AstraZeneca

Statistical Analysis Plan	
Study Code	D081KC00001
Edition Number	2.1
Date	18 Jul 2019

A Phase I/II Study of MEDI4736 (Anti-PD-L1 Antibody) in Combination with Olaparib (PARP inhibitor) in Patients with Advanced Solid Tumors

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Global Product Statistician PPD

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AML	Acute myeloid leukemia
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATM	Ataxia telangiectasia mutated (gene or protein)
AUC_{τ}	Area under the plasma concentration-time curve over the dosing
AZDD	Astra Zeneca Drug Dictionary
bid	Twice daily
BMI	Body mass index
BP	Blood pressure
BICR	Blinded Independent Central Review
BRCA	Breast cancer susceptibility gene, ie, *BRCA1* and *BRCA2*
BRCAm	Mutated breast cancer susceptibility gene
CI	Confidence interval
$C_{max\ ss}$	Maximum plasma concentration at steady state
$C_{min\ ss}$	Minimum plasma concentration at steady state
CR	Complete response
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CV (%CV)	Coefficient of variation
DAE	Discontinuation of investigational product due to adverse event
DCR	Disease control rate

Abbreviation or special term	Explanation
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DRM	Data review meeting
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full analysis set
FIGO	The International Federation of Gynecology and Obstetrics
gBRCAm	Germline mutated breast cancer susceptibility gene
%GCV	Geometric coefficient of variation
HLA-DR	Human leukocyte antigen – antigen D related
INV	Investigator
IP	Investigational product
irAE	Immune-related adverse events
KM	Kaplan-Meier
LD	Longest diameter
LOQ	Limit of quantification
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NC	Not calculable
NCI	National Cancer Institute
NE	Not evaluable
NEC	Not elsewhere classified
NQ	Non-quantifiable
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Anti-programmed cell death 1

Abbreviation or special term	Explanation
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
PID	Percentage intended dose
PK	Pharmacokinetics
PR	Partial response
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
sPD-L1	Soluble programmed death-ligand 1
STCRG	Safety and tumor cohort review group
TDT	Time to study treatment discontinuation or death
TL	Target lesion
ULN	Upper limit of normal

AMENDMENT HISTORY

Date/ SAP version	Brief description of change
31 Jul 2018/ v1.2	SAP updated to synchronise with CSP edition 4, 14 April 2018: 1. Section Study DetailsStudy objectives: • Updated the primary and secondary objectives to include the second stage ovarian cohorts. The primary and secondary objectives updated to mention bevacizumab treatment. • Added BICR analysis for DCR at 12 weeks and 28 weeks, ORR, DoR and PFS for the initial stage ovarian cohort. • Updated TDT endpoint to add 'or death': Time to study treatment discontinuation or death • Added serum concentration of bevacizumab and bevacizumab ADA in the PK analysis objectives • CCI •  • • 2. Section Study design: • Added paragraph to specify the cut-off for each cohort and data collection for patients who discontinue study treatment • Added treatment plan schematic for second stage cohorts • Added specification of the efficacy endpoints in the second stage cohorts Added Bayesian design for ovarian triplet and doublet cohorts 3. Section Number of patients: • Added details on the sample size for second stage cohorts, and specification on the interim efficacy assessment in the ovarian triplet and doublet cohorts 4. Section Analysis Sets: • Added details for second stage cohort PK analysis set and important protocol deviations 5. Section Primary and Secondary Variables: • Updated study derivation to consider the second stage cohorts • Specified the endpoints for the second stage cohorts (DCR, ORR, PFS, OS, TDT, % change in tumor size • Added details on the BOR endpoint • Added section for Supportive efficacy endpoints

