower risk (Cohort A) and olaparib plus durvalumab combination therapy higher risk (Cohort B).
- The statistical analyses of efficacy will summarise the treatment groups on the basis of allocated study intervention. When assessing safety and tolerability, summaries will be produced based on the actual treatment received.
- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding cohort. Overall totals will be calculated for baseline summaries only.
- For continuous data, mean, median, upper and lower quartiles will be rounded to 1 additional decimal place compared to the original data. The standard deviation 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 with the exception of 100% which is presented as a whole number.
- Statistical analysis Software (SAS®) version 9.4 or higher will be used for all analyses.

3.3.1 General Study Level Definitions

In general, the last observed measurement prior to first study intervention administration (i.e. prior first intake among olaparib and durvalumab) will be considered the baseline measurement. For assessments on the day of first study intervention administration where time is not captured, a nominal pre-dose indicator, if available, will serve as sufficient evidence that the assessment occurred prior to first dose.

Assessments on the day of the first study intervention administration 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:

$$Change\ from\ Baseline = Post\text{-}Baseline\ value - Baseline\ value$$

The percentage change from baseline will be calculated when the baseline value is > 0 as:

$$\%\ Change\ from\ Baseline = 100 \times \left(\frac{Post\text{-}baseline\ value - Baseline\ value}{Baseline\ value}\right)$$

3.3.2 Visit Window

Visit windows for efficacy will only be applied for the tumour volume endpoint. Details are covered in section 4.2.4.

General considerations for safety

Time windows will be defined for any presentations that summarise safety data by visit. The following conventions will apply:

- The time windows will be exhaustive so that data recorded at any time point has the potential to be summarised. Inclusion within the time window will be based on the actual date and not the intended date of the visit.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls half way between the two visits (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.
- Visit windows will be as follows:

Day time point / Week	Minimum Day	Maximum Day
Day 1 / Week 1		
Day 29 / Week 5	2	43
Day 57 / Week 9	44	71
Day 85 / Week 13	72	99
Day 113 / Week 17	100	127
Day 141 / Week 21	128	155
Day 169 / Week 25	156	183
Day 197 / Week 29	184	211

Day 225 / Week 33	212	239
Day 253 / Week 37	240	267
Etc...		

With Day computed as: (collection date of the value – first neoadjuvant dose date) + 1.
Cycle 1, Day 1 will contain 3 assessments for Vital Signs Cohort B (pre-dose, during and after infusion), for other parameters Cycle 1 Day 1 is baseline (pre-dose).

In addition, for safety assessments only, the safety follow-up visit is defined as the latest of either 30 days following last dose of olaparib or 90 days following last dose of durvalumab, or until the initiation of the first subsequent therapy (including nonpalliative radiotherapy), whichever occurs first.

3.3.3 Handling of Unscheduled Visits

- All unscheduled visit data have the potential to be included in the summaries.
- Both scheduled and unscheduled assessments are included for visit windowing.

3.3.4 Multiplicity/Multiple Comparisons

Not applicable, as there is no statistical testing or model for this study.

3.3.5 Handling of Protocol Deviations in Study Analysis

The following general categories will be considered important protocol deviations (IPDs) and will be programmatically derived from the eCRF data or manually detected. They will be listed and discussed in the CSR as appropriate:

- Patients who deviate from key entry criteria (inclusion criteria 2, 3 and exclusion criteria 2, 4, 6, 12, 13, 14, 15) per the Clinical Study Protocol (CSP).
- Received prohibited concomitant medications (including other anti-cancer therapy or chronic use of immunosuppressive medications). Please refer to the CSP appendix H2 Table 20 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 physician review of all medications prior to database lock.
- Patients who received the study treatment at an incorrect dose or received an alternative study treatment to that which they were allocated at enrolment.
- Patients who met discontinuation criteria but continued to be on study treatment.

Note any additional important protocol deviations identified beyond those listed above will be captured and documented prior to database lock.

Patients who receive the wrong treatment at any time will be included in the Safety Analysis Set as described in Section 3.2.4. During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the study team leader and/or statistician.

None of the deviations will lead to patients being excluded from the analysis sets described in Section 3.2. A per-protocol analysis excluding patients with specific IPDs is not planned.

Further details on the classification can be found in the Project specific protocol deviations list.

3.3.6 Handling of Missing Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing.

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (i.e. below the lower limit of quantification) or "> x" (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings. Note that 0 should not be used as an imputed value in case the endpoint requires a log transformation. Additionally, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

Generally, the imputation of dates is used to decide if an observation is treatment emergent for adverse events (AE) or concomitant medications (CM). The imputed dates are not advised to be used to calculate durations where the results would be less accurate.

1) Partial or missing AE or CM start dates will be imputed as follows:

   - Missing day - Impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date
   - Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date
   - 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.

- Partial or missing AE or CM end dates will be imputed as follows:

   - Missing day - impute the last day of the month. If the patient died in the same month, then set the imputed date as the death date
   - Missing day and month – impute 31st December. If the patient died in the same year, then set the imputed date as the death date
   - Completely Missing – No imputation

- 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:

  - For Missing day only – using the 1st of the month
  - For Missing day and Month – using the 1st of January
  - If there is evidence of death but the death date is entirely missing, it will be treated as missing.

3.3.7 COVID-19 Impact

If applicable, a listing of the patients affected by Coronavirus Disease of 2019 (COVID-19) and the type of COVID-19 disruption will be provided for the Full Analysis Set.
Depending on the extent of COVID-19 impact, summaries of AEs associated with new onset of COVID-19 infection, discontinuation of study treatment, discontinuation of study, missed visits, COVID-19 related protocol deviations and other missing data relating to impact of COVID-19 may be generated.

4 STATISTICAL ANALYSIS

This section provides information on definitions, derivation and analysis/data presentation per domain.

4.1 Study Population

The domain study population covers patient disposition, analysis sets, protocol deviations, demographics, baseline characteristics medical history, prior and concomitant medication and study drug compliance. The FAS will be used for summarising and analysis of study population data unless otherwise stated below.

4.1.1 Patient Disposition and Completion Status

4.1.1.1 Definitions and Derivations

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention.

Patients treated are patients who received any amount of study intervention (olaparib or durvalumab).

4.1.1.2 Presentation

Patient disposition provides details on patients screened (i.e. patients who gave informed consent), screen failure, treated and study intervention or study completion status. Patient disposition will be summarised by study intervention group and overall. The following information will be reported:

- Total number of enrolled patients screen failed.
- Number and percentage of patients who started any study treatment (olaparib or durvalumab) and each treatment (olaparib and durvalumab)
- Number and percentage of patients who started olaparib during adjuvant intervention period.
- Number and percentage of patients who discontinued all study treatments (olaparib and durvalumab) and for each treatment (olaparib and durvalumab) along with reasons for treatment discontinuation.
- Number and percentage of patients who discontinued olaparib during adjuvant intervention period along with reasons for treatment discontinuation.
- Number and percentage of patients who terminated study along with reasons for study termination.
- Number and percentage of patients assigned to each study intervention cohort by country and centre.

In addition, a listing of patients affected by Covid-19 (discontinued IP due to COVID-19 or withdrew study due to COVID-19) will be presented.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

Analysis sets are defined in section 3.2.

4.1.2.2 Presentation

The number and percentage of patients included and excluded from each analysis set together with the reasons for exclusion from the analysis set will be presented.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Important protocol deviations (IPDs) are defined as a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. List of IPDs is provided in Section 3.3.5.

4.1.3.2 Presentation

The IPDs will be listed and summarised by study intervention arm.

A separate listing will also be produced for protocol deviations related to Coronavirus disease 2019 (COVID-19).

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

The following demographic characteristics data will be collected from each patient:

- Sex: Male, Female;
- Race: Black or African American, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Asian, White, Other, Not reported;
- Ethnicity: Hispanic or Latino/Not Hispanic or Latino;
- Age (years);
- Age group

4.1.4.2 Presentation

Demographics data above will be summarised for all patients in the FAS by study intervention.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline characteristics data including height, weight and weight group (< 50, 50-90, ≥ 90 kg) will be collected from each patient.

