• Protocol number: D5336C00001
• Document title: A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including *BRCA1/2*) (VIOLETTE)
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Statistical Analysis Plan

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A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including *BRCA1/2*) (VIOLETTE)iii

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CRO Study Statistician

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PAREXEL International

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Date

Statistical Analysis Plan
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Date 14 Jun 2019

A Phase II, Open Label, Randomised, Multi-centre Study to Assess the Safety and Efficacy of Agents Targeting DNA Damage Repair in Combination with Olaparib versus Olaparib Monotherapy in the Treatment of Metastatic Triple Negative Breast Cancer Patients Stratified by Alterations in Homologous Recombinant Repair (HRR)-related Genes (including *BRCA1/2*)

Global Product Statistician

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25 July 2019

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this Statistical Analysis Plan.

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
CCI	[redacted]
ATR	Ataxia Telangiectasia and Rad3-related protein
AZ	AstraZeneca
bd	bis in die; twice daily
BICR	Blinded Independent Central Review
BRCA1 and *BRCA2*	Breast cancer susceptible gene 1 and 2
BRCAm	Breast cancer susceptible gene mutation
CCI	[redacted]
CI	Confidence interval
$C_{min\ ss}$	Minimum concentration at steady state
CR	Complete response
CRO	Contract Research Organisation
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CV	Coefficient of variation
DAE	Discontinuation of Investigational Product due to Adverse Events
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status: a performance status using scales and criteria to assess how a patient's disease is progressing

Abbreviation or special term	Explanation
eCRF	Electronic case report form
EDoR	Expected duration of response
CCI	CCI
FAS	Full analysis set
HR	Hazard ratio
HRR	Homologous Recombination Repair
HRR*m*	Homologous Recombination Repair gene mutation
ID	Identification
IPD	Important protocol deviation
ISRC	Independent Safety Review Committee
KM	Kaplan-Meier
LLoQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
CCI	
NC	Not calculable
NE	Not evaluable
NED	No evidence of disease
NPD	Non-progressive disease
NQ	Not quantifiable
NTL	Non-target lesion
MDS	Myelodysplastic syndrome
OAE	Other significant adverse event
Od	Once daily
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
CCI	
CCI	CCI CCI

Abbreviation or special term	Explanation
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable disease
SD	Standard deviation
SI	International System of Units (Système international d'unités)
TL	Target lesion
TNBC	Triple Negative Breast Cancer
tsm	Tumour size measurement
ULN	Upper limit of normal
ULoQ	Upper limit of quantification
URC	Unblinded review committee

STATISTICAL ANALYSIS PLAN AMENDMENT HISTORY

Date	Brief description of change
5Dec2017	Initial Version
Effective date of last signature	Updated for consistency with Protocol Amendment 6.0 (29 Apr 2019) in which urgent safety issue resulted in AZD1775+olaparib arm being closed to recruitment

1. STUDY DETAILS

1.1 Study objectives

Study objectives are defined for the following patient populations (strata A, B, C are explained in Section 1.2.1, *BRCAm* stands for BReast CAncer susceptible gene mutation, HRR*m*" stands for Homologous Recombination Repair gene mutation):

- "*BRCAm*" = patients from stratum A
- "HRR*m*" = patients from stratum A and patients from stratum B
- "Non *BRCAm* HRR*m*" = patients from stratum B
- "All" = patients from any stratum
- "Non HRR*m*" = patients from stratum C

1.1.1 Primary objective

Patient Population	Primary Objective	Outcome Measure
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To assess the efficacy of the combination of AZD6738+Olaparib and the combination of AZD1775+Olaparib compared with Olaparib monotherapy by assessment of progression-free survival (PFS)	PFS using Blinded Independent Central Review (BICR) according to Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1

1.1.2 Secondary objectives

Patient Population	Secondary Objectives	Outcome Measures
• HRR*m* • All	To assess the efficacy of the combination of AZD6738+Olaparib and the combination of AZD1775+Olaparib compared with Olaparib monotherapy by assessment of PFS	PFS using BICR according to RECIST 1.1 Sensitivity analysis of PFS using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To assess the efficacy of the combination of AZD6738+Olaparib and the combination of AZD1775+Olaparib compared with Olaparib monotherapy in terms of objective response rate (ORR)	ORR using BICR according to RECIST 1.1 Sensitivity analysis of ORR using Investigator assessments according to RECIST 1.1

Patient Population	Secondary Objectives	Outcome Measures
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To assess the efficacy of the combination of AZD6738+Olaparib and the combination of AZD1775+Olaparib compared with Olaparib monotherapy in terms of duration of response (DoR) and tumour change	DoR and tumour change using BICR according to RECIST 1.1 Sensitivity analysis of DoR, and tumour change using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To assess the efficacy of the combination of AZD6738+Olaparib and the combination of AZD1775+Olaparib compared with Olaparib monotherapy in terms of overall survival (OS)	Time to death for any cause
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To compare the efficacy of the combination of AZD6738+Olaparib with the combination of AZD1775+Olaparib in terms of PFS and ORR	PFS and ORR using BICR according to RECIST 1.1 Sensitivity analysis of PFS and objective response using Investigator assessments according to RECIST 1.1
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	To compare the efficacy of the combination of AZD6738+Olaparib with the combination of AZD1775+Olaparib in terms of DoR and tumour change	DoR and tumour change using BICR according to RECIST 1.1 Sensitivity analysis of DoR and tumour change using Investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	To compare the efficacy of the combination of AZD6738+Olaparib with the combination of AZD1775+Olaparib in terms of OS	Time to death for any cause
• All	To explore the frequency of and describe the nature of tumour HRR (including *BRCA*) mutation(s) in tumour samples and to compare this with germline HRR (including *BRCA*) mutation status	Mutation status of CCI genes
• All	To assess exposure to Olaparib, AZD6738 and AZD1775 in all patients	Minimum concentration at steady state ($C_{min\ ss}$)

1.1.3 Safety objectives

Patient Population	Safety Objective	Outcome Measure
• All	To assess the safety and tolerability of the combination of AZD6738+Olaparib and the combination of AZD1775+Olaparib compared with Olaparib monotherapy	• Adverse Events (AEs), severity graded by Common Terminology Criteria for Adverse Event (CTCAE) v4 • laboratory tests (clinical chemistry, haematology and urinalysis) • vital signs: pulse and blood pressure • electrocardiogram (ECG) data • Eastern Cooperative Oncology Group performance status (ECOG PS)

1.1.4 Exploratory objectives

Not all data generated as part of exploratory objectives will be included in the Clinical Study Report (CSR); respective analyses will be reported separately and are not covered by this Statistical Analysis Plan (SAP).

Patient Population	Exploratory Objectives	Outcome Measure
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	CCI [redacted]	CCI [redacted]

1.2 Study design

This is a prospective, open label, randomised, multi-centre Phase 2 study that will assess the efficacy and safety of Olaparib monotherapy versus Olaparib in combination with an inhibitor of ATR (AZD6738) and Olaparib monotherapy versus Olaparib in combination with an inhibitor of WEE1 (AZD1775) in second or third line setting in patients with Triple Negative Breast Cancer (TNBC) prospectively stratified by presence/absence of qualifying tumour mutation in genes involved in the HRR pathway.

1.2.1 Stratification of patient population

The study patient population will be stratified as described below:

- stratum A: patients with tumour mutations in *BRCA1* or *BRCA2* (*BRCAm*)
- stratum B: patients with tumour mutations in any of the following CCI genes involved in the Homologous Recombination Repair (HRR) pathway (CCI [redacted],

CCI [redacted])
and no mutation in *BRCA1* and no mutation in *BRCA2*

- stratum C: patients that have no detected tumour mutations in any of the CCI HRR genes mentioned above.

Within each stratum A, B and C, there will be further stratification by whether the patient received prior platinum-based therapy (yes/no) as defined in the study protocol

1.2.2 Treatment arms

The 3 treatment arms are:

- Treatment Arm 1: 300 mg twice daily (bd) Olaparib continuous (28-day cycle)
- Treatment Arm 2: 160 mg once daily (od) AZD6738 Days 1-7 + 300 mg bd Olaparib continuous (28-day cycle)
- Treatment Arm 3: 175 mg bd AZD1775 Days 1-3 and 8-10 + 200 mg bd Olaparib continuous (21-day cycle) (Randomization to treatment arm 3 closed April 2019. Existing patients will continue receiving Olaparib monotherapy or discontinue all study treatment.)

Due to the different schedules of administration of each of the treatment options as well as their different toxicity profiles, the study cannot be blinded for patients and site personnel. Given the open label design of the study, efforts will be made to ensure robustness of the primary endpoint assessment (including the BICR) and to avoid any unnecessary unblinding of the operational study team. Details are described in a separate study-specific Blinding Maintenance Plan.

1.2.3 Randomisation

Eligible patients will be randomised (using randomisation ratio 1:1:1) to Olaparib monotherapy, AZD6738+Olaparib or AZD1775+Olaparib. Effective April 2019, eligible patients will be randomised (using randomisation ratio 1:1) to Olaparib monotherapy or AZD6738+Olaparib.

The randomisation scheme will be stratified based on:

- the primary patient population: stratum A (*BRCAm*), stratum B (non *BRCAm* HRR*m*), stratum C (non HRR*m*) as defined in Section 1.2.1
- and patient's prior platinum-based therapy (no / yes)

so that there will be a total of 6 strata: An, Ay, Bn, By, Cn, Cy.

The 3 primary patient populations A, B, C will be capped to have approximately 150 patients each (approximately 50 patients per treatment arm). It is expected that the non-HRR*m* patient population will be recruited fastest.

1.2.4 Diagnostic journey and study flow chart

Please refer to the diagnostic journey (Figure 1) and study flow chart (Figure 2). (Randomization to AZD1775+Olaparib treatment arm closed in April 2019.)

Figure 1 Diagnostic journey

Note: Stratum A: *BRCAm*, stratum B: non *BRCAm* HRR*m*, stratum C: non HRR*m.* The AZD1775+Olaparib treatment arm was closed following the ISRC meeting on the 17 April 2019.

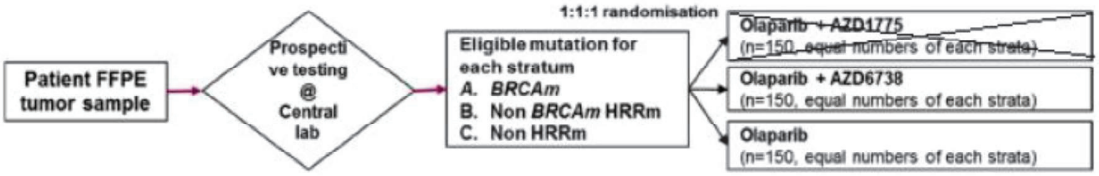
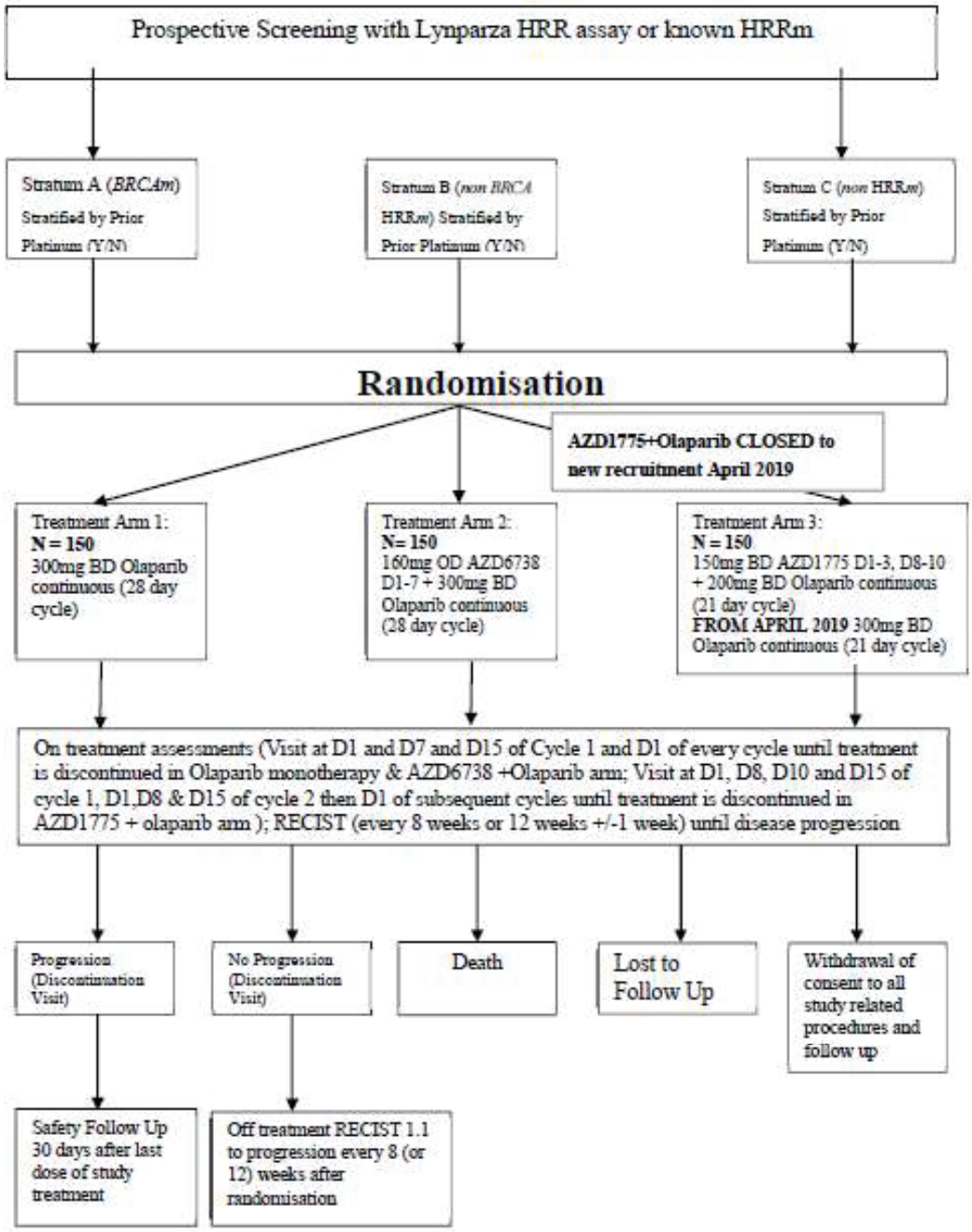


Figure 2 Study flow chart



In addition, a survival follow-up is conducted every 8 weeks (± 7 days) after the Safety Follow Up visit.

1.2.5 Study governance and oversight

AstraZeneca Unblinded Review Committee

An AstraZeneca Unblinded Review Committee (AZ URC) will be convened and will conduct a review of the planned interim efficacy analyses described in Section 5. Safety will also be reviewed at this time. Full details of the AZ URC procedures and processes can be found in the AZ URC Charter.

Independent Safety Review Committee

An independent Safety Review Committee (ISRC) will monitor safety and tolerability in the study at regular intervals. Full details of the ISRC procedures, processes and potential recommendations can be found in the ISRC Charter.

1.3 Number of events and patients

In the 3 primary patient populations A, B, C, for each of the 2 comparisons (AZD6738 + Olaparib vs Olaparib monotherapy, AZD1775 + Olaparib vs Olaparib monotherapy), 68 PFS events would have 80% power to show a statistically significant difference at the 2-sided 10% significance level if the assumed true treatment effects were hazard ratio (HR) 0.55. This translates to a 5 month benefit in median PFS over 6 months on Olaparib in the *BRCAm* patient population and a 4.17 month benefit in median PFS over 5 months on Olaparib in the non *BRCAm* HRR*m* patient population and in the non HRR*m* patient population if PFS is exponentially distributed.

Approximately 50 patients (450 patients overall) will be randomised to each of the 3 treatment arms within each of the 3 primary patient populations A, B, C so that data maturity for the PFS analysis is approximately 68%.

Following the decision of the ISRC to close recruitment to the AZD1775+olaparib arm in April 2019, fewer than 50 patients per strata will be randomised to this arm. The total number of patients randomised will be lower (approximately 350 patients overall). The study will only be sized to test for a difference between the AZD6738+olaparib vs. olaparib monotherapy arms.