Date/ SAP version	Brief description of change
	• Added details for timeframe for safety assessments in the second stage cohorts • Updated subsection Olaparib and MEDI4736 adverse events of special interest to remove reference to Appendix B and specified that the list of preferred terms for AESI is to be based on external agreed and reviewed spreadsheet • Added subsection to specify the identification of the Immune-related adverse events • Added overall exposure for the initial and second stage cohorts • Included bevacizumab to RDI definition • Added second stage details for ECGs and ECOG • Updated subsection Pharmacokinetics and immunogenicity to include details on bevacizumab 6. Section Analysis Methods: • Added subgroup analysis details for ovarian expansion cohort (subgroup of patients with BRCA status determined by Myriad) • Added tables with Formal Statistical Analyses to be Conducted • Added a section for DCR at 24 and 56 Weeks for second stage cohorts • Included details for ORR for the second stage cohorts • Specified details for drug related AEs reporting (including bevacizumab following CSP v3.0) • Subsection PK Data updated to include bevacizumab • Subsection Treatment exposure updated to add overall exposure summaries 7. Section Interim Analyses: • Added details on the second stage cohorts interim analyses plan 8. Section Changes of Analysis from Protocol: • Removed DoR note as this is no longer valid • Updated to specify the rationale for including BOR as efficacy endpoint 9. Removed Appendix B with the list of preferred terms for AESI. The list is stored in the external spreadsheet provided by AZ Programming. The PTs utilized to identify AESI will be listed in a separate appendix.
15 Feb 2019/ v1.3	1. Updated section 4.1 General principles to add Q1 and Q3, and geometric standard deviation to the list of required statistics. 2. Section 2.2: • Updated the table with important protocol deviations Violations and deviations to move the inclusion criteria for all second stage cohorts from IPD2, which excludes from the FAS, to IPD6 which is not leading to exclusion from any of the analysis sets (these IPDs are just listed). • Modified paragraph for PK data, to specify that the assessment of

Date/ SAP version	Brief description of change

PK profile eligibility will be by AZ PK Scientist
- Updated title of table 1 to "List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets"

3. Updated section 1.2.1 for the final cut-off based on CSP v5.0 as this is the plan for DBL. Removed "relapsed" in the first paragraph which was considered redundant. Added "Targets were based on efficacy observed using either standard of care or olaparib monotherapy for specific indication and aiming for superiority."
4. Added paragraph on BICR analyses in section 1.2.1 for initial stage cohorts Removed the reference to section 1.2.1 in 1.2.2.1, 1.2.2.2 as not relevant for second stage cohorts. All sections with BICR details updated to include initial breast cancer cohort as per the final BICR plan.
5. Section 1.3: Added "Figure 1 of Appendix M" to align with study protocol.
6. Specified that primary endpoint for expansion cohort is based on investigator's assessments, section 1.2.2.1
7. Modified section 2.1.3 as per comments from PK Scientist to define a sperate PK analysis set for each investigational product
8. Added details on BICR analyses in section 3.1
9. Added Not applicable category for target lesion for completeness (section 3.1.1)
10. Section 3.3.3: updated bevacizumab exposure definition to utilize word "dose" rather than "cycle" for 14 days dosing. This was confirmed that bevacizumab has two doses within one cycle.
11. Added section 3.1.4 for BICR analyses.
12. Added a sentence in section 3.2 to explain the scope of analysis for overall visit response based on BICR data.
13. Added "SD must be maintained for at least 11 weeks" in BOR section 3.2.2.1
14. Added 4+8 weeks scenario for the first two visits missed in the initial stage cohorts in section 3.2.2.3
15. Added section 3.2.2.10 for concordance shells.
16. Modified to include 3.3.2 bevacizumab on the definition of study treatment end date.
17. Updated section 3.6.1 to remove any reference to PK parameters following comments from the PK Scientist.
18. Added in analysis by prior lines of chemotherapy in section 4.2. Only applicable to initial stage breast and ovarian and extension ovarian cohort. Specified that the subset of data reports to be repeated for patients with gBRCAm status determined by Myriad will be identified prior to database lock.
19. Section 4.2.12: Removed "Both related to disease under investigation and

Date/ SAP version	Brief description of change
	with AE outcome=death" following BDR1 comment. 20. Section 4.2.14 updated to specify the summaries for each study drug. 21. CCI [redacted] 22. Removed nicotine use from section 4.2.17 as not part of the analysis. 23. Re-ordered interim analyses in section 5 to appear chronologically.
28 Jun 2019/ V2.1	1. CCI [redacted] 2. Section 3: Added new definition of baseline for tumor and immune cell PD-L1 using screening assessment and if not available, the latest assessment prior or on the day of the first study medication dose. 3. Section 3.3.1: Updated baseline definition to be explicit about considering the day of the first dose of treatment in baseline derivation. CCI [redacted] 9. Section 4.2.12 'Vital signs': Updated to exclude weight from shift tables as not applicable by Medical team. Added sentence that ranges for vital signs measurements are specified by Study Physician. 10. Section 4.2.12: Updated 'Adverse Events' and 'Laboratory assessments' to specify that AE summaries and laboratory summaries will be produced considering 90 days following discontinuation of study treatment without taking subsequent therapy into account.
08 Jul 2019/ V2.1	1. CCI [redacted] 3. Section 4.2.12: Updated 'Adverse Events' and 'Laboratory assessments' to specify that the approach for reporting is intended to capture more long-term safety events that may be related to study treatment. 4. CCI [redacted]
18 Jul 2019/ V2.1	CCI [redacted]