4.1.5.2 Presentation

Baseline characteristics data for above variables will be summarised by study intervention group.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

The following disease characteristics will be collected for all patients at baseline:

- ECOG performance status;
- BRCA mutation status [BRCA1, BRCA2 or BRCA1/2] (local and central testing);
- HER2 status;
- ER negative or ER Low;
- PgR negative or positive;
- Primary tumour location;
- Histology type;
- Tumour grade;
- CCI expression (local and central testing);
- TNM tumour stage;
- Family history of cancer (cancer type, BRCA mutation type, etc.).

4.1.6.2 Presentation

Baseline disease characteristics above will be summarised by study intervention group.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical history is defined as any medical conditions present up until just prior to the participant starting study intervention. They are entered into the Medical History eCRF.

Any medical history which is ongoing at time of informed consent will be considered an ongoing condition, otherwise it will be considered past medical history.

Relevant surgeries prior to enrolment will be recorded in eCRF.

Medical and surgical history will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) [version 23.0 or later].

4.1.7.2 Presentation

The number and percentage of patients with medical history and with surgical history will be summarised by System Organ Class (SOC) and Preferred Term (PT) and presented by study intervention group.

Tables will be sorted by international order for SOC and descending frequency for PT in all participants. A patient can have one or more PT reported under a given SOC. Participants with multiple occasions of the same medical history will be counted once per medical history.

4.1.8 Prior and Concomitant Medications

4.1.8.1 Definitions and Derivations

Any concomitant treatment, surgical procedure, or other medication considered necessary by the investigator for the participant's safety and wellbeing, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving from the time of screening or receives during the study including the safety follow-up period following the last dose of study intervention will be recorded in the eCRF.

Thereafter, only subsequent regimens of anti-cancer therapy will be recorded in eCRF. Other anti-cancer therapies, investigational agents, and radiotherapy should not be given while the patient is on study drug. For a detailed list of restricted and prohibited medications please refer to CSP Appendix H.

Medications received prior to, concomitantly, or post-treatment will be coded using the latest version of WHO Drug.

For the purpose of inclusion in prior and/or concomitant medication summaries, incomplete medication start and stop dates will be imputed as detailed in Section 3.3.6.

Prior medications, concomitant and post-treatment treatment medications are defined as follows:

- Prior medications are those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant medications are those with a stop date on or after the first dose date of study treatment (and could have started prior to or during treatment).
- Post-treatment medications are those with a start date after the safety follow-up period following the last dose study treatment date.

4.1.8.2 Presentation

The following summaries will be produced for the FAS:

- Prior cancer therapy
- Number of blood transfusions
- Allowed concomitant medications
- Disallowed concomitant medications
- Subsequent cancer therapies/medication received.

Concomitant treatment medications will be summarised by Anatomical Therapeutic Chemical category name (ATC level 4) and generic term (preferred term) by study intervention group.

Disallowed medications will be listed.

Missing coding terms should be summarised as "Not coded".

4.1.9 Study Drug Compliance

4.1.9.1 Definitions and Derivations

Compliance:
Patients who receive olaparib will be assessed for treatment compliance. Percentage compliance will be defined as:

{(No. tablets dispensed in period – no. tablets returned from period)/ (no. days of study drug exposure in period × expected tablets per day)} × 100%.

Where expected tablets per day will take into account once daily or bid dosing. Overall compliance may be calculated over various periods if the dose has been modified, to consider

the differing expected tablets per day or the protocol-specified dose interruptions. As in the determination of exposure, missed doses will not be adjusted for.

Before calculation of summary measures, individual compliance rates will be capped at 100%, however uncapped compliance rates will be listed by subject.

Percentage compliance will not be assessed for durvalumab.

4.1.9.2 Presentation

Compliance will be summarised by study intervention group.

Breast Cancer Surgery

4.1.10.1 Definitions and Derivations

The following breast cancer surgery data will be collected for all patients:

- Ability to undergo surgery with reason for surgery not done,
- Time to breast cancer surgery computed as: (Surgery date – date of first dose) + 1;
- Lateral location;
- Deviation from surgical plan;
- Surgery delay and reason;
- Type of surgery;
- Sentinel node sampling performed and sentinel node laterality;Number of Axillary Lymph Nodes Removed, Number of Positive Axillary Lymph Nodes, Number of Sentinel Lymph Nodes Removed, Number of Positive Sentinel Lymph Nodes;
- Overall Pathological Stage for Tumour after Treatment;
-

4.1.10.2 Presentation

Breast cancer surgery data will be summarised for the FAS by study intervention group.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, other endpoints including sensitivity and supportive analyses.

Objectives	Endpoints/Estimands
Primary	
To evaluate the efficacy, measured by Pathological Complete Response (pCR) rate, of olaparib monotherapy and olaparib plus durvalumab combination therapy, **as assessed by central pathology review.**	**pCR** is defined as ypT0/Tis ypN0 (ie, no invasive residual in breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes) following completion of neoadjuvant systemic therapy. The analysis will include all enrolled participants who received at least 1 dose of study intervention and assessed according to the study intervention assigned. Participants who withdraw from study intervention without pCR will not be included as responders in the primary pCR analysis (refer to Table 13 of CSP for details). The measure of interest is the rate of pCR (proportion of participants with pCR as defined above) within each study intervention group (olaparib or olaparib plus durvalumab).
Secondary	
To evaluate the efficacy, measured by pCR rate, of olaparib monotherapy and olaparib plus durvalumab combination therapy **as assessed by local pathology review.**	**pCR** is defined as ypT0/Tis ypN0 (ie, no invasive residual in breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes) following completion of neoadjuvant systemic therapy. The analysis will include all enrolled participants who received at least 1 dose of study intervention and assessed according to the study intervention assigned. Participants who withdraw from study intervention without pCR will not be included as responders in the primary pCR analysis (refer to Table 13 of CSP for details). The measure of interest is the rate of pCR (proportion of participants with pCR as defined above) within each study intervention group (olaparib or olaparib plus durvalumab).
To evaluate the efficacy, measured by **RCB**, of olaparib monotherapy and olaparib plus durvalumab combination therapy as **assessed by central pathology review.**	**RCB is an index value using 6 variables to categorize response in 1 of 4 classes: RCB 0 (pCR), I (minimal RCB), II (moderate RCB), and III (extensive RCB).** The analysis will include all enrolled participants who received at least 1 dose of study intervention and assessed according to the study intervention assigned. The measure of interest is the number and percentage of participants in each class for each study intervention group (olaparib or olaparib plus durvalumab) where possible.

Objectives	Endpoints/Estimands
To evaluate the efficacy, measured by **RCB**, of olaparib monotherapy and olaparib plus durvalumab combination therapy as **assessed by local pathology review.**	RCB is an index value using 6 variables to categorize response in 1 of 4 classes: RCB 0 (pCR), I (minimal RCB), II (moderate RCB), and III (extensive RCB). The analysis will include all enrolled participants who received at least 1 dose of study intervention and assessed according to the study intervention assigned. The measure of interest is the number and percentage of participants in each class for each study intervention group (olaparib or olaparib plus durvalumab) where possible.
To evaluate the efficacy of olaparib monotherapy and olaparib plus durvalumab combination therapy in terms of **change from baseline tumour volume**. Tumour volume will be assessed by local radiology review.	Percentage change in tumour volume from baseline after 3 and 6 cycles of treatment will be measured using MRI. Baseline is defined as the most recent measurement prior to the first administration of study intervention. Percent change from baseline is defined as: (Difference in value between post-baseline volume and baseline volume) divided by baseline volume and multiplied by 100. The analysis will include all enrolled participants who received at least 1 dose of treatment and assessed according to study intervention assigned. The measure of interest is the percent change in tumour volume from baseline within each study intervention group (olaparib or olaparib plus durvalumab).
To evaluate the efficacy of olaparib monotherapy and olaparib plus durvalumab combination therapy by assessment of EFS.	EFS is defined as time from the first dose of study intervention administration to any of the following events: progression of disease that precludes surgery, local or distant recurrence after surgery, second primary malignancy (breast or other invasive cancers), or death due to any cause. No formal analysis of EFS data will be carried out. The number of events will be summarised and the EFS data will be listed in all enrolled participants who received at least 1 dose of treatment according to the study intervention assigned.