Assuming 15 months non-linear recruitment, the required number of PFS events are expected to occur approximately 24 months after the first patient is randomised.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full analysis set

The full analysis set (FAS) will include all randomised patients with treatment arms assigned in accordance with the randomisation, regardless of the treatment actually received. Patients who were randomised but did not subsequently receive treatment are included in the FAS.

Patients randomized to the AZD1775+olaparib arm will be analysed as such, regardless of whether they discontinued study treatment entirely or received olaparib monotherapy after closure of the AZD1775+olaparib treatment arm in April 2019. The analysis of data using the FAS therefore follows the principles of intent to treat (ITT). All efficacy and CCI [redacted] data will be summarised and analysed using the FAS. Disposition, demographic data, baseline characteristics, etc will be summarized using the FAS.

2.1.2 Safety analysis set

The safety analysis set (SAF) will include all patients who received at least one dose of study treatment (regardless of whether that was the randomised therapy intended or indeed whether, in rare cases, they received therapy without being randomised), according to the study treatment they actually received, defined as below:

- if a patient received at least one dose of Olaparib, no dose of AZD6738 and no dose of AZD1775, then the patient will be counted for treatment arm 1 (Olaparib alone) in the SAF
- if a patient received at least one dose of AZD6738 and no dose of AZD1775, then the patient will be counted for treatment arm 2 (AZD6738 + Olaparib) in the SAF
- if a patient received at least one dose of AZD1775 and no dose of AZD6738, then the patient will be counted for treatment arm 3 (AZD1775 + Olaparib) in the SAF
- if a patient received at least one dose of AZD1775 and at least one dose of AZD6738, then it will be decided at the Blinded Data Review Meeting to which treatment arm the patient will be assigned for the safety analysis.

All safety data and drug exposure data will be summarised and analysed using the SAF.

2.1.3 PK analysis set

All patients who received at least one dose of study treatment per the protocol and for whom there is at least one reportable pharmacokinetics (PK) concentration will be included in the PK analysis set. The PK analysis set is a subset of the SAF and analyses using the PK analysis set will be based on study treatment patients actually received, defined as for the SAF above in Section 2.1.2.

2.2 Violations and deviations

Important protocol deviations (IPDs) are defined as 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. IPDs are defined in detail in the Protocol Deviation Specification Document.

All IPDs will be listed and summarised for the FAS by treatment arm.

Note:

- there is no per-protocol analysis set (all efficacy and CCI [redacted] data will be summarized and analysed for the FAS only, see Section 2.1)

- and the handling of patients to whom wrong study treatment pack(s) (containing study treatment different to the randomized treatment) were dispensed and subsequently taken by the patient is described in Section 2.1.2.

3. PRIMARY AND SECONDARY VARIABLES

3.1 General variables

3.1.1 Definitions of Study Day and Dose Day

For efficacy, Study Day 1 is defined as the date of randomisation. For visits (or events) that occur on or after date of randomisation, study day is defined as (date of visit [event] - date of randomisation + 1). For visits (or events) that occur prior to the date of randomisation, study day is defined as (date of visit [event] - date of randomisation). There is no Study Day 0.

For safety, Dose Day 1 is defined as the date of first dose of study treatment. For visits (or events) that occur on or after the date of first dose, dose day is defined as (date of visit [event] - date of first dose of study treatment + 1). For visits (or events) that occur prior to the date of first dose, dose day is defined as (date of visit [event] - date of first dose of study treatment). There is no Dose Day 0.

For listings that include the derivation of "days since last dose of any of the study treatments," this is defined as (event date - date of last dose of study treatment). Events that occur on the same day as the last dose of study treatment will therefore be described as occurring zero days from the last dose of study treatment.

3.1.2 Handling of partial dates

Date of birth and age

- Patients with a partial date of birth (e.g., for patients in those countries where only year of birth is provided) will have an assumed date of birth of 1st Jan [given year].
- For patients with a missing age value (because of completely missing date of birth)
  - the mean age (overall FAS) will be imputed for subgroup analysis by age and for assignment of age-specific safety laboratory normal ranges
  - no imputation will be done for descriptive table of demographics, i.e., such patients will not be included in the calculation of means, etc.

Concomitant medication and adverse events start dates

- If year is missing (or date completely missing), do not impute.
- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as 01 January.
- If year and month are present and day is missing, impute day as first day of the month.

Concomitant medication and adverse events end dates

- If year is missing (or date completely missing), do not impute.

- If (year is present and month and day are missing) or (year and day are present and month is missing), impute as 31 December, unless this is after the date of death in which case date of death will be used instead.
- If year and month are present and day is missing, impute day as last day of the month, unless this is after the date of death in which case date of death will be used instead.

In addition for AEs and concomitant medications if, for a partial start date, the start date could (when also considering the end date) potentially be on the first study medication date, the start date will be imputed with the date of first study treatment dose to assume a "worst case" scenario; e.g. AE from UNKFeb2014 to 23Mar2014 with date of first study treatment 21-Feb-2014, then the AE start date will be imputed to 21Feb2014 for further steps in the data analysis.

Death dates

- For patients where only the day in the date of death is missing and the month in the date of death shows that the death occurred in the same calendar month as the data cut-off, then it will be assumed that the death occurred on or prior to the date of the data cut-off.
- For patients where only the year in the date of death is available and it shows that the death occurred in the same calendar year as the data cut-off, then it will be assumed that the death occurred on or prior to the date of the data cut-off.

3.1.3 Handling of safety laboratory test results outside of quantification range

Safety laboratory test results below the lower limit of quantification (LLoQ) reported as "<LLoQ" or "≤LLoQ" will be imputed by LLoQ × 0.99 for tables and figures. The original test result will be listed.

Safety laboratory test results above the upper level of quantification (ULoQ) reported as ">ULoQ" or "≥ULoQ" will be imputed by ULoQ × 1.01 for tables and figures. The original test result will be listed.

3.1.4 Handling of PK results below lower limit of quantification

Individual compound concentrations below the LLoQ of the assay are reported as NQ (not quantifiable) with the LLoQ mentioned in respective tables, figures and listings.

For descriptive statistics:

- If, at a given time point, 50% or less of the plasma concentrations are NQ, the geometric mean, coefficient of variation (CV), geometric standard deviation (SD), arithmetic mean and SD are calculated by substituting the LLoQ for values which are NQ.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, CV, geometric SD, arithmetic mean and SD are reported as not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set as NQ.
- If all the concentrations are NQ, the geometric mean and arithmetic mean are reported as NQ and the CV, geometric SD and arithmetic SD as NC.
- The number of values below LLoQ is reported for each time point along with the total number of collected values.

Three observations >LLoQ are required as a minimum for a plasma concentration or PK parameter to be summarised. Two values are presented as a minimum and maximum with the other summary statistics as NC.

For consistency, the same plasma concentration values are used in the mean data graphs as those given in the descriptive statistics summary table for each time point.

3.2 RECIST-based efficacy assessments

Detailed definitions of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) and not evaluable (NE) can be found in Appendix F of the study protocol. Within the SAP, overviews are displayed in Table 1 and Table 3.

RECIST-based BICR data will be used to determine the primary endpoint PFS as well as the secondary endpoints ORR, DoR, and tumour size change for subsequent statistical analyses. RECIST-based site investigator data will be used to determine endpoints PFS, ORR, DoR, and tumour size change for subsequent statistical sensitivity analyses.

3.2.1 RECIST-based assessments by Blinded Independent Central Review

BICR of all radiological imaging data will be carried out using RECIST version 1.1. All radiological scans for all patients (including those at unscheduled visits, or outside visit windows as defined in Section 4.1.4) will be collected on an ongoing basis and sent to PAREXEL for BICR. The independent reviewers will be blinded to study treatment.

For each post-baseline visit scan, the BICR will define the RECIST 1.1 overall visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous scans by assessing target lesions (TLs), non-target lesions (NTLs) and new lesions. If a patient has had a tumour assessment that cannot be evaluated, then the patient will be assigned a visit response of NE unless there is evidence of progression in which case the response will be assigned as PD. No programmatic derivation of visit response is necessary.

The date of progression will be provided (by each reviewer) based on the earliest of the scan dates of the component that triggered the progression.

If adjudication is performed, the reviewer that the adjudicator agreed with will be selected as a single reviewer (note in the case of more than one review period, the latest adjudicator decision will be used). In the absence of adjudication, the records for all visits for a single reviewer will be used. The reviewer selected in the absence of adjudication will be the reviewer who read the baseline scan first. The records from the single selected reviewer will be used to report all BICR RECIST information including dates of progression, visit response, censoring and changes in target lesion dimensions. Endpoints will be derived programmatically from this information.

Results of this independent review will not be communicated to investigators and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the investigator.

Further details of the BICR are documented in the Independent Review Charter.

3.2.2 RECIST-based assessments by site investigators

Note: Endpoints based on RECIST data by site investigators will be based on tumour measurements provided by the site investigator and not based on electronic case report form (eCRF) boxes containing the investigator opinion on response. The overall visit response based on data provided by site investigators will be programmatically derived from the tumour lesion data.

From the investigator's review of the imaging scans, the RECIST tumour response data will be used to determine each patient's visit responses according to RECIST version 1.1. At each visit, patients will be programmatically assigned a RECIST 1.1 visit response of CR, PR, SD or PD depending on the status of their disease compared with baseline and previous assessments by using the information from TLs, NTLs and new lesions. If a patient has had a tumour assessment that cannot be evaluated then the patient will be assigned a visit response of NE unless there is evidence of progression in which case the response will be assigned as PD.

The date of progression will be based on the earliest of the scan dates of the component that triggered the progression.

3.2.2.1 Target lesions – site investigator data

For each patient, the site investigator will identify measurable tumour lesions at baseline (representative of all lesions involved and suitable for accurate repeated measurement) and these are referred to as TLs. If more than one baseline scan is recorded then measurements from the one that is closest and prior to randomisation will be used to define the baseline sum of diameters of TLs.

All other lesions (or sites of disease) not recorded as TL will be identified as NTLs at baseline. Measurements are not required for these lesions, but their status will be followed at subsequent visits.

Table 1 TL Visit Responses (RECIST 1.1)

Visit Responses	Description
Complete response (CR)	Disappearance of all TLs. Any pathological lymph nodes selected as TLs must have a reduction in short axis to <10mm.
Partial response (PR)	At least a 30% decrease in the sum of diameters of TLs, taking as reference the baseline sum of diameters as long as criteria for PD are not met.
Progressive disease (PD)	A ≥ 20% increase in the sum of diameters of TLs and an absolute increase of ≥ 5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Not evaluable (NE)	Only relevant in certain situations (i.e. if any of the TLs were not assessed or not evaluable or had a lesion intervention at this visit; and scaling up could not be performed for lesions with interventions). Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	No TLs are recorded at baseline.

Rounding of TL data

For calculation of PD and PR for TLs percentage changes from baseline and previous minimum should be rounded to one decimal point before assigning a TL response. For example 19.95% should be rounded to 20.0% but 19.94% should be rounded to 19.9%.

Missing TL data

For a visit to be evaluable all TL measurements should be recorded. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded
- A non-target lesion (NTL) visit response of PD is recorded
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared.

Note: the nadir can only be taken from assessments where all the TLs had a longest diameter (LD) recorded.

If there is at least one TL measurement missing and a visit response of PD cannot be assigned, the visit response is NE.

Lymph nodes

For lymph nodes, if the size reduces to < 10mm then these are considered non-pathological. However, a size will still be given and this size should still be used to determine the TL visit response as normal. In the special case where all lymph nodes are < 10mm and all other TLs are 0mm then although the sum may be > 0mm the calculation of TL response should be over-written as a CR.

TL visit responses subsequent to CR

CR, PD or NE can only follow a CR. If a CR has occurred then the following rules at the subsequent visits must be applied:

- Step 1: If all lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met, i.e. if a lymph node LD increases by 20% but remains < 10mm.
- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (i.e. 0mm or < 10mm for lymph nodes) then response will be set to NE irrespective of whether, when referencing the sum of TL diameters, the criteria for PD are also met.
- Step 3: If not all lesions meet the CR criteria and the sum of lesions meets the criteria for PD then response will be set to PD.
- Step 4: If after steps 1 – 3 a response can still not be determined the response will be set to remain as CR.

TL too big to measure

If a TL becomes too big to measure this should be indicated in the database and a size ('*x*') above which it cannot be accurately measured should be recorded. If using a value of *x* in the calculation of TL response would not give an overall visit response of PD, then this will be flagged and reviewed by the study team blinded to treatment assignment. It is expected that a visit response of PD will remain in the vast majority of cases.

TL too small to measure

If a TL becomes too small to measure then this will be indicated as such on the case report form and a value of 5mm will be entered into the database and used in TL calculations. However a smaller value may be used if the radiologist has not indicated 'too small to measure' on the case report form and has entered a smaller value that can be reliably measured. If a TL response of PD results then this will be reviewed by the study team blinded to treatment assignment.

Irradiated lesions/lesion intervention

Previously irradiated lesions (i.e. lesion irradiated prior to entry into the study) should be recorded as NTLs and should not form part of the TL assessment.

Any TL (including lymph nodes), which has had intervention during the study (for example, irradiation / palliative surgery / embolisation), should be handled in the following way and

once a lesion has had intervention then it should be treated as having intervention for the remainder of the study noting that an intervention will most likely shrink the size of tumours:

- Step 1: the diameters of the TLs (including the lesions that have had intervention) will be summed and the calculation will be performed in the usual manner. If the visit response is PD, this will remain as a valid response category.
- Step 2: If there was no evidence of progression after step 1, treat the lesion diameter (for those lesions with intervention) as missing and if ≤ 1/3 of the TLs have missing measurements then scale up as described in the 'Scaling' section below. If the scaling results in a visit response of PD then the patient would be assigned a TL response of PD.
- Step 3: If, after both steps, PD has not been assigned, then, if appropriate (i.e. if ≤ 1/3 of the TLs have missing measurements), the scaled sum of diameters calculated in step 2 should be used, and PR or SD then assigned as the visit response. Patients with intervention are evaluable for CR as long as all non-intervened lesions are 0 (or <10mm for lymph nodes) and the lesions that have been subject to intervention have a value of 0 (or <10mm for lymph nodes) recorded. If scaling up is not appropriate due to too few non-missing measurements then the visit response will be set as NE.

At subsequent visits, the above steps will be repeated to determine the TL and overall visit response. When calculating the previous minimum, lesions with intervention should be treated as missing and scaled up (as per step 2 above).

Scaling (applicable only for irradiated lesions/lesion intervention)

If > 1/3 of TL measurements are missing because of intervention then the TL response will be NE, unless the sum of diameters of non-missing TL would result in PD (i.e. if using a value of 0 for missing lesions, the sum of diameters has still increased by 20% or more compared to nadir and the sum of TLs has increased by ≥5mm from nadir).

If ≤ 1/3 of the TL measurements are missing because of intervention then the results will be scaled up (based on the sizes at the nadir visit to give an estimated sum of diameters and this will be used in calculations; this is equivalent to comparing the visit sum of diameters of the non-missing lesions to the nadir sum of diameters excluding the lesions with missing measurements.

Lesions that split in two

If a TL splits in two, then the LDs of the split lesions should be summed and reported as the LD for the lesion that split.

Lesions that merge

If two TLs merge, then the LD of the merged lesion should be recorded for one of the TL sizes and the other TL size should be recorded as 0cm.

Change in method of assessment of TLs

Computed tomography (CT), magnetic resonance imaging (MRI) and clinical examination are the only methods of assessment that can be used within a trial, with CT and MRI being the preferred methods and clinical examination only used in special cases. If a change in method

of assessment occurs, between CT and MRI this will be considered acceptable and no adjustment within the programming is needed.

If a change in method involves clinical examination (e.g. CT changes to clinical examination or vice versa), any affected lesions should be treated as missing.

3.2.2.2 Non-target lesions (NTLs) and new lesions – site investigator data

At each visit, the investigator should record an overall assessment of the NTL response. This section provides the definitions of the criteria used to determine and record overall response for NTL at the investigational site at each visit.

NTL response will be derived based on the investigator's overall assessment of NTLs as described in Table 2.

Table 2 NTL Visit Responses

Visit Responses	Description
Complete response (CR)	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis).
Progressive disease (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases, the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Non-CR/Non-PD	Persistence of one or more NTLs with no evidence of progression.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if there are no NTLs at baseline.