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objectives

Primary Objectives:	**Outcome Measure:**
To assess the effect of MEDI4736 in combination with olaparib (+/- bevacizumab) in patients with selected advanced solid tumors	**Initial Stage Cohorts:** • DCR (CR+PR+SD) based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 at 12 weeks ***BRCAm* ovarian cancer expansion cohort:** • ORR (CR + PR) based on RECIST 1.1 assessed by the Investigator **Ovarian cancer triplet and doublet cohorts:** • DCR (CR+PR+SD) based on RECIST 1.1 at 24 weeks
To assess the safety and tolerability of MEDI4736 in combination with olaparib (+/- bevacizumab) in patients with selected advanced solid tumors	**All cohorts:** • AEs, physical examination, vital signs including blood pressure (BP), pulse, electrocardiogram (ECG) and laboratory findings including clinical chemistry and hematology • Immune-related adverse events (irAEs) - given the intended mechanisms of action of MEDI4736, particular attention will be given to AEs that may follow enhanced T-cell activation, or other irAE; irAEs are defined in CSP Section 6.7.6. • Dose interruptions, dose reductions • Causes of olaparib and MEDI4736 discontinuation **Ovarian cancer triplet cohort:** • Causes of bevacizumab discontinuation

1.1.2 Secondary objectives

Secondary Objectives:	Outcome Measure:
To investigate the preliminary antitumor activity of MEDI4736 in combination with olaparib +/-bevacizumab in patients with selected advanced solid tumors	**Initial Stage Cohorts:** • DCR at 12 weeks assessed by BICR in the *gBRCAm* breast and ovarian cancer cohorts • DCR at 28 weeks* • ORR (CR+PR) based on RECIST 1.1* • DoR based on RECIST 1.1* • PFS based on RECIST 1.1* *Assessed by the investigator in all Initial Stage Cohorts. Also assessed by BICR in the *gBRCAm* breast and ovarian cancer cohorts • Percentage change from baseline in tumor size at 12 weeks and 28 weeks • Best percentage change from baseline in tumor size • Time to study treatment discontinuation or death • Overall survival ***BRCAm* ovarian cancer expansion cohort:** • DCR at 24 weeks and 56 weeks** • DoR based on RECIST 1.1** • PFS based on RECIST 1.1** **Assessed by the investigator and assessed by BICR • ORR (CR+PR) based on RECIST 1.1 assessed by BICR • Percentage change from baseline in tumor size at 24 weeks and 56 weeks • Best percentage change from baseline in tumor size • Time to study treatment discontinuation or death • Overall survival

Secondary Objectives:	Outcome Measure:
	Ovarian cancer triplet and doublet cohorts: • DCR at 56 weeks • DoR based on RECIST 1.1 assessed by the investigator • PFS based on RECIST 1.1 assessed by the investigator • ORR (CR+PR) based on RECIST 1.1 assessed by the investigator • Percentage change from baseline in tumor size at 24 weeks and 56 weeks • Best percentage change from baseline in tumor size • Time to study treatment discontinuation or death • Overall survival
To determine plasma concentrations of olaparib after single and multiple dosing when given orally to patients alone and in combination with MEDI4736±bevacizumab. To characterize the PK, immunogenicity and pharmacodynamics of MEDI4736 after single dosing and multiple dosing when given intravenously to patients in combination with olaparib±bevacizumab To characterize the PK and immunogenicity and pharmacodynamics of bevacizumab after single dosing and multiple dosing when given intravenously to patients in combination with MEDI4736 and olaparib	**All cohorts:** • Serum concentrations of MEDI4736, MEDI4736 anti-drug antibody (ADA). Plasma concentrations of olaparib • Presence of ADAs for MEDI4736 **Initial Stage Cohorts:** • CCI [redacted] **Ovarian cancer triplet cohort:** • Serum concentrations of bevacizumab, bevacizumab ADA • Presence of ADAs for bevacizumab
[redacted]	CCI [redacted]