Objectives	Endpoints/Estimands
Safety	
To assess the safety and tolerability profile of olaparib monotherapy and olaparib plus durvalumab combination therapy.	Safety and tolerability will be evaluated in terms of AEs/ SAEs, physical examination, vital signs including blood pressure, pulse, heart rate, body temperature, body weight, height, and BMI, clinical laboratory assessments including clinical chemistry/haematology parameters, and ECGs.
To assess the safety and tolerability profile of olaparib monotherapy when given as adjuvant therapy to participants who achieve pCR.	Assessments related to AEs cover: • Occurrence/frequency • Relationship to study intervention as assessed by investigator • CTCAE grade • Seriousness • Death • Discontinuation of study intervention • AESIs • Other significant AEs • Exposure All safety data will be summarised in all enrolled participants who received at least 1 dose of study intervention and assessed according to actual study intervention received (olaparib or olaparib plus durvalumab). Safety data will be summarised descriptively and listed only (refer to Section 9 of CSP for details).
Tertiary/Exploratory	
To investigate the CCI of CCI in CCI	Presence of detectable CCI for CCI (confirmatory results: positive or negative), and CCI
To assess CCI at baseline and changes from CCI or during the follow-up period through CCI	Evaluate CCI and changes in CCI and CCI and other CCI and CCI and CCI Analysis may include CCI to select most CCI
To collect blood and CCI samples or utilise residual samples for CCI that CCI	Exploratory CCI that may include (but is not limited to) CCI and CCI treatment: CCI and other CCI and their zygosity, CCI origin, CCI and other CCI other CCI status; CCI

Objectives	Endpoints/Estimands
To characterise CCI [redacted] in tumour and blood samples.	CCI [redacted] burden; CCI [redacted] profiles (eg, CCI [redacted] the expression and activity of CCI [redacted] and/or CCI [redacted] (eg, CCI [redacted]), secreted CCI [redacted] (eg, CCI [redacted] or protein and CCI [redacted]; presence of CCI [redacted]; the number, phenotype, and expression profile of CCI [redacted] CCI [redacted]
To explore whether CCI [redacted] to olaparib or olaparib plus durvalumab can be CCI [redacted]	Evaluation of CCI [redacted] and CCI [redacted] samples collected before CCI [redacted] mentioned above.*
Exploratory research into CCI [redacted] and/or CCI [redacted] or CCI [redacted] CCI [redacted] may be performed on the CCI [redacted] that were collected during the course of the study.	Analysis and outcome CCI [redacted]
To collect and store CCI [redacted] according to each country's local and ethical procedures for CCI [redacted] that may CCI [redacted] to study treatments and/or CCI [redacted] (optional).	CCI [redacted] for the CCI [redacted] CCI [redacted] measured by the CCI [redacted] CCI [redacted] from an CCI [redacted] sample.*
To explore the impact of olaparib and olaparib plus durvalumab on CCI [redacted] in women who C [redacted] CCI [redacted]	Evaluation of CCI [redacted] collected via central laboratory testing be CCI [redacted] CCI [redacted] for CCI [redacted]

* The results of those endpoints will be reported separately from the clinical study report.
# CCI [redacted]
Abbreviations: CCI [redacted] AE = adverse event; AESI = adverse event of special interest; CCI [redacted] BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Event; CCI [redacted] ECG = electrocardiogram; EFS = event-free survival; CCI [redacted] MoA = mechanism of action; CCI [redacted] MRI = magnetic resonance imaging; pCR = pathological complete response; CCI [redacted] RCB = residual cancer burden; CCI [redacted] SAE = serious adverse event; CCI [redacted]
Note: Pathological staging following neoadjuvant systemic therapy is recorded using the 'yp' designation.

4.2.1 Primary Endpoint – pCR rate by central pathology review

4.2.1.1 Definition

The pCR rate (ypT0/Tis ypN0) is defined as the proportion of participants among all enrolled and treated (FAS) without residual invasive cancer in breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy per current American Joint Committee of Cancer (AJCC) staging criteria assessed by central pathology review at the time of definitive surgery.

4.2.1.2 Derivations

The analysis will include all enrolled participants who received at least 1 dose of study intervention (FAS) and assessed according to the study intervention assigned.

The pCR status will be derived from RCB class. pCR will be 'Yes' if RCB Class is 0; pCR will be 'No' if RCB Class is I, II or III.

Participants who received only study intervention (at least 1 dose of olaparib or durvalumab) as neoadjuvant treatment and achieved pCR according to central pathology review will be considered as responders. All other participants in the FAS (including those who achieved pCR but after a subsequent neoadjuvant therapy) will be regarded as non-responders (refer to Table 2).

Table 2 Definitions of Responders vs. Non-responders for pCR Assessments in primary analysis

Situation	Primary Analysis
Participants that only received study intervention (at least 1 dose) and achieved pCR	Responder
Participants discontinued study intervention, received any subsequent neoadjuvant cancer treatment, and achieved pCR	Non-responder
Participants had disease progression or died from any cause prior to surgery	Non-responder
Participants with no valid records regarding pCR status due to any reason (including but not limited to withdrawal from the study, PD or death before surgery, lack of surgical specimen, or defined as not evaluable by central pathology)	Non-responder
All other participants	Non-responder

Abbreviations: pCR = pathological complete response; PD = progression of disease.

Discontinuation from study intervention will be determined using IP_DISCC variable from DOSDISC and DOSDISC1 eCRF module. Progression prior to surgery will be determined

using DISTYPE variable from the DISREC eCRF module. Death will be determined using the DD eCRF module.

4.2.1.3 Handling of Dropouts and Missing Data

As detailed above, all participants included in the FAS without valid record regarding pCR status for any reason will be considered as non-responders.

4.2.1.4 Primary Analysis of Primary Endpoint

The number and percentage of patients who met the responder definition for pCR according to Table 2 will be presented in the FAS by study intervention arms (Cohorts A and B) with 2-sided exact Clopper-Pearson 95% confidence intervals of the percentages.

4.2.1.5 Sensitivity Analyses of the Primary Endpoint

A sensitivity analysis of the primary endpoint will be performed using the same method as described above but on a subset of participants in the FAS with confirmed *BRCA*m by retrospective central test.

4.2.1.6 Supplementary Analyses of the Primary Endpoint

Two supplementary analyses will be performed.

The first supplementary analysis will consist of repeating the primary analysis as described above on the pCRES.

The second supplementary analysis will consist of repeating the primary analysis on the FAS but accounting for all responders regardless of whether the participants receive any subsequent noeadjuvant therapy. Definitions of participants who will be considered responders or non-responders for this supplementary analysis of pCR are presented in Table 3 below.

Table 3 Definitions of Responders vs. Non-responders for pCR Assessments in supplementary analysis

Situation	Primary Analysis
Participants that only received study intervention (at least 1 dose) and achieved pCR	Responder
Participants discontinued study intervention, received any subsequent neoadjuvant cancer treatment, and achieved pCR	Responder
Participants had disease progression or died from any cause prior to surgery	Non-responder
Participants with no valid records regarding pCR status due to any reason (including but not limited to withdrawal from the study, PD or death	Non-responder

before surgery, lack of surgical specimen, or defined as not evaluable by central pathology)	
All other participants	Non-responder

Abbreviations: pCR = pathological complete response; PD = progression of disease.

A swimmer plot will be produced where each bar represents the time to surgery for one patient in the study. The plot will display the CCI information where available (i.e. CCI status) as well as whether pCR was achieved or not.