To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in TLs, the overall tumour burden has increased sufficiently to merit a determination of disease progression. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

Details of any new lesions will also be recorded with the date of assessment. The presence of one or more new lesions is assessed as progression.

A lesion identified at a follow up assessment in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour.

New lesions will be identified via a Yes/No tick box. The absence and presence of new lesions at each visit should be listed alongside the TL and NTL visit responses.

A new lesion indicates progression so the overall visit response will be PD irrespective of the TL and NTL response.

If the question 'Any new lesions since baseline' has not been answered with Yes or No and the new lesion details are blank this is not evidence that no new lesions are present, but should not overtly affect the derivation. Note: This scenario (i.e. whereby new lesion response is NE), should only occur in exceptional cases, as missing data for the new lesion field should always be queried.

Symptomatic progression is not a descriptor for progression of NTLs: it is a reason for stopping study therapy and will not be included in any assessment of NTLs.

Patients with 'symptomatic progression' requiring discontinuation of treatment without objective evidence of disease progression at that time should continue to undergo tumour assessments where possible until objective disease progression is observed.

3.2.2.3 Overall visit response – site investigator data

Table 3 defines how the previously defined TL and NTL visit responses will be combined with new lesion information to give an overall visit response.

Table 3 Overall visit responses

TARGET	NON-TARGET	NEW LESIONS	OVERALL VISIT RESPONSE
CR	CR or NA	No (or NE)	**CR**
CR	Non-CR/Non-PD or NE	No (or NE)	**PR**
PR	Non-PD or NE or NA	No (or NE)	**PR**
SD	Non-PD or NE or NA	No (or NE)	**SD**
PD	Any	Any	**PD**
Any	PD	Any	**PD**
Any	Any	Yes	**PD**
NE	Non-PD or NE or NA	No (or NE)	**NE**
NA	CR	No (or NE)	**CR**
NA	Non-CR/Non-PD	No (or NE)	**SD**
NA	NE	No (or NE)	**NE**
NA	NA	No (or NE)	**NED**

(NED = no evidence of disease)

3.3 Primary outcome measure (derivation of efficacy variables)

3.3.1 Progression-free survival

PFS is defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. PFS for patients who have not progressed or died at the time of analysis will be censored at the latest date of assessment from their last evaluable RECIST assessment.

PFS will be computed as date of PFS event or censoring – date of randomisation + 1).

If, however, a patient progresses or dies after two or more missed scheduled RECIST assessments, the patient's PFS will be censored at the time of the latest evaluable RECIST assessment prior to the two missed visits.

The allowed gap between the last previous evaluable RECIST assessment and the tumour progression or death, for which the tumour progression/death will still be counted as an event, will be defined as 2 x (scheduled time between scans + allowed visit window). In details:

- If the two missed visits will occur immediately after the baseline scan then the definition of two missed visits will be calculated as 2 x (the protocol-scheduled time between scans) + the protocol-allowed visit window (since there is no need to account for an early initial visit in this case) which will be 2 x 8 weeks + 7 days + patient-specific number of days from date of randomization to date of first study treatment dose = 119 days + (patient-specific date of first study treatment dose minus date of randomization).
- If the two missed visits will occur after a post-baseline scan then the definition of two missed visits will be 2 x (the protocol-scheduled time between scans + the protocol-allowed visit window) since the previous scan may be 1 week earlier than planned and the progression visit may be 1 week later than planned.
- While a patient is in the every-8-weeks-schedule, the definition of two missed visits will be 2 x (8 weeks + 7 days) = 126 days.
- When a patient is changing from the every-8-weeks-schedule to the every-12-weeks-schedule, the definition of two missed visits will be 8 weeks + 12 weeks + 14 days = 154 days.
- While a patient is in the every-12-weeks-schedule, the definition of two missed visits will be 2 x (12 weeks + 7 days) = 182 days.

If a patient has no evaluable visits or does not have baseline data they will be censored at Study Day 1 unless the patient dies within 17 weeks (16 weeks for two potential scans plus 1 week allowing for a late assessment within the visit window) + (patient-specific date of first study treatment dose minus date of randomization).

The PFS time will always be derived based on scan/assessment or death dates, not on visit dates. RECIST assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied:

- For BICR assessments, the date of progression will be determined based on the **earliest** of the scan dates of the component that triggered the progression for the adjudicated reviewer

selecting PD or of the reviewer who read baseline first if there is no adjudication for ICR data.

- For site investigator assessments, the date of progression will be determined based on the **earliest** of the dates of the component that triggered the progression.
- For both ICR and site investigator assessments, when censoring a patient for PFS the patient will be censored at the **latest** of the dates contributing to a particular overall visit assessment.

For TLs only the latest scan date is recorded out of all scans performed at that assessment for the TLs and similarly for NTLs only the latest scan date is recorded out of all scans performed at that assessment for the NTLs.

3.4 Secondary outcome measures (derivation of efficacy variables)

3.4.1 Objective response rate

For the interim analyses, only patients fulfilling at least one of the following conditions will be included in the denominator of the ORR estimation:

- there is a post-baseline scan at least 49 days after date of randomization and up to the interim analysis data cut-off date, i.e., randomization date + 49 days ≤ post-baseline scan date ≤ interim analysis data cut-off date
- patient died up to the interim analysis cut-off date, i.e., death date ≤ interim analysis data cut-off date.

For the final analyses there will be no such sub-setting in the denominator of the ORR estimation.

The assessment of ORR will only include tumour assessment data obtained up to

- progression
- last evaluable assessment in the absence of progression
- start of a subsequent anti-cancer therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy)

whatever occurs first.

ORR based on BICR is defined as the percentage of patients with at least one BICR-assessed visit response of CR or PR, with the denominator defined as the number of patients in the FAS (exception for interim analysis see above). If a total of at least 10 randomized patients had no measurable disease at baseline as per BICR, then an additional analysis of ORR will be conducted with the denominator defined as the subset of FAS patients with measurable disease at baseline as per BICR.

For sensitivity analysis, ORR is also defined as the percentage of patients with at least one visit response of CR or PR based on site investigator data, with the denominator defined as the number of patients in the FAS.

3.4.2 Duration of response

DoR will be defined as the time from the date of first documented response according to BICR data until date of documented progression according to BICR data or death in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint per BICR. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR per BICR. If a patient does not progress following a response, then DoR will use the respective PFS censoring time per BICR.

For sensitivity analysis, DoR is defined as the time from the date of first documented response according to site investigator assessment until date of documented progression according to site investigator assessment or death in the absence of disease progression (i.e. date of PFS event or censoring – date of first response + 1). The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint per site investigator data. The time of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR per site investigator data. If a patient does not progress following a response, then DoR will use the respective PFS censoring time per site investigator.

3.4.3 Tumour size change

3.4.3.1 General guidance

Absolute change and percentage change from baseline in TL tumour size at Week 16 will be based on RECIST TLs measurements taken at baseline and at Week 16. Tumour size is the sum of the longest diameters of the TLs. Baseline for RECIST is defined to be the last evaluable assessment prior to randomisation.

The percentage change in TL tumour size at Week 16 will be obtained for each patient taking the difference between the TLs' tumour size at Week 16 and the TLs' tumour size at baseline divided by the TLs' tumour size at baseline multiplied by 100: (Week 16 – baseline) / baseline x 100 (where it is assumed that all patients have measurable disease at baseline, i.e. TL tumour size at baseline is > 0; in case there is a patient with non-measurable disease at baseline, this patient will excluded from the analysis of percentage change from baseline in TL tumour size at Week 16).

The absolute change in TL tumour size at Week 16 will be obtained for each patient by the difference between the TLs' tumour size at Week 16 and the TLs' tumour size at baseline.

Patients who progress before Week 16 should have had a tumour assessment performed at the time of progression prior to Week 16. Tumour size from their latest progression assessment will be used instead of the Week 16 assessment for these patients.

Best percentage change from baseline in TL tumour size is defined as the minimum of percentage change from baseline in TL tumour size calculated from all tumour assessments prior to progression or start of subsequent anti-cancer therapy.

3.4.3.2 Missing data imputation methods

All imputed data will be derived within the reporting dataset with a corresponding flag against the imputed value to show that this value has been programmatically derived. This flag should indicate the method of imputation used from the methods outlined in the sections below (0=not imputed, 1=linear, 2=median, 3=maximum, 9=missing). Imputed values should not be used in the derivation of any other RECIST endpoints.

For change in TL tumour size at week 16

- Apply a window around the Week 16 visit:

  Whenever TL tumour size data for the Week 16 visit (or visit at which progression was documented if before week 16) is available then this will be used in the analysis. A windowing rule will be applied and will follow the protocol allowed visit window; therefore any RECIST assessment performed within ± 7 days of the protocol scheduled visit will be used for that visit.

- If, after applying the above considerations, there is missing TL tumour size measurement data (tsm data) at Week 16, the imputation process outlined below for each individual patient where data is missing (applied during the blind data review) will be applied:

  a) If there is no observed TL tsm data at Week 16, but there is TL tsm data collected at a visit prior to Week 16 or the first visit after Week 16, all of the available data up to and including the first visit after Week 16 (i.e. baseline and all visits up to and including the first visit after Week 16) will be used to fit a linear regression to the individual patient's baseline and follow-up assessment(s). Actual day of the measurement rather than planned day will be used in fitting of this model. The model will then be used to generate an estimated value for TL tsm at Week 16 and hence impute a change from baseline at Week 16 (imputation=linear).

  b) If there is no observed TL tsm data at Week 16 but there is evidence of progression for the individual prior to the end of the time window used to select Week 16 data, where evidence of progression is defined
     - as progression of NTLs,
     - as the appearance of new lesions
     - or as determined by a site investigator (i.e. site investigator’s opinion of response recorded on the RECIST eCRF is PD at that assessment or study treatment was discontinued for progression in the assessment time window)
     - and there are at least 5 patients with non-missing TL tumour size who have also progressed for each treatment arm

     then impute a change from baseline at Week 16 as the median percentage change from patients with non-missing TL tumour size who also have progressed (imputation=median).

     This will be performed separately for each treatment arm. If the patient has an imputed value from a), use the maximum of this median value or the imputed value in the tumour size analysis (imputation=median or imputation=linear as appropriate).

If, however, there are less than 5 patients with non-missing tumour size who have also progressed in any treatment arm then impute a change from baseline at Week 16 as 20%. If the patient has an imputed value from a), use the maximum of 20% or the imputed value in the tumour size analysis (imputation=maximum or imputation=linear as appropriate).

c) If there is no evidence of progression for the individual, use the imputed value calculated in a) if data available (imputation=linear). If there is no evidence of progression for the individual and no observed TL tsm data is collected at a visit prior to Week 16 or the first visit after Week 16, assume that the data is missing completely at random. The patient will be excluded from the analysis (imputation=missing).

d) If it is known that the patient has died prior to the end of the time window used to select Week 16 data, impute a change from baseline at Week 16 as the maximum of the observed or imputed (from step b) percentage change reported in the study for week 16 (imputation=maximum).

- Assess level of missing data and change statistical analysis if appropriate

If after TL imputation and applying a window around the Week 16 visit there remains a reasonable amount of missing TL tumour size measurement data, a non-parametric statistical analysis method, see Section 4.2.8.5, will be considered. What constitutes a reasonable amount of data will require judgement on a case-by-case basis but > 10% missing data would be cause for consideration.

Following imputation the blinded data still needs to be assessed for normality and if appropriate, a decision to change to a non-parametric statistical analysis method, see Section 4.2.8.5, may still be made after an assessment of the combined actual and imputed data.

For best percentage change in tumour size

- Select the best percentage change for each patient: this is the biggest decrease or the smallest increase in TL tumour size from baseline.
- For patients without any post-baseline TL tumour size assessments, the following imputation rules will be applied:

a) If

- o there is evidence of progression during the study, where evidence of progression is defined as progression of NTLs, the appearance of new lesions or as determined by an investigator (i.e. investigator's opinion of response recorded on the RECIST CRF is PD at that assessment or study treatment was discontinued for progression in the assessment time window)
- o and there are at least 5 patients with non-missing TL tumour size who have also progressed for each treatment group

then the median best percentage change from patients with non-missing TL tumour size who also have progressed during the study will be imputed as best percentage change from baseline. This will be performed separately for each treatment arm. However, if there are less than 5 patients with non-missing TL tumour size who have also progressed during study in any treatment group, then impute the change from baseline at Week 16 as 20%.

b) If there is no evidence of progression, assume that the data is missing completely at random; the patient will be excluded from the analysis.
c) If it is known that the patient has died, impute the minimum (i.e. corresponding to the biggest increase in TL tumour size) best percentage change reported on the study as a best percentage change from baseline.

3.4.4 Overall survival

Overall survival (time to death for any cause) is defined as the time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy (i.e. date of death or censoring – date of randomisation + 1). 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.

For each OS analysis, survival calls will be made within 2 weeks following the respective data cut-off (DCO) date, and if a patient is confirmed to be alive, or if the patient's death date is post the DCO date, these patients will be censored at the DCO date.

The status of patients completely withdrawn from the study or "lost to follow-up" at the time of each 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.

3.4.5 CCI

In this study, CCI will be assessed using the CCI CCI

CCI will be given to the patients during screening, on Day 1 of Cycle 1 (baseline prior to first dosing of study treatment) and every 8 weeks thereafter until discontinuation of study treatment. Patients are to CCI during their clinic visit. The site staff will enter the information directly into the Clinical Database.

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3.4.6 Non-progressive disease (futility interim analysis only)

Non-progressive disease (NPD) at Week 8 based on site investigator data is defined as

- a visit response of SD, PR or CR at Week 8 (earlier visit responses of CR, PR that become PD at Week 8 or NE responses at Week 8 do not constitute NPD at Week 8)
- if the Week 8 response is missing or NE but the next evaluable response is SD or better, then the patient will be defined as having NPD at Week 8

- if an earlier visit is defined as PD then the visit response at Week 8 would also be defined as PD.

A time window around the Week 8 visit will be applied, such that any visits occurring 7 weeks or more after dosing are acceptable.

3.5 Secondary outcome measures (derivation of safety variables)

3.5.1 General considerations for safety assessments

Missing safety data will generally not be imputed. As an exception, adverse events that have missing causality (after data querying) will be assumed to be related to study drug.

3.5.2 Exposure and dose interruptions

Study treatment exposure will be defined by:

- total exposure = min(last dose date where dose > 0 mg, date of death, date of DCO) – first dose date +1 (for combination treatment arms, this will be done separately for each study drug)
- actual exposure = total exposure – total duration of dose interruptions, where total exposure will be calculated as above and a dose interruption is defined as number of days where the patient has not taken any planned study treatment dose. The actual exposure calculation makes no adjustment for any dose reductions that may have occurred. For combination treatment arms, this will be done separately for each study drug.
- the number of cycles received:
  - for Olaparib in the Olaparib treatment arm, a cycle corresponds to a period of 28 days
  - for AZD6738 and Olaparib in the AZD6738+Olaparib treatment arm, a cycle corresponds to a period of 28 days
  - for AZD1775 and Olaparib in the AZD1775+Olaparib treatment arm, a cycle corresponds to a period of 21 days.

  If a cycle is prolonged due to toxicity, this will still be counted as one cycle. A cycle will be counted if treatment is started even if the full dose or complete dosing is not delivered.

Missed or forgotten doses

Missed and forgotten doses should be recorded on the DOSE 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 will be used in the programming.

Safety follow-up

For each patient, the total duration of the safety follow-up is defined as

total safety follow-up duration = min((last dose date + 30 days), date of withdrawal of consent, date of death, date of DCO) – first dose date +1.

3.5.3 Dose intensity

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation. For combination treatment arms, RDI will be calculated separately for each study drug.

RDI will be defined as RDI = 100% * d/D, where

- d is the actual cumulative dose delivered up to the actual last day of dosing
- D is the intended cumulative dose up to the actual last day of dosing (D is the total dose that would be delivered, if there were no modification to dose or schedule).

3.5.4 Adverse events

AEs will be collected throughout the study, from date of informed consent until 30 days after the last dose of study treatment. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in the data listings.