1.1.3 Exploratory objectives

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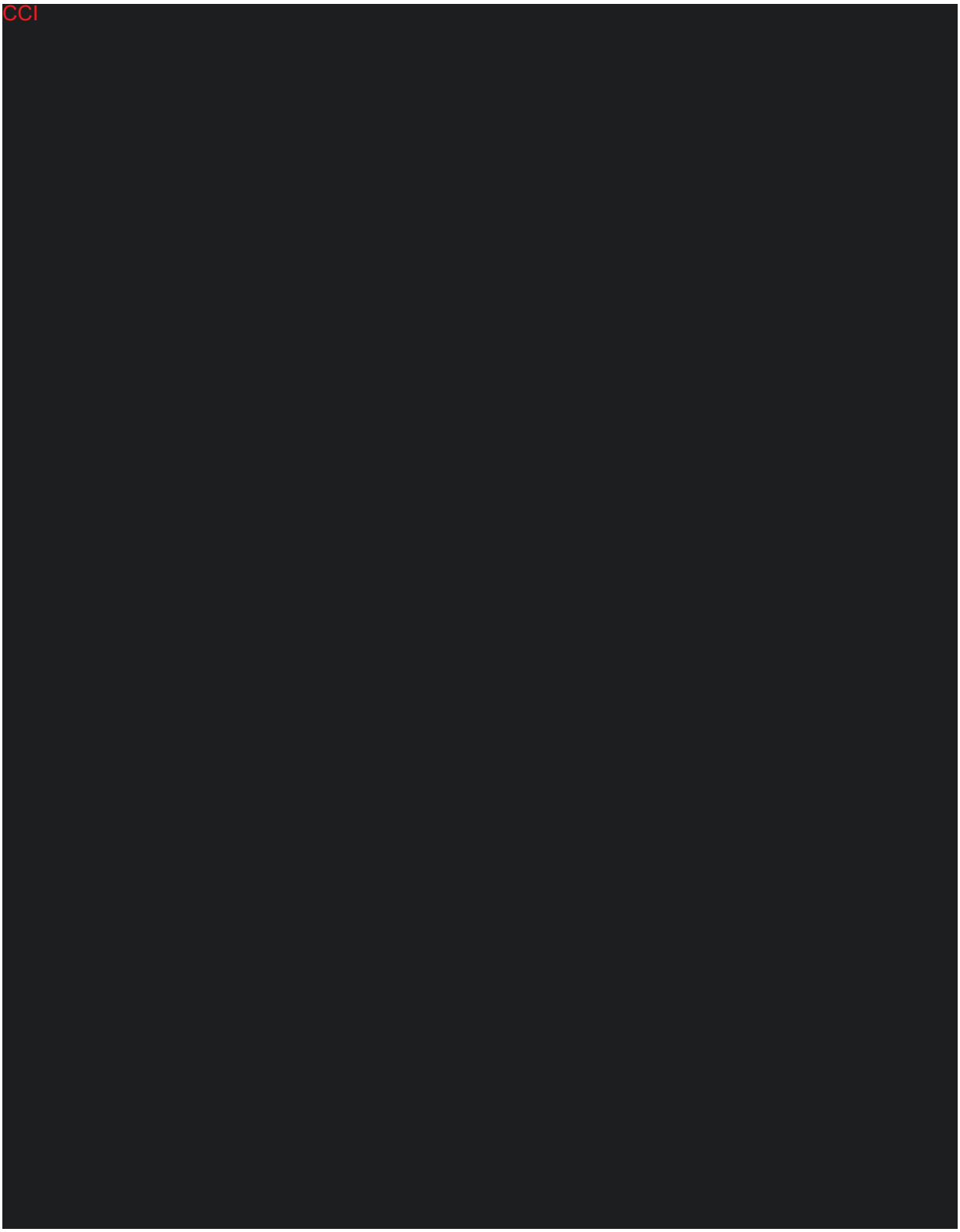

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1.2 Study design

This is a phase I/II open-label, multicenter study to evaluate the safety, tolerability, PK, and antitumor activity of MEDI4736 in combination with olaparib (±bevacizumab) in patients with advanced solid tumors, selected based on a rationale for response to olaparib.

1.2.1 Initial Stage Cohorts

In the initial stage of the study, patients were enrolled concurrently into 4 exploratory cohorts, which include patients with relapsed small cell lung cancer (SCLC), germline *BRCA* mutated (*gBRCAm)* metastatic HER2-negative breast cancer, *gBRCAm* platinum-sensitive relapsed ovarian cancer and relapsed gastric cancer. Additional tumor types may be added at a later date based on emerging data. The results from this study form decision-making for future studies.