4.2.1.7 Subgroup Analyses

Not applicable.

4.2.2 Secondary Endpoint – pCR rate by local pathology review

4.2.2.1 Definition

The secondary pCR analysis for this study will be based on the local pathology review of histopathology slides. The local site pathologist will assess pCR based upon examination of surgical specimens per local institutional standards and procedures. Pathology information from the definitive breast surgery will be entered into the eCRF when the pathology report is available.

The pCR rate (ypT0/Tis ypN0) is defined as the proportion of participants among all enrolled and treated (FAS) without residual invasive cancer in breast and the axillary lymph nodes on evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy per current AJCC staging criteria assessed by the local pathology review at the time of definitive surgery.

4.2.2.2 Derivations

Derivations will follow the same rules as detailed for primary endpoint in Section 4.2.1.2 and Table 2 but using local assessments instead of central assessments.

4.2.2.3 Handling of Dropouts and Missing Data

As for the primary endpoint, all participants included in the FAS without valid record for any reason regarding pCR status by local review will be regarded as non-responder for the secondary endpoint.

4.2.2.4 Primary Analysis of Secondary Endpoint

pCR rates according to the local pathologist will be presented in the same way as for the primary analysis of the primary endpoint described in Section 4.2.1.4.

4.2.2.5 Sensitivity Analyses of the Secondary Endpoint

The sensitivity analysis described for the primary endpoint in Section 4.2.1.5 will be performed similarly using local pathology assessments.

4.2.2.6 Supplementary Analyses of the Secondary Endpoint

The two supplementary analyses described for the primary endpoint in Section 4.2.1.6 will be performed similarly using local pathology assessments.

4.2.2.7 Subgroup Analyses

Not applicable.

4.2.3 Secondary Endpoint – Residual cancer burden (RCB) by local and central pathology review

4.2.3.1 Definition

The RCB is a numerical index to measure residual disease in either the breast or lymph node at the time of definitive surgery as assessed by both central and local pathology review by combining histopathologic components of residual disease (cellularity, overall diameter, number, and extent of nodal involvement).

The RCB is an index value using 6 variables to categorize response in 1 of 4 classes:

- RCB 0 (pCR),
- RCB I (minimal RCB),
- RCB II (moderate RCB),
- RCB III (extensive RCB).

4.2.3.2 Derivations

The following 6 variables are required for the calculation of RCB after neoadjuvant treatment:

1) The largest 2 dimensions of the residual tumour bed in the breast.
2) Submission of the entire largest cross-sectional area of the residual tumour bed for histologic mapping, with specific identification of those slides in the pathology report.
3) Histologic assessment of the percentage of the tumour bed area that contains carcinoma (all carcinoma [ie, invasive and in situ]).
4) Histologic estimate of the percentage of the carcinoma in the tumour bed that is in situ.
5) The number of positive (metastatic) lymph nodes.
6) The largest diameter (mm) of the largest nodal metastasis.

Additional pathology documentation guidelines are provided in Appendix J of the CSP.

The RCB will be calculated by the pathologist and entered into the eCRF PCROM module.

Patients who progressed in the neoadjuvant period and received subsequent anti-cancer treatment prior to surgery will be graded as RCB III. However patients who decided to stop study treatment early or have toxicity/tolerability issues will have an RCB of "missing".

For bilateral patients with 2 RCB scores (1 per side), their overall RCB score will be defined as the highest of the two scores.

4.2.3.3 Handling of Dropouts and Missing Data

Participants without valid record for RCB by central/local review will be classified in a missing category.

4.2.3.4 Primary Analysis of Secondary Endpoint

RCB will be analyzed in FAS.

The number and percentage of participants in each of the 4 RCB classes will be presented by study intervention group.

Number and percentage of participants with low residual disease (RCB-0 and RCB-I combined) will be calculated for each cohort, and exact Clopper-Pearson 95% confidence interval presented, where possible/appropriate.

Analyses will be done per central pathology review and per local pathology review separately.

4.2.3.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.3.6 Supplementary Analyses of the Secondary Endpoint

The same analysis as described above for primary analysis will be performed on the pCRES. This will be done per central pathology review and per local pathology review separately.

4.2.3.7 Subgroup Analyses

Not applicable.

4.2.4 Secondary Endpoint – Percentage change from baseline in tumour volume

4.2.4.1 Definition

Tumour assessments will use volume images from MRI with IV contrast of the breast (bilateral) collected during screening/baseline and at Week 12 (Cycle 4) and at Week 24 (prior

to definitive surgery, if applicable), and will be assessed locally. If MRI has been performed at Week 12 (ie, start of Cycle 4) and the participant proceeds to definitive surgery following Cycle 4 or Cycle 5, the MRI scan does not need to be repeated prior to definitive surgery, unless clinically indicated.

For MRI tumour volume assessments, only breast lesions should be taken into consideration (ie, lymph nodal involvement if any should be disregarded). In case a participant has multifocal, multicentric, or bilateral breast lesions, then only the largest primary breast lesion at baseline should be considered for this MRI volumetric analysis and the same lesion should be assessed at subsequent time points.

The MRI technique used for baseline should be kept the same consistently at each subsequent follow-up assessment throughout the study if possible.

Screening/baseline imaging should be performed no more than 28 days before start of study intervention and ideally should be performed as close as possible to and prior to the start of study intervention.

4.2.4.2 Derivations

The tumour volume as calculated by the site's MRI software at each assessment time point will be calculated locally at site and reported on the eCRF. If the tumour volume must be calculated by hand by the site it will be calculated as follows:

$$(length \times width \times height \times \pi)/6$$

Tumour volume will be determined from the eCRF TARGRN module.

Absolute and percent change from baseline in tumour volume will be computed as defined in Section 3.3.1. The percentage change in tumour volume will be set as -99% if the tumour becomes too small to measure at the post-baseline visit.

The following analysis visit windows will be considered for Week 12 and Week 24 tumour volume assessments:

Assessment	Minimum Day	Target Day	Maximum Day
Week 12	43	85	126
Week 24	127	169	210

With Day computed as: (collection date of the MRI – first neoadjuvant dose date) + 1.

Assessments (planned and unscheduled) will be re-mapped into the analysis windows with the following rules:

- If several MRIs fall into the same analysis window, the closest to the target day will be considered;

- When there are 2 MRIs at equal distance to the target day, the MRI corresponding to the mapped visit in the CRF (Week 12 or Week 24) will be preferred compared to an unscheduled MRI; if none of the MRIs are mapped to the planned visit then the average of the tumour volumes will be taken.

For waterfall plots, the best percentage change in tumour volume, for a given patient, will be derived as either (a) the largest percentage 'decrease' in tumour volume from baseline (if there was any tumour shrinkage) or (b) the smallest percentage 'increase' in tumour volume from baseline (if there was no tumour shrinkage), at any post-baseline timepoint (scheduled or unscheduled) prior to surgery or until the initiation of the first subsequent therapy (whichever occurs first). If a patient did not undergo surgery or start subsequent therapy all tumour volumes recorded in the database will be considered to compute best percentage change.

4.2.4.3 Handling of Dropouts and Missing Data

All participants included in the FAS without valid record for tumour volume will be classified in a missing category.

4.2.4.4 Primary Analysis of Secondary Endpoint

Absolute value, absolute change and percentage changes from baseline of tumour volumes will be summarised by study intervention group at Baseline, at Week 12 and at Week 24 (considering the visit windows described above) using descriptive statistics.

All tumour volumes at any time (planned and unscheduled) will be listed with changes from baseline and a flag indicating if the value was used in summaries as well as if the tumor volume was post post surgery or initiation of subsequent therapy.

In addition, percentage change in tumour volume will be presented graphically using waterfall plots for each study intervention group, to present each participant's best percentage change in tumour volume as a separate bar, with the bars ordered from the largest increase to the largest decrease (Hammer et al 2010). Best percentage change will be computed as detailed in derivation section.