Adverse events will be defined as treatment emergent if they onset, or worsen (by investigator report of a change in intensity), during the study treatment period (defined from date of first dose of any study treatment to date of last dose of any study treatment) or safety follow-up period (30 days after last dose of study treatment).

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE Version 4.03).

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 serious adverse events (SAEs) and 'Discontinuation of Investigational Product due to Adverse Events' (DAEs). Based on the expert's judgement, significant adverse events of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

AEs of special interest

The following AEs of special interest (AESIs) have been identified by the patient safety team and included in the study protocol:

AESIs for Olaparib are myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML), new primary malignancy (other than MDS/AML) and pneumonitis.

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 higher-level terms and which preferred terms contribute to each AESI. Further reviews may take place prior to database lock (DBL) to ensure any further terms not already included are captured within the categories.

There are no AESIs for AZD1775 or AZD6738 which require additional data collection.

3.5.5 Safety laboratory test results

Continuous local safety laboratory test results (see study protocol Table 5) will be converted to values in International System of Units (Système international d'unités, SI) units in the clinical database. The test results in SI units will be exported from the clinical database, together with the original test results/units reported by the sites. The specific choice of the SI unit for the safety laboratory test results (as well as the respective conversion factors) will follow the most recent AZ Labcodes_plus_CDISC file. Exceptions are liver function tests alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT]) for which IU/L will be used rather than the SI unit ukat/L.

3.6 Secondary outcome measures (derivation of PK variables)

The minimum concentrations at steady state ($C_{min\ ss}$) will be derived from the drug concentration data for Olaparib, AZD6738 and AZD1775, and provided to PAREXEL Biostatistics.

Given the sparse PK schedule, other PK parameters will be derived using population PK modelling described in a separate analysis plan. The results of any such analyses will be reported separately from the CSR.

3.7 Exploratory outcome measures (CCI [redacted])

Not applicable as CCI [redacted] will not be analysed by PAREXEL.

4. ANALYSIS METHODS

4.1 General principles

4.1.1 Use of analysis sets

Study population, demography, efficacy and CCI [redacted] data will be summarised based upon the FAS.

Safety and study treatment exposure data will be summarised based upon the SAF.

Study drug concentration and PK data will be summarised based upon the PK analysis set.

4.1.2 Handling of 3 treatment arms in the outputs

All outputs (tables, figures, listings) will display all 3 treatment arms. Only tables for study population, disposition and demographics will include an overall column displaying pooled results.

In the outputs, the three treatment arms will be labelled as:

- "Olaparib" for treatment arm Olaparib monotherapy
- "AZD6738+Olaparib" for treatment arm AZD6738 + Olaparib
- "AZD1775+Olaparib" for treatment arm AZD1775 + Olaparib

4.1.3 Definition of baseline and change from baseline

The baseline value will be defined differently for efficacy and safety analyses:

- For efficacy (including CCI), baseline value will be the last value obtained prior to randomisation. Note the following instructions:
  - If there are two assessments on the same last day prior to the randomisation, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline value.
  - Assessments on the day of randomization where no time is captured will be considered prior to randomization if such procedures are required by the protocol to be conducted before randomization.
  - If an evaluable assessment is only available after randomization but before the first dose of study treatment then this assessment will be used as baseline value.
  - In listings or figures displaying individual efficacy data over time, study day will be calculated in relation to date of randomization (= Study Day 1).
- For safety, baseline value will be the last value obtained prior to the first dose of study treatment. Note the following instructions:
  - If there are two assessments on the same last day prior to the first dose of study treatment, one with time recorded and the other without time recorded, the one with time recorded would be selected as baseline value.
  - Assessments on the day of the first dose of study treatment where no time is captured will be considered prior to the first dose of study treatment if such procedures are required by the protocol to be conducted before the first dose of study treatment.
  - In listings or figures displaying individual safety data over time, study day will be calculated in relation to date of first treatment (= Dose Day 1).

Absolute change from baseline will be calculated as post-treatment value minus baseline value. Percentage change from baseline will be calculated as (post-baseline value minus baseline value) divided by baseline value multiplied by 100. Percentage change from baseline will not be used for variables for which the baseline value can be equal to 0.

4.1.4 Time windows for summaries by visit

Visit windows will be used for any presentations that summarise values by visit. The following conventions will be applied:

- The window for visit D1 (at the day of first intake of study medication but assessments to be done prior to that first intake) is limited to Dose Day 1.
- The windows for post-baseline visits are constructed in such a way that the upper limit of the interval falls half way between the two visits. If an odd number of days exists between two consecutive visits then the upper limit is taken as the midpoint value minus 1 day.
- Visit windows are exhaustive so that all unscheduled visit data have the potential to be included in the visit windows.
- Inclusion of data within a visit window is based on actual assessment/visit date and not intended assessment/visit date.

Table 4 VIOLETTE visit windows using a calendar days / weeks metric

(SP = Screening Period D = Day W = Week CCI)

Treatment arms Olaparib and AZD6738+Olaparib with cycle length 28 days		Treatment arm AZD1775+Olaparib with cycle length 21 days	
Visit window label	**Visit window**	**Visit window label**	**Visit window**
SP1	> 28 days prior to Dose Day 1	SP1	>28 days prior to Dose Day 1
SP2	[28 days prior to Dose Day 1; 1 day prior to Dose Day 1]	SP2	[28 days prior to Dose Day 1; 1 day prior to Dose Day 1]
D1	Dose Day 1 (exact)	D1	Dose Day 1 (exact)
D7	[1 day after Dose Day 1; 9 days after Dose Day 1]	–	–
–	–	D10	[1 day after Dose Day 1; 11 days after Dose Day 1]
D15	[10 days after Dose Day 1; 20 days after Dose Day 1]	D15	[12 days after Dose Day 1; 16 days after Dose Day 1]
–	–	W3 / D22	[17 days after Dose Day 1; 31 days after Dose Day 1]
W4 / D29	[21 days after Dose Day 1; 41 days after Dose Day 1]	–	–
–	–	W6 / D43	[32 days after Dose Day 1; 52 days after Dose Day 1]
W8 / D57 (except scan, CCI)	[42 days after Dose Day 1; 69 days after Dose Day 1]	–	–
W8 / D57 (only scan, CCI)	[1 day after Dose Day 1; 83 days after Dose Day 1]	W8 / D57 (only scan, CCI)	[1 day after Dose Day 1; 83 days after Dose Day 1]
–	–	W9 (D64)	[53 days after Dose Day 1; 73 days after Dose Day 1]
W12 / D85	[70 days after Dose Day 1; 97 days after Dose Day 1]	W12 / D85	[74 days after Dose Day 1; 94 days after Dose Day 1]

Treatment arms Olaparib and AZD6738+Olaparib with cycle length 28 days		Treatment arm AZD1775+Olaparib with cycle length 21 days	
Visit window label	**Visit window**	**Visit window label**	**Visit window**
–	–	W15 / D106	[95 days after Dose Day 1; 115 days after Dose Day 1]
W16 / D113 (except scan, CCI	[98 days after Dose Day 1; 125 days after Dose Day 1]	–	–
W16 / D113 (only scan, CCI	[84 days after Dose Day 1; 139 days after Dose Day 1]	W16 / D113 (only scan, CCI	[84 days after Dose Day 1; 139 days after Dose Day 1]
–	–	W18 / D127	[116 days after Dose Day 1; 136 days after Dose Day 1]
W20 / D141	[126 days after Dose Day 1; 153 days after Dose Day 1]	–	–
–	–	W21 / D148	[137 days after Dose Day 1; 157 days after Dose Day 1]
W24 / D169 (except scan, CCI	[154 days after Dose Day 1; 181 days after Dose Day 1]	W24 / D169 (except scan, CCI	[158 days after Dose Day 1; 178 days after Dose Day 1]
W24 / D169 (only scan, CCI	[140 days after Dose Day 1; 195 days after Dose Day 1]	W24 / D169 (only scan, CCI	[140 days after Dose Day 1; 195 days after Dose Day 1]
and so on			

Table 5 VIOLETTE visit windows using a cycle metric

(SP = Screening Period C = Cycle D = Day)

Treatment arms Olaparib and AZD6738+Olaparib with cycle length 28 days		Treatment arm AZD1775+Olaparib with cycle length 21 days	
Visit window label	**Visit window**	**Visit window label**	**Visit window**
SP1	> 28 days prior to Dose Day 1	SP1	>28 days prior to Dose Day 1
SP2	[28 days prior to Dose Day 1; 1 day prior to Dose Day 1]	SP2	[28 days prior to Dose Day 1; 1 day prior to Dose Day 1]
C1 D1	Dose Day 1 (exact)	C1 D1	Dose Day 1 (exact)
C1 D7	[1 day after Dose Day 1; 9 days after Dose Day 1]	–	–
–	–	C1 D10	[1 day after Dose Day 1; 11 days after Dose Day 1]
C1 D15	[10 days after Dose Day 1; day before first dosing in Cycle 2]	C1 D15	[12 days after Dose Day 1; day before first dosing in Cycle 2]
C2	[day of first dosing in Cycle 2; day before first dosing in Cycle 3]	C2	[day of first dosing in Cycle 2; day before first dosing in Cycle 3]
C3	[day of first dosing in Cycle 3; day before first dosing in Cycle 4]	C3	[day of first dosing in Cycle 3; day before first dosing in Cycle 4]

Treatment arms Olaparib and AZD6738+Olaparib with cycle length 28 days		Treatment arm AZD1775+Olaparib with cycle length 21 days	
Visit window label	**Visit window**	**Visit window label**	**Visit window**
and so on			

The timing of scan visits (including CCI is not cycle-based; hence they are not included in the Table 5.

For visit based summaries, the following convention will be applied:

- If there is more than one value per patient within a time window then the closest value to the scheduled visit date is summarised, or the earlier, in the event the values are equidistant from the nominal visit date. The listings highlight the value for the patient that contributed to the summary table, wherever feasible.

4.1.5 Inclusion of data in summaries at patient level

For summaries at a patient level, all values will be included, regardless of whether they appear in a corresponding visit based summary e.g. when deriving a patient level statistic such as a worst (maximum or minimum) value.

4.1.6 Descriptive statistics

Descriptive statistics will be used according to the variable's measurement scale.

Descriptive statistics for continuous variables

Continuous variables (except those with censoring) will be summarised by

- the number of observations (n), mean, SD, minimum, 1st quartile, median, 3rd quartile and maximum (if the quartiles are being included)
- the number of observations (n), mean, SD, median, min, max (if the quartiles are being excluded).

For original variables (i.e., variables not derived), the mean, 1st quartile, median and 3rd quartile will be rounded to 1 additional decimal place compared to the original variable; the SD will be rounded to 2 additional decimal places compared to the original variable. Minimum and maximum will be displayed with the same number of decimals as the original variable.

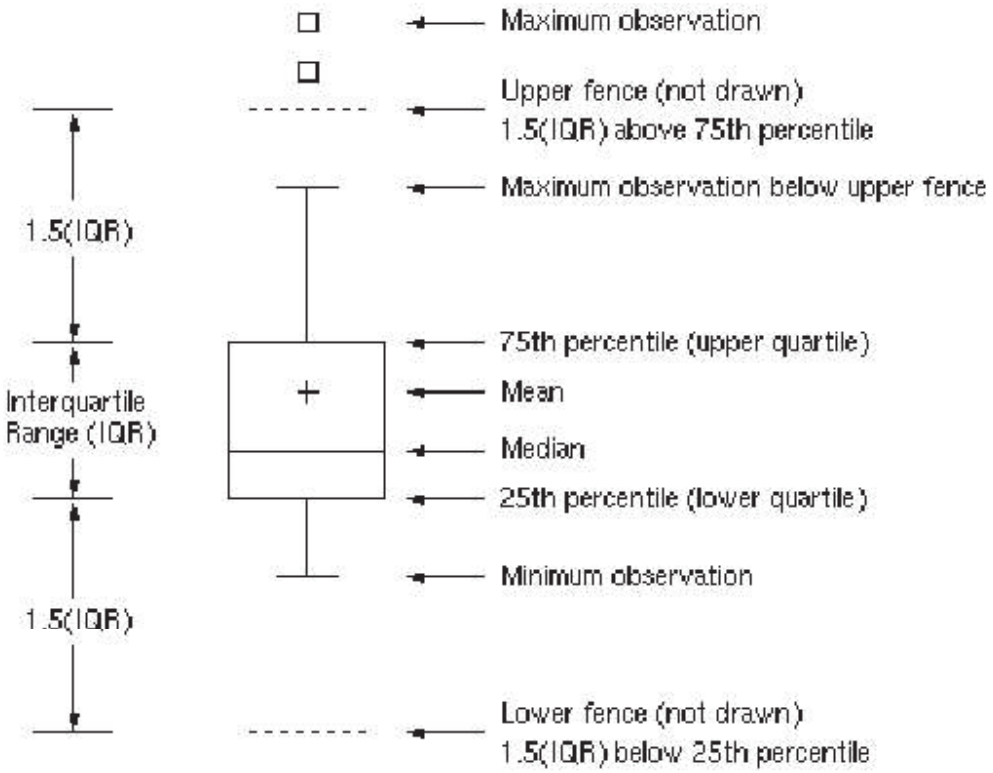
For derived variables, the number of decimals will be determined in the Analysis Datasets Specification; subsequently the rule above will be applied.

Boxplots

Boxplots may be used to illustrate important distribution characteristics for continuous variables. Figure 3 below illustrates the boxplot elements. If boxplots will be provided for several measurements (e.g., visits) over time, then the means or medians for the same treatment arm will be connected. If more than one treatment arm is displayed within a figure, then the

treatment arms will be distinguished by different colours and different line styles connecting mean/medians over time.

Figure 3 Boxplot elements



By default, individual values are marked if there are any above the upper fence (as shown in Figure 3 above) or below the lower fence (not the case in Figure 3 above). If, however, the display of such extreme values would bring the entire figure out of scale (e.g., a comparison of boxes across time or treatment group would hardly be feasible), then the option to not display such extreme values can be discussed with AstraZeneca.

Frequency tables for categorical variables

Categorical variables will be summarised by frequency counts and percentages for each category. Percentages will be calculated using the number of observations with non-missing values as the denominator. As an exception, frequency tables displaying categorical demographics and baseline disease characteristics will include the number of missing observations in the denominator for calculating percentages.

A missing category shall be included only for categorical variables where any records with missing values are available; this case only the number of missing values will be displayed but not percentages. The missing category will be omitted if there were no missing values for that variable.

Kaplan-Meier figures for right-censored time to event variables

Survival functions are of interest for right-censored time to event variables (in this study for PFS and OS). These will be estimated by Kaplan-Meier (KM) product limit estimators and plotted over time (called "KM curves") with SAS PROC LIFETEST. Treatment arms will have different colour / line styles and censored observations will be marked. At the bottom of KM figures the number of patients still at risk at baseline Week 8, 16, 24, etc will be displayed for each treatment arm.

Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up and those who have withdrawn consent will be provided for each treatment arm. If estimable, median time to event and 2-sided 90% confidence intervals (CIs) according to Brookmeyer and Crowley 1982 will be provided for each treatment arm.

4.1.7 Data listings

Data listings will not be produced for every single data domain but only for those required from a regulatory and AZ perspective according to AZ CSR Appendix 12.2 Global Specification.

Data listings will:

- display all values contributing to a time point for a patient and will highlight the value used in the summary table where appropriate
- be presented and sorted by randomised treatment arm (by actual treatment arm for safety listings), subject identifier, visit and date as appropriate.

4.1.8 General principles for statistical modelling and hypothesis testing

All statistical tests will be pairwise, i.e. comparing two treatment arms and there will be no "overall" tests of global null hypotheses (same distribution in all three treatment arms).

Any stratification in the statistical modelling will be based on the values entered into Interactive Voice Recognition System (IVRS) at randomisation, even if it is subsequently discovered that these values were incorrect. In case of at least 10% of mis-stratified patients (across all strata),), a sensitivity analysis will be carried out using the (correct) baseline data collected in the eCRF.

Results of statistical analyses will be presented using 2-sided 90% CIs and 2-sided p-values for pairwise comparisons between

- AZD6738+Olaparib versus Olaparib monotherapy
- AZD1775+Olaparib versus Olaparib monotherapy
- and AZD6738+Olaparib versus AZD1775+Olaparib (as secondary analysis).