The analysis will be performed on the FAS by study intervention group.

4.2.4.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.4.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

4.2.4.7 Subgroup Analyses

Not applicable.

4.2.5 Secondary Endpoint – Event-Free Survival (EFS)

4.2.5.1 Definition

EFS is defined as the time from the date of first dose of study intervention administration to the date of progression of disease that precludes surgery, local or distant recurrence after surgery, second primary malignancy (breast or other invasive cancers) after surgery, or death due to any cause whichever comes first.

4.2.5.2 Derivations

Type of event will be determined using DISTYPE variable from DISREC eCRF module. Assessment date will be determined using ASM_DAT variable. Death will be determined using DD eCRF module. Date of death will be determined from DTHDAT variable.

Time will be calculated in months as follows:

$$EFS\ (months) = \frac{(Date\ of\ event\ or\ censoring - Date\ of\ first\ dose\ of\ study\ intervention\ (olaparib\ or\ durvalumab) + 1)}{30.4375}$$

For patients with an event, the earliest date among date of progression of disease that precludes surgery, date of local or distant recurrence, date of second primary malignancy (breast or other invasive cancers) and date of death will be considered as event date.

Patients who reached the time point of analysis or lost to follow-up without a known record of any event will be censored at time of last evaluable assessment date or at Day 1 if there is no evaluable assessment post-baseline .

4.2.5.3 Handling of Dropouts and Missing Data

Participants with missing assessments will be handled as detailed above.

4.2.5.4 Primary Analysis of Secondary Endpoint

No formal analysis of EFS data will be carried out. The number and percentage of events as well as the number and percentage of censored patients will be summarised. EFS data will be listed and will be presented in a swimmer plot, where each bar represents the EFS time for one patient in the study. The plots will present the censored patients as well as those who had an event as well as CCI information where available (i.e. CCI status).

The analysis will be performed on the FAS by study intervention group.

4.2.5.5 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.5.6 Supplementary Analyses of the Secondary Endpoint

Not applicable.

4.2.5.7 Subgroup Analyses

Not applicable.

4.2.6 Other Endpoint – Reccurrence-Free Interval (RFI)

4.2.6.1 Definition

Participants who achieve pCR according to local pathologist will have their RFI status recorded per local standard clinical practice. A participant's RFI status is defined as the time from date of surgery at which pCR is identified to the date of local or distant recurrence of breast cancer, or date of death due to breast cancer, whichever occurs first. RFI status will be determined every 3 months for the first 2 years post intervention and then every 6 months thereafter.**Derivations**

Type of reccurrence event will be determined using DISTYPE variable from DISREC eCRF module. Assessment date will be determined using ASM_DAT variable. Death will be determined using DD eCRF module. Date of death will be determined from DTHDAT variable.

Time will be calculated in months as follows:

$$RFI\ (months) = \frac{(Date\ of\ event\ or\ censoring - Date\ of\ surgery\ at\ which\ pCR\ is\ identified\ + 1)}{30.4375}$$

For patients with an event, the earliest date among the date of local or distant recurrence of breast cancer and date of death due to breast cancer will be considered as event date.

Patients who reached the time point of analysis or lost to follow-up without a known record of any event will be censored at time of last evaluable assessment date or at date of surgery (at which pCR is identified) if there is no evaluable assessment post-surgery.

4.2.6.3 Handling of Dropouts and Missing Data

Participants with missing data will be handled as detailed above.

4.2.6.4 Primary Analysis of Other Endpoint

RFI will be analysed on FAS patients who achieved pCR. The same analysis as for the EFS will be performed for RFI as described in Section 4.2.5.4. The swimmer plot will distinguish patients who receive no adjuvant treatment to those receiving adjuvant treatment (olaparib versus other chemotherapy).

4.2.6.5 Additional Analyses of the Other Endpoint

Not applicable.

4.2.6.6 Subgroup Analyses

Not applicable.

4.3 Pharmacodynamic Endpoint

Whole blood samples and whole blood soluble [CCI] are pharmacodynamics parameters in this study. Summary and analyses for exploratory [CCI] and [CCI] data will be documented in a separate analysis plan and may be reported outside the CSR.

4.4 Pharmacokinetics

Not applicable.

4.5 [CCI]

This section is applicable for Cohort B only (participants treated with durvalumab).

[CCI] results will be listed by participant, and a summary will be provided by the number and percentage of participants who develop [CCI] (confirmed positive) following study intervention. The [CCI] and [CCI] will be listed for samples confirmed positive for the presence of [CCI]

This analysis will be performed on the [CCI]

The effect of [CCI] as well as the effect of its [CCI] on pharmacodynamics, efficacy, and safety will be evaluated, if the data allow and may be reported outside the CSR. A detailed plan will be written by the AstraZeneca Clinical Pharmacology group or designee.

4.6 Safety Analyses

Safety data will be presented using descriptive statistics unless otherwise specified. No formal statistical comparisons will be performed on the safety data. Safety and tolerability data will be presented by actual treatment group combining data from all cycles of treatment.

Safety and tolerability will be evaluated in terms of AEs/ SAEs, physical examination, vital signs, clinical laboratory assessments including clinical chemistry/haematology parameters, and ECGs.

General considerations for safety assessments:

- Visit windows for safety assessments are described in Section 3.3.2.
- For summaries showing the worst values (ECOG, laboratory parameters), the worst value recorded on treatment (i.e. from first dose of study intervention to within 30 days following discontinuation with olaparib, including neoadjuvant and adjuvant administrations, or 90 days following discontinuation with durvalumab, whichever is longer) will be used (regardless of where it falls in an interval).
- Listings should display all values contributing to a time point for a patient.
- For visit based summaries
  - If there is more than one value per patient within a time window then the closest value to the scheduled visit date will be summarised, or the earlier, in the event the values are equidistant from the nominal visit date. The listings will highlight the value for the patient that contributed to the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date.
  - To prevent very large tables or plots being produced that contain many cells with meaningless data, visit data will only be summarised or plotted if the number of observations is greater than 5 in at least one cohort.
- For summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum/worst value.
- Baseline for safety assessments will generally be the last non-missing measurement prior to first dose of study medication. Alternatively, if two visits are equally eligible to assess patient status at baseline (e.g., screening and baseline assessments both on the same date prior to first dose) the average can be taken as a baseline value. For non-numeric laboratory tests (i.e. some of the urinalysis parameters) where taking an average is not possible then the best value would be taken as baseline as this is the most conservative. In the scenario where there are two assessments on Day 1, one with time recorded and

the other without time recorded, the one with time recorded would be selected as baseline. Where safety data are summarised over time, study day will be calculated in relation to date of first study treatment intake (durvalumab or olaparib).

- Methods for imputation of missing or incomplete AE dates are detailed in Section 3.3.6.

4.6.1 Exposure

4.6.1.1 Definitions and Derivations

Exposure (i.e. duration of treatment) will be determined separately for durvalumab and for olaparib overall and by intervention period (neoadjuvant versus adjuvant intervention period).

Total exposure:

Total (or intended) exposure for **durvalumab** (days) = [earliest date among (last durvalumab dose date where dose > 0 [mg] + 27 days, date of death, date of DCO) – (first durvalumab dose date) + 1] .

Total (or intended) exposure for **olaparib in neoadjuvant period** (days) = [earliest date among (last olaparib dose prior surgery where dose > 0 [mg] date, date of death, date of DCO) – first olaparib dose date + 1] .

Total (or intended) exposure for **olaparib in adjuvant period** (days) = [earliest date among (last olaparib dose after surgery where dose > 0 [mg] date, date of death, date of DCO) – first olaparib dose date after surgery + 1] .

Total (or intended) exposure for **olaparib overall** (days) = Total (or intended) exposure for olaparib in neoadjuvant period + Total (or intended) exposure for olaparib in adjuvant period.

Actual exposure:

Actual exposure for **durvalumab** (days) = [intended exposure – total duration of dose delays] where intended exposure will be calculated as above and total duration of dose delays calculated as: Sum (for all dosing dates) of (Date of the dose – Date of previous dose – 27 days). Thus, if no delays were encountered, the duration would sum up to 0, since infusions were done every 28 days. Dose reductions of durvalumab are not permitted and the calculation of actual exposure makes no adjustment for any dose reductions that may have occurred.

Actual exposure for **olaparib in neoadjuvant period** (days) = [intended exposure – total duration of dose interruptions during neoadjuvant period] 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 during the neoadjuvant period [i.e. sum of (end date of each interruption - start date of the interruption + 1)]. To calculate actual exposure, dose interruptions will include those where a patient forgot to take a dose. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Actual exposure for **olaparib in adjuvant period** (days) = [intended exposure – total duration of dose interruptions during adjuvant period] 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 during the adjuvant period [i.e. sum of (end date of each interruption - start date of the interruption + 1)]. To calculate actual exposure, dose interruptions will include those where a patient forgot to take a dose. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred.

Actual exposure for **olaparib overall** (days) = Actual exposure for olaparib in neoadjuvant period + Actual exposure for olaparib in adjuvant period.

Number of treatment cycles received:

Exposure of durvalumab will also be measured by the number cycles (i.e. total number of infusions received). A cycle corresponds to a period of 28 days. If a cycle is prolonged due to toxicity, this should still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose is not delivered.

Missed or forgotten doses of olaparib:

Missed and forgotten doses of olaparib should be recorded on the EX module as a dose interruption with the reason recorded as "Subject forgot to take dose". These missed or forgotten doses will not be included as dose interruptions in the summary tables but the information will appear in the listing for dosing. However, these missed and forgotten doses will be considered in the derivation of actual exposure.

Patients who permanently discontinue during a dose interruption:

If a patient permanently discontinues study treatment during a dose interruption, then the date of last administration of study medication recorded on DOSDISC, DOSDISC1 or DOSDISC2 will be used in the programming. The dose interruption that happens immediately before patients permanently discontinue the study treatment will not be included in the summary table as interruption (i.e. an interruption will only be included if the drug was restarted).

Safety Follow-up:

Total Safety Follow-up = min[(last dose date + xx days), date of withdrawal of consent, date of death, date of DCO)] – first dose date + 1, where the 'last dose date + xx days' will be the 'last dose date of olaparib + 30 days' or 'last dose date of durvalumab + 90 days', whichever is later.

Dose reduction and interruption:

Dose reductions and dose interruptions will be based on investigator initiated dosing decisions. Dose interruptions of olaparib due to "Subject Forgot to Take Dose" will be omitted from these summaries.

4.6.1.2 Presentation

Exposure will be summarised for the Safety Analysis Set by actual study intervention. The following summaries will be produced:

- Total exposure duration of durvalumab and olaparib (overall and during the neoadjuvant and adjuvant phases separately);
- Actual exposure duration of durvalumab and olaparib (overall and during the neoadjuvant and adjuvant phases separately);
- Total number of cycles will be produced;
- Summary of dose reductions and dose interruptions/dose delays together with reasons for each dose modification will be produced (overall and during the neoadjuvant and adjuvant phases separately).

All dosing data will be listed.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

Adverse events (AEs) will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be assigned CTCAE grades (National Cancer Institute (NCI) CTCAE version 5.0). Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE.

Treatment-emergent AEs

Treatment-emergent AEs (TEAEs) are those events with an onset date (or worsening) on or after the first dose of study intervention and within 30 days following discontinuation with

olaparib (including neoadjuvant and adjuvant administrations) or 90 days following discontinuation with durvalumab, whichever is longer.

Most common TEAEs

Most common TEAEs are events that occur in at least 5% of patients in the Safety Analysis Set. The cut-off value of 5% may be modified after review of the data. When applying the cut-off value (i.e., 5%), the raw percentage will be compared to the cut-off value and no rounding will be applied (i.e., an AE with frequency of 4.9% will not be included in this table if a cut-off is 5%).

Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of intervention. Based on the expert's judgement, AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered other significant AEs and reported in the CSR. A similar review of laboratory values, vital signs, ECGs, and other safety assessments will be performed for identification of other significant AEs.

AEs of special interest (AESI)

Olaparib AEs of special interest

Olaparib adverse events of special interest (AESI) are events of scientific and medical interest specific to the further understanding of the safety profile of olaparib and may require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI may be serious or non-serious.

These AESIs are identified as a list of categories provided by the patient safety team. Other categories may be added as necessary or existing terms may be merged.

An AstraZeneca medically qualified expert, after consultation with the Global Patient Safety Physician, has reviewed the AEs of interest and identified which preferred terms contribute to each AESI. A further review will take place prior to DBL to ensure any further terms not already included are captured within the categories.

Durvalumab AEs of special interest and AEs of possible interest

Some clinical concepts (including some selected individual preferred terms and higher level terms) have been considered "AEs of special interest" (AESI) and "AEs of possible interest" (AEPI) to the durvalumab program.

AESI are defined as AEs that include, but are not limited to, events with a potential inflammatory or immune mediated mechanism that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy. Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (for example, therapies for hyperthyroidism include beta blockers [e.g., propranolol], calcium channel blockers [e.g., verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate).

The AEPIs reported in the AstraZeneca-sponsored durvalumab studies are defined as AEs that could have a potential inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab but are more likely to have occurred due to other pathophysiological mechanisms, thus, the likelihood of the event being inflammatory or immune-mediated in nature is not high and/or is most often or usually explained by the other causes.

The AESIs and AEPIs have been categorized into the following AESI/AEPI categories: Pneumonitis, Hepatic events, Diarrhoea/Colitis, Intestinal perforations, Adrenal Insufficiency, Type 1 diabetes mellitus, Hyperthyroid events, Hypophysitis, Hypothyroid events, Thyroiditis, Renal events, Dermatitis/Rash, Pancreatic events, Myocarditis, Myasthenia gravis, Guillain-Barre syndrome, Myositis, Infusion/hypersensitivity reactions and Other rare/miscellaneous. Other categories may be added or existing terms may be merged as necessary.

An AstraZeneca medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which preferred terms contribute to each AESI/AEPI. A further review will take place prior to Database lock (DBL) to ensure any further terms not already included are captured within the categories.

Immune-mediated Adverse Events (imAE)

imAE will be identified from both the Durvalumab AEs of special interest (AESIs) and AEs of possible interest (AEPIs) based on programmatic rules that consider interventions involving systemic steroid therapy, immunosuppressant use, and/or endocrine therapy (which, in the case of AEPIs, occurs after first considering an Investigator's causality assessment and/or an Investigator's designation of an event as immune-mediated). Endocrine therapies include standard endocrine supplementation, as well as treatment of symptoms resulting from endocrine disorders (for example, therapies for hyperthyroidism include beta blockers [e.g., propranolol], calcium channel blockers [e.g., verapamil, diltiazem], methimazole, propylthiouracil, and sodium perchlorate).

Further details are provided in a separate imAE charter. In addition, the Sponsor may perform medical review of those AESIs and classify them as imAEs or not imAEs via an independent manual adjudication process.

Counting incidence proportions of adverse events

Key guidelines for counting incidence proportions of adverse events are as follows:

- When a patient has the same AE reported multiple times during an analysis period based on SOC and PT, the patient will only be counted once within a level of MedDRA in an AE incidence table.

- When assessing investigator-reported relationship to study drug of the AEs, if an AE changes in causal relationship during an analysis period for a patient, the related event will be chosen. Causally related AEs will include those reported as related by the investigator and those with a missing relationship. AE with a missing relationship will be presented as related in summary tables but will be presented in the data listing with a missing relationship.
- When summarising intensity of the AEs, if an AE changes in CTCAE grade during an analysis period for a patient, the AE with the maximum CTCAE grade will be chosen. In case the AE term (SOC and PT) is reported more than once, one of them with missing grade, and at least another with non-missing grade, the maximum CTCAE grade will be chosen from the non-missing grade values and the missing grade can be ignored. If all are of missing grade, then the AE severity will be summarised in an additional "Unknown" intensity category.