Two-sided p-values will be presented using 3 decimal places for all values ≥ 0.001. The only categorical presentation to be used is when $p < 0.001$.

The types of statistical test(s) used to generate p-values or CIs, together with details of any stratification or prognostic factors, should be included in a footnote to the presentation or in

the text as appropriate. Any 'post-hoc' analyses (i.e., not pre-specified) will be clearly indicated on any outputs either by using the titles or footnotes as appropriate.

Primary statistical analyses comparing PFS based on BICR for each combination treatment arms to Olaparib will be conducted for the 3 patient populations *BRCAm*, Non *BRCAm* HRR*m* and Non HRR*m*.

Comparisons of PFS based on BICR for each of the combination treatment arms to Olaparib in the 2 patient populations HRR*m* and All will be conducted as secondary statistical analyses.

Secondary outcome measures will be analysed for the 3 patient populations *BRCAm*, Non *BRCAm* HRR*m* and Non HRR*m*, except

- ORR and OS, which will be analysed for all 5 patient populations
- Tumour and germline mutation status, which will be analysed only for the All patient population
- PK outcome measure $C_{min,ssss}$, which will be analysed only for the All patient population

RECIST-based primary and secondary outcome measures based on Investigator assessments will also be analysed for sensitivity purposes.

Safety outcome measures and exploratory outcome measures will be analysed for the All patient population only, except

- selected AE summary tables, which will also be provided for the 3 primary patient populations
- CCI, which will be analysed for all 5 patient populations.

4.2 Analysis Methods

4.2.1 Handling of multiplicity

Multiplicity adjustment will be considered within each of the 3 primary patient populations for PFS. The overall 2-sided alpha for each primary patient population will be 0.2, and a simple Bonferroni adjustment assigns 2-sided alpha of 0.1 to each of the 2 pairwise treatment arm comparisons to Olaparib monotherapy.

No further adjustments for multiplicity are planned, in particular no adjustments for interim analyses.

4.2.2 Overview of timings of interim and final analyses

For the non HRR*m* population an interim futility analysis will be triggered when 75 patients have been recruited and assessed for at least 8 weeks, in order to assess the proportion of patients with Non Progressive Disease (NPD), based on the Investigator assessment at 8 weeks in each of the treatment arms. Recruitment will be paused after the 75th patient has been recruited into this patient population, until the AZ URC confirms which treatment arms should be reopened. In April 2019, the AZ URC determined that recruitment to the AZD1775+olaparib arm should not be reopened. This parallels the ISRC recommendation to close recruitment to the AZD1775+olaparib arm in all three populations for safety concerns.

A further NPD futility interim analysis in the non *BRCAm* HRR*m* population may be performed, if the outcome of the interim analysis in the non HRR*m* population resulted in treatment arms being stopped.

For each of the 3 primary patient populations (*BRCAm*, non *BRCAm* HRR*m*, non HRR*m*) a further interim analysis for PFS is triggered when 44PFS events for the AZD6738+olaparib vs. olaparib monotherapy pairwise comparison in that particular patient population have occurred. As the non HRR*m* patient population is expected to be enrolled quicker than the other patient populations, it is expected the interim analysis for this patient population will occur first, followed by interim analysis for the 2 other primary patient populations. These PFS interim analyses may be concurrent or separate depending on the recruitment and PFS event rates for the 3 patient populations and other operational requirements.

For each of the 3 primary patient populations (*BRCAm*, non *BRCAm* HRR*m*, non HRR*m*) the final analysis for PFS is triggered when 68 PFS events in that particular patient population have occurred. These final analyses may be concurrent or separate depending on the recruitment and PFS event rates for the 3 patient populations and other operational requirements.

An initial OS analysis will be performed at the same time as the primary analysis of PFS. A further analysis of OS will be performed when the OS data for the AZD6738+olaparib vs. olaparib monotherapy pairwise comparison are approximately 70% mature.

4.2.3 General time-to-event analysis considerations

Stratification of log rank test and proportional hazards model

Time-to-event endpoints will be analysed using stratified log-rank tests for generation of the p-value and using the Breslow approach for handling ties (Breslow 1974). Hazard ratios and their CIs will be estimated from stratified proportional hazards models (with ties = Efron) and the CIs calculated using a profile likelihood approach. For both approaches, the stratification variables will be included in the STRATA statement of SAS PROC LIFETEST and SAS PROC PHREG, respectively.

Where applicable, stratification factors will be those used in the randomization. It is sensible to have at least 5 events in each stratification cell (combination of the marginal strata). One stratification factor with 2 levels and 3 treatment arms would lead to 2 x 3= 6 stratification cells. Two stratification factors with 2 and 3 levels, respectively, and 3 treatment arms would lead to 2 x 3 x 3 = 18 stratification cells. If the minimum of 5 events in each stratification cell is not reached, then also unstratified analyses will be conducted.

Proportionality assumption

The assumption of proportional hazards will be examined by plots of log-log (event times) versus log (time). If these raise concerns, by fitting a time dependent covariate (adding a treatment-by-time or treatment-by-log(time) interaction term) to assess the extent to which this represents random variation. If a lack of proportionality is evident, the variation in treatment effect can be described by presenting piecewise HR calculated over distinct time-periods (0-16 weeks, 16-32 weeks, 32-48 weeks, etc).

4.2.4 PFS primary analyses based on BICR for patient populations *BRCAm*, *non BRCAm HRRm* and non HRR*m*

The study treatment status at progression of patients at the DCO date used for analysis will be summarised. This will include

- the number (%) of patients who were on study treatment at the time of progression
- the number (%) of patients who discontinued study treatment prior to progression
- the number (%) of patients who have not progressed and were on study treatment
- the number (%) of patients who have not progressed and discontinued study treatment.

Primary analyses of PFS will be based on data from the BICR and conducted separately for the patient populations *BRCAm*, *non BRCAm HRRm* and non HRR*m*, respectively.

In each of these 3 patient populations, PFS will be analysed using pair-wise log rank tests stratified for prior platinum-based therapy (no, yes) for generation of the p-value. Pairwise HRs and two-sided 90% CIs will be estimated from a proportional hazards model stratified for prior platinum-based therapy (no, yes). The two-sided 80% and 60% CIs will also be estimated.

For each of these 3 patient populations, KM curves for PFS will be presented by treatment arm, overall and separately by prior platinum-based therapy (no/yes).

The number of events, median PFS with two-sided 90% CIs, and the percentage PFS as well as two-sided 90% CIs at 3, 6, 12, 18 and 24 months will be summarised. For calculating these CIs:

- KM estimates will be transformed to an unrestricted range by the log(-log(x)) function
- calculation of CIs by applying normal approximation methods to the transformed scaled
- re-transformation of CIs to the original scale.

This approach is triggered by option CONFTYPE=LOGLOG in SAS PROC LIFETEST.

The progression status at the time of the PFS analysis will also be summarised, including the number and percentage of patients who progressed due to RECIST progression (separately for TLs, NTLs and new lesions) or due to death, or did not progress due to being progression free or due to being lost to follow up or due to withdrawn consent.

4.2.5 PFS sensitivity analyses for the 3 primary patient populations

The following PFS sensitivity analyses will be considered:

- ascertainment bias: refers to possible bias introduced by disagreement between site investigator and BICR assessments and subsequent informative censoring in PFS analyses of the BICR data.
- evaluation-time bias: refers to the possibility that the PFS effect is partly an artefact of one arm being assessed more frequently
- attrition bias: refers to the possibility that the rate and nature of censoring has resulted in bias

Ascertainment bias

The primary analyses of PFS will be repeated using investigator assessed RECIST data. The p-value from the stratified log-rank test, and the HR and 90% CI from the stratified proportional hazards model will be presented for each pairwise comparison.

Disagreements between investigator and central reviews of RECIST progression will be presented for each treatment group. The summary will include the early discrepancy rate which is the frequency of central review declared progressions before the investigator review as a proportion of all central review progressions and the late discrepancy rate which is the frequency of central review declared progressions after the investigator review as a proportion of all discrepancies.

If there is an important discrepancy between the primary analysis using BICR RECIST-based data and this sensitivity analysis using the site investigator RECIST-based data then the proportion of patients with site but no central confirmation of progression will be summarised; such patients have the potential to induce bias in the BICR RECIST-based PFS analysis due to informative censoring. An approach of imputing an event at the next visit in the central review analysis may help inform the most likely HR value (Fleischer et al 2011), but only if an important discrepancy exists between site investigator and BICR data exists. Note: it is the blinded study team's responsibility to determine whether there is an important discrepancy upon blinded review of the data, and whether such further analyses are required.

Evaluation-time bias

A sensitivity analysis will be performed to assess possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points. The midpoint between the time of progression and the previous evaluable RECIST assessment (using the final date of the assessment) will be analysed using a stratified log-rank test, as described for the primary analysis of PFS. Note that midpoint values resulting in non-integer values should be rounded down. For patients whose death was treated as a PFS event, the date of death will be used to derive the PFS time used in the analysis. This approach has been shown to be robust to even highly asymmetric assessment schedules (Sun and Chen 2010). The p-value from the stratified log-rank test, and the HR and 90% CI from the stratified proportional hazards model will be presented for each pairwise comparison.

To support this analysis, the patient-level mean inter-assessment times, will be summarised using descriptive statistics for each treatment, separately for assessments up to Week 72 and post-Week 72. This approach will use the BICR RECIST assessments.

Attrition bias

Attrition bias will be assessed by repeating the PFS analysis except that the actual PFS event times, rather than the censored times, of patients who progressed or died in the absence of progression immediately following two, or more, non-evaluable tumour assessments will be included. In addition, and within the same sensitivity analysis, patients who take subsequent therapy (note that for this analysis radiotherapy is not considered a subsequent anti-cancer therapy) prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable assessment prior to taking the subsequent therapy. The p-value

from the stratified log-rank test, and the HR and 90% CI from the stratified proportional hazards model will be presented for each pairwise comparison.

This analysis will be supported by a Kaplan-Meier plot of the time to censoring using the PFS data from the primary analysis and where the censoring indicator of the PFS analysis is reversed.

Additional supportive summaries

In addition, the number of patients prematurely censored (see definition below) will be summarised by treatment arm. A patient would be defined as prematurely censored if they had not progressed (or died in the absence of progression) and the latest scan prior to DCO was more than one scheduled tumour assessment interval plus 2 weeks prior to the DCO date.

Additionally, summary statistics will be given for the number of days from censoring to DCO for all censored patients.

A summary of the duration of follow-up will be summarised using median time from randomisation to date of censoring (date last known to have not progressed) in censored (not progressed) patients only, presented by treatment arm.

Additionally, summary statistics for the number of weeks between the time of progression and the last evaluable RECIST assessment prior to progression will be presented for each treatment arm.

Summaries of the number and percentage of patients who miss two or more consecutive RECIST assessments will be presented for each treatment arm. In addition, a summary of new lesions (i.e. sites of new lesions) will be produced.

4.2.6 PFS subgroup analyses

Subgroup analyses will be conducted comparing PFS between two treatment arms in the following subgroups of the FAS, separately within each of the 3 primary patient populations:

- prior platinum treatment (no versus yes)
- Sex (male versus female)
- Age at randomisation (<65 versus ≥65 years of age), see Section 3.1.2 for handling of patients with a missing age at randomisation.

The subgroup analyses for the stratification factor (prior platinum treatment) will be based on the values entered into the IVRS, all other factors will be based on values recorded on the eCRF as indicated above.

No adjustment to the significance level for testing will be made since all these subgroup analyses will be considered exploratory and may only be supportive of the primary analysis of PFS.

For each subgroup level of a factor, the HR and 90% CI will be calculated from an un-stratified Cox proportional hazards model with treatment as only covariate. These HRs and associated 2-sided 90% CIs will be summarised and presented on a forest plot, along with the results of the overall primary analysis. In a forest plot the hazard ratio is plotted on a log-scale and the hazard ratio from the primary analysis should also be plotted to enable comparison.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 10 PFS events in a subgroup category), the relationship between that subgroup and PFS will not be formally analysed. In this case, only KM curves will be provided.

4.2.7 Other secondary efficacy analyses

Other secondary efficacy analyses will be performed according to the overview below.

Patient Population	Outcome Measures	Analysis Method(s)
• HRR*m* • All	PFS using BICR according to RECIST 1.1	Weighted proportional hazards model stratified by prior platinum-based therapy Weighted KM curves by treatment arm, overall and separately by prior platinum-based therapy Sensitivity analyses: • unweighted stratified proportional hazards model and unweighted stratified log rank test • unweighted KM curves • analyses using site investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	Objective response using BICR according to RECIST 1.1	Logistic regression model with covariates study treatment and prior platinum-based therapy. Sensitivity analysis using site investigator assessments according to RECIST 1.1

Patient Population	Outcome Measures	Analysis Method(s)
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	DoR using BICR according to RECIST 1.1	Expected duration of response (EDoR) will be derived for each treatment arm as the product of the proportion of patients responding to study treatment and the mean DoR in responding patients. Mean and standard error of DoR in responding patients will be estimated using a suitable parametric model. For pairwise comparisons of treatment arms the ratio of EDoRs and its 90% CI will be estimated. DoR in responding patients will be estimated by KM curves by treatment arms. Sensitivity analysis using site investigator assessments according to RECIST 1.1
• *BRCAm* • Non *BRCAm* HRR*m* • Non HRR*m*	Percentage change in TL tumour size at Week 16 using BICR according to RECIST 1.1	Parametric / non-parametric Analysis of Covariance model with • factor treatment arm • factor prior platinum therapy • covariate baseline TL tumour size • covariate time from baseline scan to randomisation. Sensitivity analysis using site investigator assessments according to RECIST 1.1
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	Time to death for any cause	Same main analysis methods as described for analysis of PFS.
• All	Tumour and germline mutation status of CCI genes	Cross-tabulation summary of tissue HRR mutation status versus plasma HRR mutation status for each mutation type for all screened subjects with both tumour and plasma samples analysed.

4.2.8 PFS secondary analyses

4.2.8.1 PFS analyses based on BICR for patient population HRR*m*

To achieve estimated pairwise HRs for PFS that are representative of the HRR*m* patient population, the following approach will be implemented:

1. pairwise HRs (separately for patient population strata A and B) will be obtained from a proportional hazards model stratified for prior platinum-based therapy (no, yes)
2. a weighted estimate of the HR_{HRRm} will be calculated using the estimated HR in patient population stratum A (HR_A) and the estimated HR in patient population stratum B (HR_B):
   $ln(HR_{HRRm}) = w_1 ln(HR_A) + w_2 ln(HR_B)$
   where weights w_1 and w_2 will be estimated from external literature and the study's screening records (the details of the weight estimation will be described in a separate appendix to the SAP)
3. For calculation of CIs, the overall variance (log scale) will take into account the variance of both groups (that are independent), and thus be calculated as:
   $var(ln(HR_{HRRm})) = w_1^2\, var(ln(HR_A)) + w_2^2\, var(ln(HR_B))$

As sensitivity analyses,

- PFS will be analysed using an unweighted log rank test stratified for patient population (stratum A, stratum B) and prior platinum-based therapy (no, yes)
- pairwise HRs and CIs will be estimated from an unweighted proportional hazards model stratified for patient population (stratum A, stratum B) and prior platinum-based therapy (no, yes).

KM curves for PFS will be presented by treatment arm, overall and separately by prior platinum-based therapy (no, yes). These KM curves will be presented both in an unweighted manner (i.e., each patient receives the same weight of 1) and weighted by the weights for the two patient populations described above.

A sensitivity analysis of PFS using site investigator data will be performed.

4.2.8.2 PFS analyses based on BICR for patient population All

Similar summaries and weighted and unweighted analyses as described in Section 4.5.2.1 will be conducted for the All patient population; now with 3 weights to combine the HR estimates and its variances for the 3 patient population strata A, B and C.

A sensitivity analysis of PFS using site investigator data will be performed.

4.2.8.3 Analysis of objective response based on BICR for all five patient populations

Note: take into account the statement in Section 3.4.1 on the denominator when calculating percentages for ORR.

Frequency tables by treatment arm will be produced that present

- number and percentage of patients with / without objective response (the former is the ORR) according to BICR
- number and percentage of patients with / without objective response according to site investigator assessment.