4.6.2.2 Presentation

The AE summaries, unless otherwise stated, will be based on treatment-emergent AEs up until the start of subsequent anti-cancer therapy (including non-palliative radiotherapy) or until the end of safety follow-up period (latest of either 30 days following discontinuation of olaparib or 90 days following discontinuation of durvalumab), whichever occurs first. This will more accurately depict AEs attributable to only the study treatment as a number of AEs following discontinuation of the study treatment are likely to be attributable to subsequent therapy. In order to assess the longer-term toxicity profile, a selection of AE summaries may be produced containing AEs observed up until the end of follow-up period (i.e. without taking subsequent therapy into account).

All adverse event summary tables will include treatment-emergent AEs observed overall and will be summarised by phase: neo-adjuvant intervention period (ie, up to surgery) and adjuvant intervention period (ie, from first dose of olaparib after surgery up to 30 days after discontinuation of olaparib).

An overview table will summarize the number and percentage of patients in each category listed below as well as the number of individual occurences in those categories by actual study intervention group (overall and by treatment phase). Each AE category will be separately summarised by SOC and PT:

- All TEAEs
- TEAEs by maximum CTCAE grade
- TEAEs with maximum CTCAE grade 3 or 4
- TEAEs causally related to olaparib/durvalumab *
- TEAEs with maximum CTCAE grade 3 or 4, causally related to olaparib/durvalumab *
- TEAEs with outcome of death
- TEAEs with outcome of death causally related to olaparib/durvalumab *
- All serious treatment emergent adverse events (SAEs)
- All SAEs causally related to olaparib/durvalumab *
- TEAEs leading to discontinuation of study intervention
- TEAEs leading to discontinuation of study intervention, causally related to olaparib/durvalumab *
- AEs leading to a dose interruption of durvalumab/olaparib
- AEs leading to a dose reduction of olaparib
- Other significant AEs (OAEs)
- Immune mediated AEs as determined by reporting investigator
- Infusion related AEs as determined by the reporting investigator

**Causality as determined by the reporting investigator*

Sorting will be by internationally agreed order for SOC, and alphabetically for PT within SOC.

Additionally, the most common AEs will be summarised by PT, by decreasing frequency based on the total number of AEs across treatment groups. This cut-off may be modified after review of the data.

Listings

All reported AEs (including pre- and post-treatment AEs) will be listed including the date of onset, date of resolution (if AE is resolved) and investigator's assessment of CTCAE grade and relationship to study treatment.

In addition, key patient information will be listed separately for participants with AEs with outcome of death, SAEs, AEs leading to discontinuation of study intervention.

A flag indicating the phase (neoadjuvant or adjuvant) during which TEAE occurred will be added and any events that occur after a patient has received further therapy for cancer will be flagged in the data listings.

Death

A separate summary of all deaths will be provided with number and percentage of patients by treatment group, categorized as:

- Total number of death (regardless of date of death)
- Death related to disease under investigation only as determined by the investigator
- AE with outcome of death only
- Death related to disease under investigation and an AE with outcome of death
- Deaths after end of safety follow up period (latest of either last treatment dose of olaparib + 30 days or last infusion of durvalumab + 90 days), and not due to disease under investigation
- Unknown reason for death
- Other deaths

A list of all deaths will also be produced.

Adverse events of special interest (AESI) and adverse events of possible interest (AEPI)

Preferred terms used to identify AESI and adverse events possible interest (AEPIs are for durvalumab only) will be listed before DBL and documented in the Study Master File.

For Durvalumab: Grouped summary tables of certain MedDRA preferred terms will be produced and may also show the individual preferred terms which constitute each AESI/AEPI grouping. Groupings will be based on preferred terms provided by the medical team prior to DBL, and a listing of the preferred terms in each grouping will be provided.

For Olaparib: A separate summary table will also be produced capturing any toxicities of interest. Note the summary table capturing the toxicities of interest of MDS/AML and new primary malignancy includes events from first dose of study drug until the end of the study (i.e. not restricted to treatment emergent events).

The toxicities of interest are:

- Myelodysplastic syndrome/Acute Myeloid Leukaemia
- New Primary Malignancy
- Pneumonitis

Immune-mediated Adverse events (imAEs)

The imAEs (as classified by the Sponsor) will be summarized in the similar manner as for the summaries for durvalumab AESI/AEPI described above. See further details in the durvalumab imAE Charter with respect to derivation rules.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Assessments of safety laboratory tests will be performed at a local laboratory at or near to the investigator site. Parameters related to blood sample laboratory data including haematology, clinical chemistry and coagulation (see CSP, Tables 9 for a list of laboratory tests) will be assessed based on samples that will be collected throughout the study, from screening to end of safety follow-up visit.

Absolute values will be compared to the local laboratory reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings.

Derivation rules for post baseline visit values determination including visit window and multiple records are described in Section 3.3.

As applicable, values will be converted to standard units and will be graded using CTCAE version 5.0. Maximum post-baseline CTCAE grade will also be calculated.

4.6.3.2 Presentations

Data obtained up until the end of safety follow-up period (latest of 90 days after last dose of durvalumab or 30 days after the last dose of olaparib intervention period) or until the initiation of the subsequent therapy (including nonpalliative radiotherapy) following discontinuation of treatment (whichever occurs first) will be used for reporting. This will more accurately depict laboratory toxicities attributable to only the study treatment as a number of toxicities in the follow-up period are likely to be attributable to subsequent therapy.

Any data collected after the end of survival follow-up period (i.e. after the last safety follow-up visit) will not be summarised.

A small selection of summaries of laboratory data may also be produced containing data from initiation of the first subsequent therapy following discontinuation of study treatment until

the latest of 90 days following discontinuation of durvalumab or 30 days following discontinuation of olaparib (i.e. summarising the laboratory data collected on patients taking subsequent therapy during the safety collection follow-up window post discontinuation of study treatment). These outputs will only be produced if the number of laboratory toxicities observed warrant the inclusion of such outputs for interpretational purposes.

Data summaries will be provided in International System (SI) of units.

Box-plots of absolute values and change from baseline for a selection of continuous laboratory assessments will be presented.

For all continuous laboratory assessments, absolute value, change from baseline and percentage change from baseline will be summarised using descriptive statistics at each scheduled assessment time by actual study intervention group. For categorical laboratory assessments, shift from baseline will be summarised using frequency and proportion at each scheduled assessment time by actual study intervention group.

Shift tables for laboratory values by worst common toxicity criteria (CTCAE) grade will be produced, and for specific parameters the indication of hyper- and hypo-directionality of change will be produced. The laboratory parameters for which CTCAE grade shift outputs will be produced are:

- Haematology: Haemoglobin, Total white cell count (Leukocytes), Absolute lymphocyte count, Absolute neutrophil count, Platelet count
- Clinical chemistry: Albumin– hypo and – hyper, ALP, ALT, Amylase, AST, Bilirubin (total), Creatinine, Total calcium – hypo and – hyper, Gamma glutamyltransferase, Glucose – hypo and – hyper, Lactate Dehydrogenase, Lipase, Magnesium- hypo and-hyper, Potassium – hypo and – hyper, Sodium – hypo and – hyper, TSH.

The denominator used in shift tables will only include evaluable patients, i.e., those who had sufficient data to have the possibility of an abnormality.

For example:

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

Clinically significant laboratory results will be flagged and listed. Reference ranges will also be listed. All laboratory summaries and listings will be presented by actual study intervention group.

Liver Function

For liver biochemistry, the following summaries will include the number and percent of patients who have:

- Elevated ALT, AST, and Total bilirubin during the study
  - ALT ≥ 3x –≤ 5x, > 5x – ≤8x, > 8x - ≤ 10x, >10x - ≤ 20x and >20x Upper Limit of Normal (ULN) during the study
  - AST ≥ 3x- –≤ 5x, > 5x – ≤8x, > 8x - ≤ 10x, >10x - ≤ 20x,and >20x ULN during the study
  - Total bilirubin ≥2x-≤3x, >3x-≤5x, >5x ULN during the study
  - ALT or AST ≥3x - ≤5x, >5x - ≤8x, >8x - ≤ 10x, >10x - ≤ 20x, and >20x ULN during the study
  - ALT or AST ≥3x ULN and Total bilirubin ≥2x ULN during the study (Potential Hy's law: The onset date of ALT or AST elevation should be prior to or on the date of Total Bilirubin elevation)

Liver biochemistry test results over time for patients with elevated ALT or AST (i.e. ≥ 3x ULN), and elevated Total bilirubin (i.e. ≥ 2x ULN) (at any time) will be plotted. Individual patient data where ALT or AST (i.e. ≥ 3x ULN) plus Total bilirubin (i.e. ≥ 2x ULN) are elevated at any time will be listed also.

Plots of ALT and AST vs. Total bilirubin all expressed as multiples of ULN by treatment group will also be produced with reference lines at 3×ULN for ALT, AST, and 2×ULN for Total bilirubin. In each plot, Total bilirubin will be in the vertical axis.

Assessment of Thyroid Function Test Results

The following summaries will include the number and percentage of patients who have elevated or low TSH.

- TSH > ULN
- TSH > ULN with TSH ≤ ULN at baseline
- TSH > 3 X ULN
- TSH > 3 X ULN with TSH ≤ ULN at baseline
- TSH > 10 X ULN
- TSH > 10 X ULN with TSH ≤ ULN at baseline;
- TSH < LLN
- TSH < LLN with TSH ≥ LLN at baseline
- Number of patients with at least one baseline and post-baseline TSH result
  - On-treatment elevated TSH > ULN and above baseline
  - On-treatment decreased TSH < LLN and below baseline
- Grade change from baseline to on treatment minimum and maximum

Absolute value and change from baseline of TSH, free T3 and free T4 will be summarised using descriptive statistics at each scheduled assessment time.

Assessment of Renal Function Test Abnormalities

In addition to the analysis for serum creatinine, the number and percentage of patients with creatinine clearance (CrCl) rate during treatment period meeting the following categories will be presented:

- Normal: CrCl $\geq$ 90 mL/min
- Mild Impairment: CrCl $\geq$ 60 - < 90 mL/min
- Moderate Impairment: CrCl $\geq$ 30 - < 60 mL/min
- Severe Impairment: CrCl $\geq$ 15 - < 30 mL/min
- Kidney Failure: CrCl < 15 mL/min

Creatinine clearance rate will be calculated using serum Creatinine and the Cockcroft-Gault formula (Cockcroft and Gault 1976), as specified in the protocol.

Pregnancy

A listing of pregnancy results and, if applicable, a pregnancy report will be provided for safety analysis set.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Urine samples for determination of urinalysis including Colour and appearance, pH and specific gravity, Blood, Bilirubin, Glucose and Ketones will be taken at the visits indicated in the protocol SOA.

4.6.4.2 Presentations

Categorical data of urinalysis results will be listed only.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Not applicable

4.6.5.2 Presentations

Not applicable

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs parameters such as systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiratory rate, temperature and weight will be evaluated at screening, at each neoadjuvant and adjuvant cycles, at post-neoadjuvant safety follow-up visit and at safety follow-up visit. Height will be measured at screening only.

For Cohort B only, on the first durvalumab infusion day, vital signs will be collected/recorded in eCRF 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)
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±10 minutes)

For Cohort B only, on subsequent infusion days, blood pressure, pulse, and other vital signs should be measured, collected/recorded in the eCRF prior to the start of the infusion.

Participants should be carefully monitored, and blood pressure and other vital signs should be measured during and after infusions, as per institution standards and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF page.

For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

For derivation of post-baseline visit values, visit window and multiple records handling will be handled as described in Section 3.3.

4.6.6.2 Presentations

Vital signs parameters defined above will be summarised over time in terms of absolute values and changes from baseline at each scheduled visit.

For assessments related to the first infusion of durvalumab (cohort B only Cycle 1), data for the 3 timepoints (pre-dose, during and after infusion) will also be summarised. Change from pre-dose to during/after infusion will be also summarised for during and after infusion vital signs.

Vital signs data will be listed by actual treatment arm.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

Single 12-lead electrocardiograms (ECGs) will be performed for participant receiving durvalumab only at screening, when clinically indicated during the neoadjuvant intervention period and at post-neodajuvant safety assessment (90 days from last infusion of durvalumab).

All ECGs should be assessed by the investigator, on the study days that the ECGs were performed, as to whether they are clinically significantly abnormal. Any clinically significant abnormalities detected require triplicate ECG results. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.

Baseline and post-baseline values will be derived as average of assessments collected using triplicate measurements.

If there is a clinically significant abnormal finding, the investigator will record it as an AE on the eCRF.

4.6.7.2 Presentations

ECG data obtained before study treatment and up until the 90-day safety follow-up visit will be listed for the Safety Analysis Set (olaparib + durvalumab arm only). The listing will include the ECG interpretation (Normal, Borderline, Abnormal Not Clinically Significant, and Abnormal Clinically Significant).

4.6.8 Other Safety Assessments – ECOG performance status

4.6.8.1 Definitions and Derivations

ECOG performance status will be assessed at screening and the first day of each neoadjuvant and adjuvant cycle 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.

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

ECOG performance status will be determined using ECOG eCRF module.

Analysis visit windows as described in section 3.3.2 will be applied.

4.6.8.2 Presentations

ECOG performance status data will be listed for each actual study intervention group.

5 INTERIM ASSESSMENT

An interim assessment of efficacy will be performed in Cohort A and Cohort B and will include the first CCI participants in each cohort who have completed neoadjuvant therapy or discontinue study intervention for any reason. Within each cohort, if CCI participant experiences clinical progressive disease (cPD)/death, enrolment will continue in that same cohort until approximately 25 participants are enrolled. If CCI of the initial CCI participants experience cPD/death, enrolment will be paused for additional review.

Demographics and baseline characteristics will be summarised for this interim assessment (including the BRCA status and TNM tumour stage). A summary of the number (%) of patients with cPD disease or death will be performed by cohort. In addition, the investigator's decision to change neoadjuvant therapy or proceed to definitive surgery prior to completion of neoadjuvant therapy as a rescue intervention will be summarised and listed. This will be retrieved from the BCSURG module of the eCRF.

No Data Monitoring Committee is planned, as this is an open-label non-randomised Phase II study. A Steering Committee comprised of the principal investigators for Study D931CC00001 and members of the AstraZeneca olaparib and durvalumab development programs will convene throughout the study to review accruing efficacy and safety data and to provide advice on any aspect of the study design or conduct based upon requests from the sponsor. The Steering Committee review will be described in a separate charter.

6 REFERENCES

Hammer et al 2010
Hammer, S., Sommer, A., Fichtner, I.D., Becker, M.W., Rolff, J., Merk, J., Klar, U., & Hoffmann, J. (2010). Comparative Profiling of the Novel Epothilone, Sagopilone, in Xenografts Derived from Primary Non–Small Cell Lung Cancer. Clinical Cancer Research, 16, 1452 - 1465.

Cruz et al 2018
Cruz, C., Llop-Guevara, A., Garber, J. E., Arun, B. K., Perez Fidalgo, J. A., Lluch, A., Telli, M. L., Fernández, C., Kahatt, C., Galmarini, C. M., Soto-Matos, A., Alfaro, V., De La Haza, A. P., Domchek, S. M., Antolin, S., Vahdat, L., Tung, N. M., Lopez, R., Arribas, J., ... Isakoff, S. J. (2018). Multicenter phase II study of lurbinectedin in BRCAMutated and unselected metastatic advanced breast cancer and biomarker assessment substudy. Journal of Clinical Oncology, 36(31), 3134-3143.

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