Objective response will be analysed using logistic regression with covariates study treatment and prior platinum-based therapy (no/yes). The results of the analysis will be presented in terms of odds ratio comparing treatment arms in pairwise manner together with associated 90% profile likelihood CI (using the option 'LRCI' in SAS PROC GENMOD) and 2-sided p-value. P-values will be based on twice the change in log-likelihood resulting from the addition of covariate study treatment to the model containing only the covariate related to prior platinum-based therapy. The three pairwise odds ratio will be the following:

- objective response odds ratio for AZD6738+Olaparib over Olaparib alone
- objective response odds ratio for AZD1775+Olaparib over Olaparib alone
- objective response odds ratio for AZD6738+Olaparib over AZD1775+Olaparib.

If there are not enough responses for a meaningful analysis using logistic regression then a Fisher's exact test using mid p-values will be presented for each pairwise comparison of treatment arms. The mid-p-value modification of Fisher's exact test amounts to subtracting half of the probability of the observed table from Fisher's p-value, i.e., mid p-value = 2-sided p-value − table probability/2.

A sensitivity analysis of objective response using site investigator data will be performed.

4.2.8.4 Analysis of duration of response based in BICR for the 3 primary patient populations

In order to analyse the secondary outcome variable DoR between treatment arms, the expected duration of response (EDoR) will be derived for each treatment arm (Ellis et al 2008). The EDoR is the product of the proportion of patients responding to study treatment and the mean DoR in responding patients, so EDoR is based on all randomised patients within the respective patient population. The variance of EDoR, on a log-scale, is given in Ellis et al 2008. Mean and standard error of DoR in responding patients will be estimated using a parametric model in SAS PROC LIFEREG; Ellis et al 2008 provides formulae for the exponential, Weibull and log-normal distributions. The best fitting distribution will be selected during the blind data review and detailed in a SAP Amendment prior to respective unblinding.

For pairwise comparisons of treatment arms the ratio of EDoRs (including 90% CIs) will be estimated, using the selected probability distribution for DoR in responding patients. This EDoR analysis will be stratified by prior platinum therapy (no/yes), weighting each stratum inversely proportional to the within-stratum variance of the log of the ratio of EDoRs (see also Whitehead and Whitehead 1991):

- obtain stratum-specific estimates $\hat{x}_{i,\text{no}}$ and $\hat{x}_{i,\text{yes}}$ of EDoR for all 3 treatment arms i =1,2,3
- obtain stratum-specific treatment arm contrasts of the logs of the ratios of EDoRs:
  - contrasts $\ln \hat{x}_{i,\text{no}} - \ln \hat{x}_{j,\text{no}}$ for i =1,2, $i < j \leq 3$
  - contrasts $\ln \hat{x}_{i,\text{yes}} - \ln \hat{x}_{j,\text{yes}}$ for i =1,2, $i < j \leq 3$
- each overall pairwise treatment arm contrast will be obtained by combining the two strata-specific treatment arm contrasts by weighting them inversely proportionately according to each within stratum variance and finally transformation to the original scale by applying the exp function.

Additionally, descriptive data will be provided for DoR in responding patients, including associated KM curves (including estimated median DoRs) and swimmer plots by treatment arm (without any formal comparison or p-value attached).

A sensitivity analysis of DoR using site investigator data will be performed.

4.2.8.5 Analysis of tumour size change at Week 16 based in BICR for the 3 primary patient populations

Absolute and percentage change from baseline in TL tumour size at Week 16 will be summarised and presented by treatment arm. The number and percentage of patients in each treatment arm whose Week 16 data is imputed will also be presented.

Percentage change in TL tumour size at Week 16 will be presented graphically using waterfall plots for each treatment arm: each patient's Week 16 percentage change in tumour size as a separate bar, with the bars ordered from the largest increase to the largest decrease. A reference line at the –30% change in TL tumour size level will be added to the plots, which corresponds with the definition of 'partial' response. All progressions will be marked with a '●' or designated with patterns or colours for overall response categories. The scale in these plots will be fixed to be from -100 to 100 to avoid presenting extreme values. Values that are capped as a result of this restriction to the scale are marked with '#'. Values are ordered in descending order with the imputations due to death appearing first followed by a gap followed by all other patients. Imputed values are clearly marked with '*' and patients with imputation where there was a death or evidence of progression have different shading to each other and the other patients to make it clear that these are different.

Pairwise treatment arm comparisons on percentage change in TL tumour size at Week 16 will be estimated from an Analysis of Covariance (ANCOVA) model including

- factor treatment arm
- factor prior platinum therapy (no/yes)
- covariate baseline TL tumour size
- covariate time from baseline scan to randomisation.

The number of patients, unadjusted mean and least squares means (lsmeans) for each treatment arm will be presented, together with the pairwise differences in lsmeans, 90% CIs and corresponding p-values.

A histogram of the residuals from fitting the ANCOVA model to the data (including both actual and imputed data) will be produced and used to assess whether ANCOVA is appropriate to analyse the data using percentage change in TL tumour size from baseline at Week 16. This decision will be made after unblinding when the model can be fitted. If ANCOVA assumptions are sufficiently met, these data will be analysed as described previously. If not, then the use of log-transformed data or a non-parametric approach will be used as described below.

If a log transformation of the data is decided, the percentage change in TL tumour size at Week 16 will be assessed as the natural logarithm of the ratio of the Week 16 TL tumour size over the baseline TL tumour size. Pairwise treatment arm comparisons on the log-transformed data will be performed with ANCOVA model as defined above (using covariate log-

transformed baseline TL tumour size). The ratios of the geometric least squares means (glsmeans), corresponding 90% CIs and p-values will be presented. In order to aid interpretation, the geometric mean ratios will also be presented as a percentage change from baseline (for example a glsmean of 0.8 would correspond to a 20% reduction).

In any case, an analysis of percentage change in TL tumour size at Week 16 will also be performed using the non-parametric method of an ANCOVA model on the ranked percentage change in tumour size with the same factors and covariates listed above. Ranking will be performed on the analysis data set following appropriate imputation of missing data:

- the patient with the greatest percentage reduction in TL tumour size at Week 16 will be assigned the lowest rank, with smaller changes and increases in tumour sizes taking increasing ranks
- deaths prior to the end of the window used to select Week 16 data will be assigned the highest rank (i.e. those patients for whom a value equal to the maximum percentage change in TL tumour size was imputed because the patient died).

The p-value from the non-parametric ANCOVA model will be presented together with the Hodges-Lehmann estimate of the median difference and corresponding 90% CI. The median, minimum and maximum percentage change will be presented for each treatment arm, together with the number of patients and percentage of patients in each treatment arm whose Week 16 data is imputed in the non-parametric analysis.

A sensitivity analysis of percentage change from baseline in TL tumour size at Week 16 using site investigator data will be performed in the same way as described above.

In addition, a descriptive summary table and a waterfall plot for best percentage change in TL tumour size will be provided.

4.2.8.6 Analysis of overall survival for all five patient populations

The analysis of OS for the three main patient populations will be performed in analogy to the primary analysis of PFS described in Section 4.2.4; the analysis of OS for patient populations Non HRR*m* and All will be performed in analogy to the methods described in Section 4.2.8.1 and 4.2.8.2.

Survival status at the time of the analysis will be summarised by treatment arm, including the number and percentage of patients who died, were still in survival follow-up or who discontinued the study (withdrew consent, lost to follow-up, other).

A sensitivity analysis for OS will examine the censoring patterns to rule out attrition bias (see Section 4.2.6): KM curves for time to censoring (where the censoring indicator of OS is reversed) will be generated by treatment arm.

The number of patients prematurely censored will be summarised by treatment arm. A patient would be defined as prematurely censored if their survival status was not defined at the DCO (i.e. patient not censored for administrative reason). If at least 10 patients (across treatment groups) were prematurely censored, the following characteristics will be summarized for prematurely censored patients and patients censored for administrative reason:

- prior platinum therapy
- patient population (in case of analyses of pooled patient populations)

- time to progression
- reason for withdrawal from study treatment.

4.2.8.7 Analysis of tumour and germline mutation status of CCI genes

A cross-tabulation summary of the tissue HRR mutation status (Positive, Negative, Invalid, Not Tested) versus the plasma HRR mutation status (Positive, Negative, Invalid, Not Tested) for each mutation type at Baseline will be produced for all screened subjects with both tumour and plasma samples analysed.

4.2.8.8 Analysis of exposure data

Total and actual exposure (expressed in days) of exposure for all 3 study treatments will be summarised by treatment arm.

A frequency table for number of treatment cycles for all 3 study treatments will be produced by treatment arm.

Analysis of dose interruptions and reductions

Descriptive summaries by treatment arm and study treatment will be produced for

- number and duration of dose of dose interruptions
- number, type and duration of dose of dose reductions.

Analysis of the duration of the safety follow-up

A frequency table for the duration of the safety follow-up will be produced by treatment arm.

4.2.8.9 Analysis of dose intensity

Summary statistics will be presented for relative dose intensity, although the data are unlikely to be normally distributed so it may be more appropriate to focus the interpretation on the medians, quartiles and the minimum and maximum values.

4.2.9 Analysis of drug concentration data

Plasma concentrations for each measured drug substance(s) will be listed by nominal sample time and by treatment arm.

In addition, minimum concentrations at steady state ($C_{min\ ss}$) will be summarised using summary statistics (number of non-missing observations, geometric mean, geometric coefficient of variation, arithmetic mean, standard deviation, minimum, and maximum).

The plasma concentration data for Olaparib, AZD1775 and/or AZD6738 will be analysed using a population PK and PKPD approach which is described in a separate analysis plan.

4.2.10 Analysis of safety and tolerability data

4.2.10.1 Analysis of adverse events

Summary tables mentioned below will include all treatment emergent AEs (as defined in Section 3.5.4). Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of study treatment) will be flagged in AE data listings.

Summaries by treatment arm, displaying MedDRA System Organ Class (SOC) and Preferred Term (PT) of treatment emergent AEs will include number (%) of patients who have:

- At least one AE (for All patient population and each of the 3 primary patient populations)
- At least one AE with CTCAE grade ≥ 3 (for All patient population and each of the 3 primary patient populations)
- At least one AE by maximum CTCAE grade
- At least one AE causally related to study medication (separately for investigational product in the combination treatment arms)
- At least one AE with CTCAE grade ≥ 3 causally related to study medication (separately for investigational product in the combination treatment arms)
- At least one AE leading to discontinuation of study treatment (for All patient population and each of the 3 primary patient populations)
- At least one OAE
- At least one SAE (for All patient population and each of the 3 primary patient populations)
- At least one SAE causally related to study medication (separately for investigational product in the combination treatment arms)

An overall summary of the number and percentage of patients in each category bulleted above will be presented, as well as an overall summary of the number of events in each category. In addition, a truncated AE table of most common AEs, showing all PTs that occur in at least 5% of patients overall will be summarised by preferred term, by decreasing frequency. This cut-off may be modified after review of the data.

4.2.10.2 Analysis of adverse events of special interest

A listing of the MedDRA Preferred Terms used for each AESI category will be provided by AZ and will be attached as an Appendix to the SAP.

Summaries by AESI category will include number (%) of patients who have:

- At least one AESI by maximum CTCAE grade
- At least one AESI leading to discontinuation of study treatment.

4.2.10.3 Deaths

A summary of deaths will be provided by treatment arm with number and percentage of patients, categorised as:

- Related to disease under investigation,
- AE outcome = death,
- Both related to disease under investigation and with AE outcome=death,
- AE with outcome = death ≥ 30 days after last treatment dose,
- Deaths ≥ 30 days after last treatment dose, unrelated to AE or disease under investigation, and
- Patients with unknown reason for death.

4.2.10.4 Analysis of safety laboratory test results

If any safety laboratory tests results other than those in Study Protocol Table 5 are reported by the investigator then these results will be listed only.

All safety laboratory test results will be classified as low (below range), normal (within range) and high (above range) based on the applicable local laboratory reference / normal ranges; for patients with missing or incomplete date of birth, age will be imputed as described in Section 3.1.2 when assigning laboratory reference ranges for those tests where normal ranges have upper and lower age limits. As applicable, values will be graded using CTCAE v4.03.

Shifts in continuous safety laboratory test results will be summarized

- graphically by scatter plots displaying the worst (lowest or highest, as applicable, or both separately for laboratory tests with hyper- and hypo-directionality of change) post-baseline laboratory test result against the baseline laboratory test result (one figure per safety laboratory test, treatment arms identified by different colour/symbol, identity (45°) line added)
- by shift tables displaying the worst (lowest or highest, as applicable, or both separately for laboratory tests with hyper- and hypo-directionality of change) post-baseline laboratory test result against the baseline laboratory test result.

Shift tables for categorical urinalysis test results from baseline to worst post-baseline test result will be provided.

Time course of continuous safety laboratory test results will be summarized

- graphically by boxplots showing laboratory test results over time (one figure per laboratory test, treatment arms identified by different colours / line styles connecting the medians)
- graphically by boxplots showing absolute change from baseline in laboratory test results over time (one figure per laboratory test, treatment arms identified by different colours / line styles connecting the medians)
- in tables showing the measured laboratory test results, absolute changes from baseline over time using descriptive statistics by visit.

A scatter plot of alanine aminotransferase (ALT) versus total bilirubin, both expressed as multiples of upper limit of normal (ULN) (calculated as ULN divided by maximum observed post-baseline result), will be produced. The scatter plot will be repeated for aspartate aminotransferase (AST) versus total bilirubin.

Liver biochemistry test results over time for patients with elevated ALT or AST (AST or ALT ≥3xULN), and elevated total bilirubin (≥2xULN) will be tabulated and plotted.

4.2.10.5 Analysis of vital signs and weight

Time course of continuous vital signs variables (including weight) will be summarized

- graphically by boxplots showing vital signs variables over time (one figure per vital signs variable, treatment arms identified by different colours / line styles connecting the medians)

- graphically by boxplots showing absolute change from baseline in vital signs variables over time (one figure per vital signs variable, treatment arms identified by different colours / line styles connecting the medians)
- by tables displaying measured vital signs values and changes from baseline over time using descriptive statistics by visit
- graphically by scatter plots displaying the maximum (minimum) post-baseline vital sign value against the baseline vital sign value (one figure per vital sign variable, treatment arms identified by different colour/symbol, identity (45°) line added)

4.2.10.6 Analysis of ECG data

QTcF will be summarised (absolute values and change from baseline) over time by treatment arm; boxplots for observed QTcF and change from baseline in QTcF over time will be presented.

Shift plots of the value corresponding to the maximum absolute change from baseline versus the baseline value for QTcF, with reference lines for 450 ms, ±30 ms and ±60 ms change, will be produced.

Shifts in QTcF results will be summarized

- graphically by scatter plots displaying the highest post-baseline QTcF value against the baseline QTcF value (treatment arms identified by different colour/symbol, identity (45°) line and reference lines for 450 ms as well as 30 ms and 60 ms increases)
- by tables displaying the following (partly cumulative) categories:
  - QTcF >450 ms, QTcF >480 ms, QTcF >500 ms
  - increase in QTcF from baseline >30 ms, increase in QTcF from baseline >60 ms, increase in QTcF from baseline >90 ms
  - QTcF >450 ms and increase in QTcF from baseline >30 ms
  - QTcF >500 ms and increase in QTcF from baseline >60 ms.

Such notable QTcF results will be flagged in QTcF data listings.

Frequency shift tables (baseline versus worst post-baseline) for categorical ECG variables will be provided.

4.2.10.7 Analysis of ECOG PS data

A shift table for ECOG PS data, baseline versus worst assessment on treatment will be produced.

4.2.10.8 Analysis of subject disposition and analysis sets

Summaries will include the number and percentage of patients by treatment arm:

- enrolled (informed consent received)
- randomised
- treated
- ongoing study treatment at the data cut-off (applicable for interim analyses)
- included in the FAS, SAF, or PK analysis set.

In addition, the number and percentage of patients who discontinued treatment and who discontinued the study, including a breakdown of the primary reason for discontinuation will be presented by treatment arm.

The number and percentage of patients randomized to AZD1775+olaparib who continue on olaparib monotherapy following the closure of the AZD1775+olaparib treatment arm in April 2019 will be presented.

4.2.10.9 Analysis of demographic and other baseline characteristics

Demographic and baseline characteristics will be summarised by treatment arm.

Descriptive statistics will be presented for continuous variables age (years), weight (kg), height (cm), body mass index (kg/m2), calculated as $\frac{weight}{height^2}$.

Number and percentages of patients will be presented by treatment arm for categorical variables age group (years) (grouped as <50, ≥50-<65, ≥65-<75, ≥75 and "missing", if required), sex, race, ethnic group and cancer-related baseline characteristics.

The number of patients recruited in each country and each centre will be presented by treatment group and in total.

4.2.10.10 Analysis of medical and surgical history

Medical and surgical history (past and current) will be summarized by number and percentage of patients with any medical / surgical history by SOC and PT.

4.2.10.11 Analysis of concomitant and other medications and therapies

For the purpose of inclusion in prior and/or concomitant mediation and therapy summaries, incomplete medication or therapy start and stop dates will be imputed as detailed in Section 3.1.2.

Prior, concomitant and post-study treatment medications and therapies are defined based on imputed start and stop dates as follows:

- Prior medications and therapies are those taken prior to study treatment with a stop date prior to the first dose of study treatment.
- Concomitant medications and therapies 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-study treatment medications and therapies are those with a start date after the last dose date of study treatment.

In addition, all post-study treatment anti-cancer medications and surgical procedures will be summarised by treatment arm.

The following summaries will be provided by treatment arm using ATC classification codes:

- summary of prior medications or therapies
- summary of concomitant medications or therapies
- summary of post-study treatment cancer medications or therapies.

4.2.11 Exploratory analyses of CCI

Exploratory analyses of CCI will be performed according to the overview below.

Patient Population	Outcome Measure	Analysis Method
• *BRCAm* • HRR*m* • Non *BRCAm* HRR*m* • All • Non HRR*m*	CCI CCI	CCI CCI

CCI CCI (defined in Section 3.4.5) will be reported by visit and treatment arm.

Descriptive statistics for the CCI CCI (defined in Section 3.4.5) will be provided by visit and treatment arm.

5. INTERIM ANALYSES

5.1 Safety interim analyses for ISRC

The ISRC for the VIOLETTE study is constituted to provide an independent, external, and unbiased assessment of safety and tolerability during the conduct of the trial. The ISRC is an independent external group of experts with experience in the monitoring of randomized clinical studies.

The ISRC will review unblinded safety interim analysis outputs in intervals specified in the ISRC Charter and will make recommendations to AZ. Such recommendation may include

- continuation of the study according to the protocol and any relevant amendments
- modifying the study procedures to ensure continued safety of study participants
- discontinuation of a study patient population or study treatment or the study (with provisions for orderly discontinuation in accordance with good clinical practice).

5.2 Futility interim analyses for AZ URC

For the non HRR*m* population an interim analysis will be triggered when 75 patients have been recruited and assessed for at least 8 weeks, in order to assess the proportion of patients with NPD based on the Investigator assessment at 8 weeks in each of the treatment arms. With approximately 25 patients in each treatment arm, if the 80% 2-sided upper CI limit for the proportion of patients with NPD is less than 56% (O'Shaughnessy et al 2014) and with consideration of this analysis in context with the totality of the clinical data (safety and efficacy) available, the AZ URC may recommend to cease recruitment in this arm and no further patients will be recruited into that treatment arm in the non HRRm population. Recruitment will be paused after the 75th patient has been recruited into the population, until

the AZ URC confirms the strata and which treatment arms should be reopened. In April 2019, the AZ URC determined that recruitment to the AZD1775+olaparib arm should not be reopened. This parallels the ISRC recommendation to close recruitment to the AZD1775+olaparib arm in all three populations for safety concerns.

A further NPD futility interim analysis, using the same criteria, in the non *BRCAm* HRR*m* population may be performed, if the outcome of the interim analysis in the non HRR*m* population resulted in treatment arms being stopped.

5.3 Interim analyses of PFS for AZ URC

As the "non HRR*m*" patient population is expected to be enrolled quicker than the other patient populations, the first PFS interim analysis for patient population "non HRR*m*" is triggered when 44 PFS events (65% of planned number of PFS events) for the AZD6738+olaparib vs. olaparib comparison have occurred in stratum C.

The second PFS interim analysis for patient populations "*BRCAm*" and "non BRCA*m* HRR*m*" is triggered when at least 44 PFS events (65% of planned number of PFS events)) for the AZD6738+olaparib vs. olaparib comparison have occurred in each of the two strata A and B.

The PFS interim analyses may be concurrent or separate depending on the PFS event rates in the three strata and operational requirements, so if the timings for the 44 PFS events in the *BRCAm* and non *BRCAm* HRR*m* populations are not concurrent, separate interims may be needed for each patient population. The purpose of the interim analyses is to provide the opportunity to stop for futility (details will be specified in the URC Charter) and for an early trigger to commence a phase III study, if the results are strong enough.

5.4 Analyses of OS

An initial OS analysis will be performed at the same time as the final analysis of PFS.

A further analysis of OS will be performed when the OS data for the AZD6738+olaparib vs. olaparib comparison are approximately 70% mature. .

6. CHANGES OF ANALYSIS FROM PROTOCOL

Not applicable.

7. REFERENCES

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O'Shaughnessy J, Schwartzberg L, Danso MA, Miller KD, Rugo HS, Neubauer M, Robert N, Hellerstedt B, Saleh M, Richards P, Specht JM, Yardley DA, Carlson RW, Finn RS, Charpentier E, Garcia-Ribas I, Winer E. Phase III Study of Iniparib plus Gemcitabine and Carboplatin versus Gemcitabine and Carboplatin in patients with Metastatic Triple-Negative Breast Cancer. JCO. 2014; 32(34):3840-3847

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8. APPENDIX

Not yet applicable – but may be added later.

AZ ECD BIOMETRICS SAP TABLE OF CONTENTS FOR TABLES, FIGURES AND LISTINGS

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	Patient disposition						
T 11.1.1 (a b c e)	Patient disposition (all enrolled patients)	T TDEM010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
F 11.1.1 (a b c e)	Patient disposition (all enrolled patients)	F SP1	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
	Protocol deviations						
T 11.1.2 (a b c e)	Important protocol deviations (FAS)	T SP2	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
	Analysis sets						
T 11.1.3 (a b c e)	Analysis sets	T TDEM030	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All No analysis set to be stated in the table title as per AZ reporting standards.	X		X	
F 11.1.2 (a b c e)	Analysis sets	F SP2	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			

[1] Letter extensions in TFL number indicate the patient population throughout the table, a: *BRCAm*, b: Non *BRCAm* HRR*m*, c: Non HRR*m*, d: HRR*m*, e: All
[2] Efficacy outputs will only include the Non HRR*m* patient population. Other outputs will include the Non HRR*m* patient population and the overall population, unless the output is only designated for the overall population.
[3] Efficacy outputs will only include the patient population(s) of interest for the respective URC meeting. Other outputs will include the patient population(s) of interest and the overall population, unless the output is only designated for the overall population

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
			No analysis set to be stated in the table title as per AZ reporting standards.				
	Demography and patient characteristics						
T 11.1.4 (a b c e)	Demographic characteristics (FAS)	T SP4	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.1.5 (a b c e)	Patient characteristics (FAS)	T SP8	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
T 11.1.6 (a b c e)	Randomization stratification factors recorded by IRT and eCRF (FAS)	T ASP6	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	
T 11.1.7 (a b c e)	Discrepancies between randomization stratification factors recorded by IRT and eCRF (FAS)	T NEW	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
T 11.1.8 (a b c e)	Patient recruitment by country and centre (FAS)	T ASP1	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	Previous treatments and medical history						
T 11.1.9 (a b c e)	Previous disease-related treatment modalities (FAS)	T TDEM060	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
T 11.1.10 (a b c e)	Previous disease-related treatment modalities by preferred group (FAS)	T TDEM065	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All				
T 11.1.11 (a b c e)	Number of regimens of previous anti-cancer therapies at baseline (FAS)	T TDEM070	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.1.12 (a b c e)	Previous disease-related chemotherapy treatments (FAS)	T TDEM080	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
T 11.1.13 (a b c e)	Disease-related medical history (FAS)	T SP7(i)	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
T 11.1.14 (a b c e)	Relevant surgical history (FAS)	T SP7(ii)	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
T 11.1.15 (a b c e)	Disease characteristics at baseline (FAS)	T TDEM110	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.1.16 (a b c e)	Extent of disease at baseline (FAS)	T TDEM130	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
T 11.1.17 (a b c e)	Time from most recent disease progression to randomization (FAS)	T TDEM200	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
T 11.1.18 (a b c e)	Time from completion of previous anti cancer therapy to randomization (FAS)	T TDEM190	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			
	Concomitant medications						
T 11.1.19 (a b c e)	Disallowed concomitant medications post randomization (FAS)	T SP9	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X		X	
T 11.1.20 (a b c e)	Post-discontinuation disease-related anticancer therapy (FAS)	T TDEM180	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X		X	
T 11.1.21 (e)	All allowed concomitant medications post randomization (FAS)	T SP10	Patient population: All	X			
T 11.1.22 (a b c e)	Patients requiring treatment with G-CSF	T SP10	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			X
	Extent of exposure						
T 11.3.1.1 (a b c e)	Duration of exposure (SAF)	T TEXP010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.3.1.2.1 (a b c e)	Treatment interruptions and dose reductions (SAF)	T AS13	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.3.1.2.2 (a b c e)	Treatment interruptions and dose reductions - Cycle 1 and 2 (SAF)	T AS13	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
F 11.3.1.1 (a b c e)	Exposure over time (SAF)	F S1	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.3.1.6 (a b c e)	Treatment cycles received (SAF)	T TEXP080	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.3.1.7 (a b c e)	Dose intensity (SAF)	T TEXP100	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			X
	Progression-free survival per BICR						
F 11.2.1.1 (a b c)	Progression-free survival per BICR, assessment of the proportional hazards assumption (FAS)	F NEW	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.1 (a b c)	Progression-free survival, primary analysis per BICR (FAS)	T TEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.1.2 (a b c)	Progression-free survival, primary analysis per BICR, K-M plot (FAS)	F ZEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.1.3 (a b c)	Progression-free survival per BICR, K-M plots by prior platinum-based therapy (no, yes) (FAS)	F ZEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.2 (d e)	Weighted progression-free survival, secondary analysis per BICR (FAS)	T TEFF010	Patient populations: HRR*m*, All	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
F 11.2.1.4 (d e)	Weighted progression-free survival, secondary analysis per BICR, K-M plot (FAS)	F ZEFF010	Patient populations: HRR*m*, All	X			
T 11.2.1.3 (d e)	Unweighted progression-free survival, sensitivity analysis per BICR (FAS)	T TEFF010	Patient populations: HRR*m*, All	X			
F 11.2.1.5 (d e)	Unweighted progression-free survival, sensitivity analysis per BICR, K-M plot (FAS)	F ZEFF010	Patient populations: HRR*m*, All	X			
T 11.2.1.4 (a b c)	Treatment status at progression per BICR (FAS)	T TEFF450	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.5 (a b c)	Time from last tumour assessment to data cut-off in patients censored per BICR (FAS)	T TEFF510	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.6 (a b c)	Progression-free survival per BICR, sensitivity analysis for evaluation-time bias (FAS)	T TEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
T 11.2.1.7 (a b c)	Progression-free survival per BICR, sensitivity analysis per BICR, with censoring and event flags reversed (FAS)	T TEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m* Patients who take subsequent anti-cancer therapy prior to their last evaluable RECIST assessment or progression or death will be censored at their last	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
			evaluable RECIST assessment prior to taking the subsequent therapy.				
F 11.2.1.6 (a b c)	Progression-free survival per BICR, sensitivity analysis per BICR, K-M plot with censoring and event flags reversed (FAS)	F ZEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m* Patients who take subsequent anti-cancer therapy prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable RECIST assessment prior to taking the subsequent therapy.	X			
T 11.2.1.8 (a b c)	New lesions per BICR (FAS)	T TEFF220	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.9 (a b c)	Subsequent cancer therapy relative to progression per BICR (FAS)	T TEFF170	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.10 (a b c d e)	Disagreements between BICR and site investigator assessment of RECIST progression (FAS)	T TEFF100	All 5 patient populations	X		X	
T 11.2.1.11 (a b c)	Progression-free survival per BICR, descriptive subgroup analyses (FAS)	T TEFF060	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
F 11.2.1.7 (a b c)	Progression-free survival per BICR, descriptive subgroup analyses, K-M plots (FAS)	F ZEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
F 11.2.1.8 (a b c)	Progression free survival per BICR, forest plot by subgroup (FAS)	F ZEFF020	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
	Progression-free survival per site investigator data						
F 11.2.1.9 (a b c)	Progression-free survival, sensitivity analysis per site investigator data, assessment of the proportional hazards assumption (FAS)	F NEW	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.12 (a b c)	Progression-free survival, sensitivity analysis per site investigator data (FAS)	T TEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X	X	X	
F 11.2.1.10 (a b c)	Progression-free survival, sensitivity analysis per site investigator data, K-M plot (FAS)	F ZEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X	X	X	
F 11.2.1.11 (a b c)	Progression-free survival, sensitivity analysis per site investigator data, K-M plots by prior platinum-based therapy (no, yes) (FAS)	F ZEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.13 (d e)	Weighted progression-free survival, sensitivity analysis per site investigator data (FAS)	T TEFF010	Patient populations: HRR*m*, All	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
F 11.2.1.12 (d e)	Weighted progression-free survival, sensitivity analysis per site investigator data, K-M plot (FAS)	F ZEFF010	Patient populations: HRR*m*, All	X			
T 11.2.1.14 (d e)	Unweighted progression-free survival, sensitivity analysis per site investigator data (FAS)	T TEFF010	Patient populations: HRR*m*, All	X			
F 11.2.1.13 (d e)	Unweighted progression-free survival, sensitivity analysis per site investigator data, K-M plot (FAS)	F ZEFF010	Patient populations: HRR*m*, All	X			
T 11.2.1.15 (a b c)	Treatment status at progression per site investigator data (FAS)	T TEFF450	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.16 (a b c)	Time from last tumour assessment to data cut-off in patients censored per site investigator data (FAS)	T TEFF510	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.17 (a b c)	Progression-free survival per site investigator data, sensitivity analysis for evaluation-time bias (FAS)	T TEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
T 11.2.1.18 (a b c)	Progression-free survival per site investigator data, sensitivity analysis with censoring and event flags reversed (FAS)	T TEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m* Patients who take subsequent anti-cancer therapy prior to their last evaluable RECIST assessment or progression or	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
			death will be censored at their last evaluable RECIST assessment prior to taking the subsequent therapy.				
F 11.2.1.14 (a b c)	Progression-free survival, sensitivity analysis per site investigator data, K-M plot with censoring and event flags reversed (FAS)	F ZEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m* Patients who take subsequent anti-cancer therapy prior to their last evaluable RECIST assessment or progression or death will be censored at their last evaluable RECIST assessment prior to taking the subsequent therapy.	X			
T 11.2.1.19 (a b c)	New lesions per site investigator data (FAS)	T TEFF220	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.20 (a b c)	Subsequent cancer therapy relative to progression per site investigator data (FAS)	T TEFF170	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.1.21 (a b c)	Progression-free survival per site investigator data, descriptive subgroup analyses (FAS)	T TEFF060	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
F 11.2.1.15 (a b c)	Progression-free survival per site investigator data, descriptive subgroup analyses, K-M plots (FAS)	F ZEFF010	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
F 11.2.1.16 (a b c)	Progression free survival per site investigator data, forest plot by subgroup (FAS)	F ZEFF020	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	Objective Response Rate and Duration of Response						
T 11.2.2.1 (a b c d e)	Best objective response per BICR (FAS)	T TEFF110	All 5 patient populations	X		X	
T 11.2.2.2 (a b c d e)	Objective response rate per BICR, logistic regression (FAS)	T TEFF140	All 5 patient populations	X		X	
T 11.2.2.3 (a b c d e)	Onset of response per BICR relative to subsequent cancer therapy (FAS)	T TEFF180	All 5 patient populations	X		X	
T 11.2.2.4 (a b c)	Duration of response per BICR, EDoR method (FAS)	T TEFF165	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.2.5 (a b c)	Duration of response per BICR in patients with objective response (FAS)	T TEFF150	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.2.1 (a b c)	Duration of response per BICR in patients with objective response, K-M plot (FAS)	F ZEFF070	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.2.2 (a b c)	Duration of response per BICR in patients with objective response, swimmer plot (FAS)	NEW	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.2.6.1 (a b c d e)	Best objective response per site investigator data (FAS)	T TEFF110	All 5 patient populations	X	X	X	
T 11.2.2.6.2 (a b c d e)	Objective response rate per site investigator data, logistic regression (FAS)	T TEFF140	All 5 patient populations	X		X	

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
T 11.2.2.7 (a b c d e)	Onset of response per site investigator data relative to subsequent cancer therapy (FAS)	T TEFF180	All 5 patient populations	X		X	
T 11.2.2.8 (a b c)	Duration of response per per site investigator data, EDoR method (FAS)	T TEFF165	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.2.9 (a b c)	Duration of response per site investigator data in patients with objective response (FAS)	T TEFF150	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.2.3 (a b c)	Duration of response per site investigator data in patients with objective response, K-M plot (FAS)	F ZEFF070	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.2.4 (a b c)	Duration of response per site investigator data in patients with objective response, swimmer plot (FAS)	NEW	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
	Non-progressive disease at Week 8						
T 11.2.2.10 (c)	Non-progressive disease at Week 8 based on site investigator data (FAS)	NEW	Patient population: Non HRR*m*		X		

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	Target lesion size						
T 11.2.3.1 (a b c)	Target lesion size per BICR, percentage change from baseline to week 16 (FAS)	T TEFF190	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.3.2 (a b c)	Target lesion size per BICR, percentage change from baseline to week 16, ANCOVA (FAS)	T TEFF460	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.3.3 (a b c)	Target lesion size per BICR, percentage change from baseline to week 16, non-parametric analysis (FAS)	T TEFF540	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.3.4 (a b c)	Target lesions at week 16 scaled per BICR data (FAS)	T TEFF500	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.3.1 (a b c)	Target lesion size per BICR, percentage change from baseline to week 16, waterfall plot (FAS)	F ZEFF030	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.3.5 (a b c)	Target lesion size per BICR, percentage change from baseline (FAS)	T TEFF200	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
T 11.2.3.6 (a b c)	Best percentage change from baseline in target lesion size per BICR (FAS)	T TEFF190	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.3.2 (a b c)	Best percentage change from baseline in target lesion size per BICR, waterfall plot (FAS)	F ZEFF030	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
T 11.2.3.7 (a b c)	Target lesion size per site investigator, percentage change from baseline to week 16 (FAS)	T TEFF190	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.3.8 (a b c)	Target lesion size per site investigator, percentage change from baseline to week 16, ANCOVA (FAS)	T TEFF460	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.3.9 (a b c)	Target lesion size per site investigator, percentage change from baseline to week 16, non-parametric analysis (FAS)	T TEFF540	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.3.10 (a b c)	Target lesions at week 16 scaled per site investigator (FAS)	T TEFF500	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
F 11.2.3.3 (a b c)	Target lesion size per site investigator, percentage change from baseline to week 16, waterfall plot (FAS)	F ZEFF030	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X		X	
T 11.2.3.11 (a b c)	Target lesion size per site investigator, percentage change from baseline (FAS)	T TEFF200	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
T 11.2.3.12 (a b c)	Best percentage change from baseline in target lesion size per site investigator (FAS)	T TEFF190	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X	X	X	
F 11.2.3.4 (a b c)	Best percentage change from baseline in target lesion size per	F ZEFF030	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X	X	X	

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	site investigator, waterfall plot (FAS)						
	Overall Survival						
T 11.2.4.1 (a b c d e)	Overall survival (FAS)	T TEFF280	All 5 patient populations	X		X	
F 11.2.4.1 (a b c d e)	Overall survival, Kaplan-Meier plot (FAS)	F ZEFF050	All 5 patient populations	X		X	
T 11.2.4.2 (a b c d e)	Patients censored for OS at more than 8 weeks before the data cut-off (FAS)	T TEFF310	All 5 patient populations	X			
T 11.2.4.3 (a b c)	Overall survival, sensitivity analysis with censoring and event flags reversed (FAS)	T TEFF280	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
F 11.2.4.2 (a b c)	Overall survival, sensitivity analysis K-M plot with censoring and event flags reversed (FAS)	F ZEFF010C	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
	Tumour and germline mutation status						
T 11.2.5.1 (e)	Tumour and germline mutation status of CCI genes (All screened patients)	NEW	Patient population: All	X			
	CCI						
T 11.2.6.1 (a b c d e)	CCI CCI by visit (FAS)	T HO4	All 5 patient populations	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
T 11.2.6.2 (a b c d e)	CCI CCI by visit (FAS)	T HO1(i)	All 5 patient populations HO4 but with median instead of CIs, no difference between treatment arms	X			
	PK						
T 11.2.7.1 (e)	Summary of plasma concentrations of olaparib (PK analysis set)	T PK3	Patient population: All All 3 treatment arms	X			
T 11.2.7.2 (e)	Summary of plasma concentrations of AZD6738 (PK analysis set)	T PK3	Patient population: All AZD6738 treatment arm	X			
T 11.2.7.3 (e)	Summary of plasma concentrations of AZD1775 (PK analysis set)	T PK3	Patient population: All AZD1775 treatment arm	X			
T 11.2.7.4 (e)	Summary of olaparib $C_{min,ss}$ (PK analysis set)	T PK6(i)	Patient population: All All 3 treatment arms	X			
T 11.2.7.5 (e)	Summary of AZD6738 $C_{min,ss}$ (PK analysis set)	T PK6(i)	Patient population: All AZD6738 treatment arm	X			
T 11.2.7.6 (e)	Summary of AZD1775 $C_{min,ss}$ (PK analysis set)	T PK6(i)	Patient population: All AZD1775 treatment arm	X			
	Adverse events						
T 11.3.2.1 (e)	Adverse events in any category - patient level (SAF)	T TAE010	Patient population: All	X	X	X	X

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
T 11.3.2.2 (e)	Adverse events in any category - episode level (SAF)	T TAE020	Patient population: All	X			
T 11.3.2.3 (a b c e)	Adverse events, by system organ class and preferred term (SAF)	T S9(i)	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.3.2.4 (a b c e)	Adverse events, most common (frequency of >10% in any treatment arm) (SAF)	T S8	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X		X	X
T 11.3.2.5 (e)	Adverse events by system organ class, preferred term and maximum CTCAE grade (SAF)	T TAE050	Patient population: All	X			
T 11.3.2.6 (a b c e)	Adverse events of CTCAE grade 3 or higher, by system organ class and preferred term (SAF)	T TAE060	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.3.2.7 (e)	Adverse events causally related to olaparib, by system organ class and preferred term (SAF)	T S9(ii)	Patient population: All All 3 treatment arms	X			X
T 11.3.2.8 (e)	Adverse events causally related to AZD6738 or AZD1775, by system organ class and preferred term (SAF)	T S9(ii)	Patient population: All Only the two combination treatment arms	X			X
T 11.3.2.9 (e)	Adverse events of CTCAE grade 3 or higher and causally related to olaparib, by system	T S9(ii)	Patient population: All All 3 treatment arms	X			X

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	organ class and preferred term (SAF)						
T 11.3.2.10 (e)	Adverse events of CTCAE grade 3 or higher and causally related to AZD6738 or AZD1775, by system organ class and preferred term (SAF)	T S9(ii)	Patient population: All Only the two combination treatment arms	X			X
T 11.3.2.11 (a b c e)	Adverse Events leading to discontinuation of olaparib, by system organ class and preferred term (SAF)	T S19(i)	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All All 3 treatment arms	X	X	X	X
T 11.3.2.12 (a b c e)	Adverse Events leading to discontinuation of AZD6738 or AZD1775, by system organ class and preferred term (SAF)	T S19(i)	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All Only the two combination treatment arms	X	X	X	X
T 11.3.2.13 (e)	Adverse Events leading to discontinuation of study treatment - Listing of key information (SAF)	T TAE210	Patient population: All	X		X	X
T 11.3.2.14 (e)	Adverse events of special interest - list of preferred terms	T AS9	Patient population: All	X			
T 11.3.2.15 (e)	Adverse events of special interest by CTCAE grade (SAF)	T TAE100	Patient population: All	X			
T 11.3.2.16 (e)	Adverse events of special interest leading to	T S19(i)	Patient population: All All 3 treatment arms	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	discontinuation of olaparib (SAF)						
	Deaths						
T 11.3.3.1 (e)	All Deaths (FAS)	TDTH010	Patient population: All	X	X	X	X
T 11.3.3.2 (e)	Adverse events with outcome of death by system organ class and preferred term (SAF)	T S13(i)	Patient population: All	X	X	X	
T 11.3.3.3 (e)	Listing of deaths (FAS)	T TDTH040	Patient population: All	X		X	X
T 11.3.3.4 (e)	Adverse Events with outcome of death - key patient information (SAF)	T S14	Patient population: All	X		X	X
	Serious adverse events						
T 11.3.4.1 (a b c e)	Serious adverse events by system organ class and preferred term (SAF)	T S17(i)	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X	X	X	X
T 11.3.4.2 (e)	SAEs causally related to olaparib, by system organ class and preferred term (SAF)	T S17(ii)	Patient population: All All 3 treatment arms	X			
T 11.3.4.3 (e)	SAEs causally related to AZD6738 or AZD1775, by system organ class and preferred term (SAF)	T S17(ii)	Patient population: All Only the two combination treatment arms	X			
T 11.3.4.4 (a b c e)	SAEs leading to discontinuation of AZD6738 or AZD1775, by	T S19(i)	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*, All	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	system organ class and preferred term (SAF)		Only the two combination treatment arms				
T 11.3.4.5 (e)	Serious adverse events - Listing of key information for SAEs (SAF)	T TAE180	Patient population: All	X		X	X
	Other significant adverse events						
T 11.3.6.1 (e)	Other significant adverse events by category (SAF)	T S21	Patient population: All	X			
T 11.3.6.2 (e)	Adverse events assessed by the sponsor to be significant, by system organ class and preferred term (SAF)	T S24	Patient population: All	X			
T 11.3.6.3 (e)	Other significant adverse events - Listing of key information (SAF)	T TAE250	Patient population: All	X			
	Clinical laboratory tests						
T 11.3.7.1 (e)	Haematology and clinical chemistry laboratory tests over time (SAF)	T S25(lab)	Patient population: All Includes only absolute change from baseline.	X			
F 11.3.7.1 (e)	Haematology laboratory tests, box plots of absolute values (SAF)	F S11(lab)	Patient population: All	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
F 11.3.7.2 (e)	Clinical chemistry laboratory tests, box plots of absolute values (SAF)	F S11(lab)	Patient population: All	X			
F 11.3.7.3 (e)	Haematology laboratory test, box plots of change from baseline (SAF)	F S11(lab)	Patient population: All	X			
F 11.3.7.4 (e)	Clinical chemistry laboratory tests, box plots of change from baseline (SAF)	F S11(lab)	Patient population: All	X			
T 11.3.7.2 (e)	Haematology and clinical chemistry, CTCAE grade change from baseline to maximum value on treatment for laboratory tests with uni-directional grades (SAF)	T TLAB020	Patient population: All	X			
T 11.3.7.3 (e)	Hematology and clinical chemistry, CTCAE grade change from baseline to maximum value on treatment for laboratory tests with bi-directional grades (SAF)	T TLAB020a	Patient population: All	X			
F 11.3.7.5 (e)	Hematology and clinical chemistry, baseline versus maximum/minimum value on treatment - shift plot (SAF)	F S8	Patient population: All	X			X

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
T 11.3.7.4 (e)	Clinically important changes in haematology laboratory tests (SAF)	T TLAB060	Patient population: All	X			X
T 11.3.7.5 (e)	Clinically important changes in clinical chemistry laboratory tests (SAF)	T TLAB060	Patient population: All	X			X
T 11.3.7.6 (e)	Urinalysis, baseline versus maximum value on treatment, shift table (SAF)	T S33	Patient population: All	X			
T 11.3.7.7 (e)	Subjects with potential Hy's Law - individual patient data (SAF)	T S32	Patient population: All	X			
F 11.3.7.6 (e)	ALT versus total bilirubin, expressed as multiples of ULN (SAF)	F S9	Patient population: All	X			
F 11.3.7.7 (e)	AST versus total bilirubin, expressed as multiples of ULN (SAF)	F S9	Patient population: All	X			
F 11.3.7.8 (e)	Liver biochemistry test results over time - patients with elevated ALT or AST, and elevated total bilirubin, at any time (SAF)	F S10	Patient population: All	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
	Vital signs (including weight) / ECG						
T 11.3.8.1 (e)	Vital signs variables over time (SAF)	T S25(vital)	Patient population: All Includes only absolute change from baseline	X			
F 11.3.8.1 (e)	Vital signs data, box plots of absolute values (SAF)	F ZVIT010	Patient population: All	X			
F 11.3.8.2 (e)	Vital signs data, box plots of change from baseline (SAF)	F ZVIT010	Patient population: All	X			
F 11.3.8.3 (e)	Vital signs, baseline to maximum value during treatment (SAF)	F S8(vital)	Patient population: All	X			
F 11.3.8.4 (e)	Vital signs, baseline to minimum value during treatment (SAF)	F S8(vital)	Patient population: All	X			
T 11.3.8.2 (e)	Summary of descriptive statistics for QTcF (SAF)	T S25(ecg)	Patient population: All Includes absolute change from baseline	X			
F 11.3.8.5 (e)	Box-plot of QTcF, absolute values (SAF)	F S11(ecg)	Patient population: All	X			
F 11.3.8.6 (e)	Box-plot of QTcF, change from baseline (SAF)	F S11(ecg)	Patient population: All	X			
T 11.3.8.3 (e)	QTcF and QTcF changes from baseline, at any observation on treatment (SAF)	T S35	Patient population: All	X			X

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
T 11.3.8.4 (e)	ECG, baseline versus worst assessment on treatment (SAF)	T S41(ecg)	Patient population: All	X			X
	ECOG PS						
T 11.3.8.7 (e)	ECOG PS, baseline versus worst assessment on treatment (SAF)	T S41(ecg) but for ECOG PS	Patient population: All	X			X
	Regional safety requirements						
T RegUS1 (e)	Non-serious adverse events occurring in greater than 5% of patients by system organ class and preferred term (SAF)	T FDAAA1	Patient population: All	n	n	n	n
	Patient Data Listings as per Global Specification for Clinical Study Report Appendix 12.2 (version 2.2, 20 Dec 2016)						
L 12.1.6 (a b c)	Patients receiving the various batches of investigational products (SAF)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
L 12.1.7 (a b c)	Randomization scheme and codes (FAS)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			X
L 12.2.1.1 (a b c)	Disposition of patients (FAS)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			X
L 12.2.2.1 (a b c)	Patients with important protocol deviations (FAS)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
L 12.2.3.1 (a b c)	Patients excluded from the safety analysis set or the PK analysis set (FAS)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
L 12.2.4.1 (a b c)	Demographics and baseline characteristics (FAS)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
L 12.2.4.2 (a b c)	Other baseline characteristics (FAS)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
L 12.2.5.1 (a b c)	Administration of investigational product (SAF)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			X
L 12.2.6.1 (a b c)	RECIST tumour assessment per BICR and per site investigator data (FAS)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X	X	X	
L 12.2.6.2 (a b c)	Progression-free survival: per BICR and per site investigator data (FAS)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
L 12.2.6.3 (a b c)	Drug concentration data (PK set)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
L 12.2.7.1 (a b c)	Adverse events (SAF)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			X
L 12.2.8.2 (a b c)	Safety laboratory tests (SAF)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
L 12.2.9.1 (a b c)	Vital signs (SAF)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			
L 12.2.10.1 (a b c)	Electrocardiogram data (SAF)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			

TFL Number[1]	Title	Standard	Additional Information (details will be provided when drafting TFL shells)	CSR	1st URC[2]	≥ 2nd URC[3]	ISRC
L 12.2.10.2 (a b c)	Abnormalities in electrocardiogram (SAF)	Not applicable	Patient populations: *BRCAm*, Non *BRCAm* HRR*m*, Non HRR*m*	X			

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