Starting doses for the study treatments will be olaparib 300 mg bid/MEDI4736 1.5g Q4W (hereafter referred to as "Full Dose"). For each cohort, a safety and tumor cohort review group (STCRG – see Section 5) will be convened and will review pre-specified safety and efficacy data when the first 10 patients in each cohort have been followed for 12 weeks.

To ensure uniform decision making, a Bayesian predictive probability design will be consistently employed across the Initial Stage Cohorts (Lee and Liu 2008). After evaluating DCR (defined as: complete response [CR] or partial response [PR] or stable disease [SD] evaluated at 12 weeks) and selected safety data from the first 10 patients in the cohort, DCR will be monitored every 5 patients until the maximum sample size is reached. If the doses used in combination demonstrate evidence of antitumor activity based on DCR, and are considered safe and tolerable, then the alternative hypothesis can be accepted at any of these interim looks. If the DCR is such that the null hypothesis will not be able to be rejected at the end of the trial then additional screening activities for new patients into that cohort may be stopped.

Figure 1 summarizes, in graphical form, the Bayesian predictive probability design and includes the target DCR for each Initial Stage Cohort. Targets were based on efficacy observed using either standard of care or olaparib monotherapy for specific indication and aiming for superiority. Details of the derivation of the target DCRs can be found in Section 1.3).

Figure 1 Study design: Bayesian predictive probability design – initial stage cohorts

OVARIAN CANCER	BREAST CANCER	SCLC	GASTRIC CANCER
Target DCR 12 weeks 90%	Target DCR 12 weeks 75%	Target DCR 12 weeks 60%	Target DCR 12 weeks 70%

Treated with olaparib for 4 weeks followed by olaparib+MEDI4736 until objective radiological disease progression [a]

Eval. Pts	Decision Futility	Decision Efficacy
10	≤5/10	10/10
15	≤10/15	≥14/15
20	≤14/20	≥18/20
25	≤19/25	≥22/25
30	≤24/30	≥26/30
31	≤25/31	≥26/31

Eval. Pts	Decision Futility	Decision Efficacy
10	≤3/10	≥9/10
15	≤6/15	≥12/15
20	≤10/20	≥16/20
25	≤15/25	≥19/25
30	≤20/30	≥21/30

Eval. Pts	Decision Futility	Decision Efficacy
10	≤1/10	≥8/10
15	≤3/15	≥11/15
20	≤6/20	≥13/20
25	≤9/25	≥16/25
30	≤12/30	≥18/30
35	≤17/35	≥20/35
38	≤20/38	≥21/38

Eval. Pts	Decision Futility	Decision Efficacy
10	≤4/10	≥8/10
15	≤7/15	≥12/15
20	≤10/20	≥15/20
25	≤14/25	≥18/25
30	≤17/30	≥21/30
34	≤21/34	≥22/34

DCR[b] reviewed after 10 evaluable patients and then every 5 patients until maximum sample size reached. At each review, cohort may be stopped for futility or efficacy. If decision threshold not reached recruitment continues. Selected safety data included in initial review.

DCR=disease control rate; Eval. Pts=evaluable patients;

[a] Per RECIST 1.1 as assessed by the investigator or as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Imaging assessments are required for patients who continue receiving the study drug combination beyond disease progression.

[b] DCR: defined as CR + PR + SD, evaluated at 12 weeks.

There will be an initial run-in period of 4 weeks monotherapy treatment with olaparib in the Initial Stage Cohorts, in order for olaparib to induce changes in the tumor microenvironment as a result of DNA damage and cell death with release of potential immunogenic antigens. Following the monotherapy treatment patients will receive olaparib and MEDI4736 combination treatment.

Patients should continue to receive study treatment (ie, MEDI4736 + olaparib) until objective radiological disease progression as per the RECIST version 1.1 as assessed by the investigator or as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria. Clinically stable patients, with objective radiological disease progression identified after olaparib monotherapy has started but before receiving combination therapy, may start combination therapy if the investigator believes they may derive benefit from study therapy.

Additionally to assessments by the investigator, the scans will undergo a Blinded Independent Central Review (BICR) assessment in the initial stage *gBRCAm* breast and ovarian cancer cohorts. For secondary analyses, DCR at 12 and 28 weeks, ORR, DoR and PFS will be analyzed using BICR data.

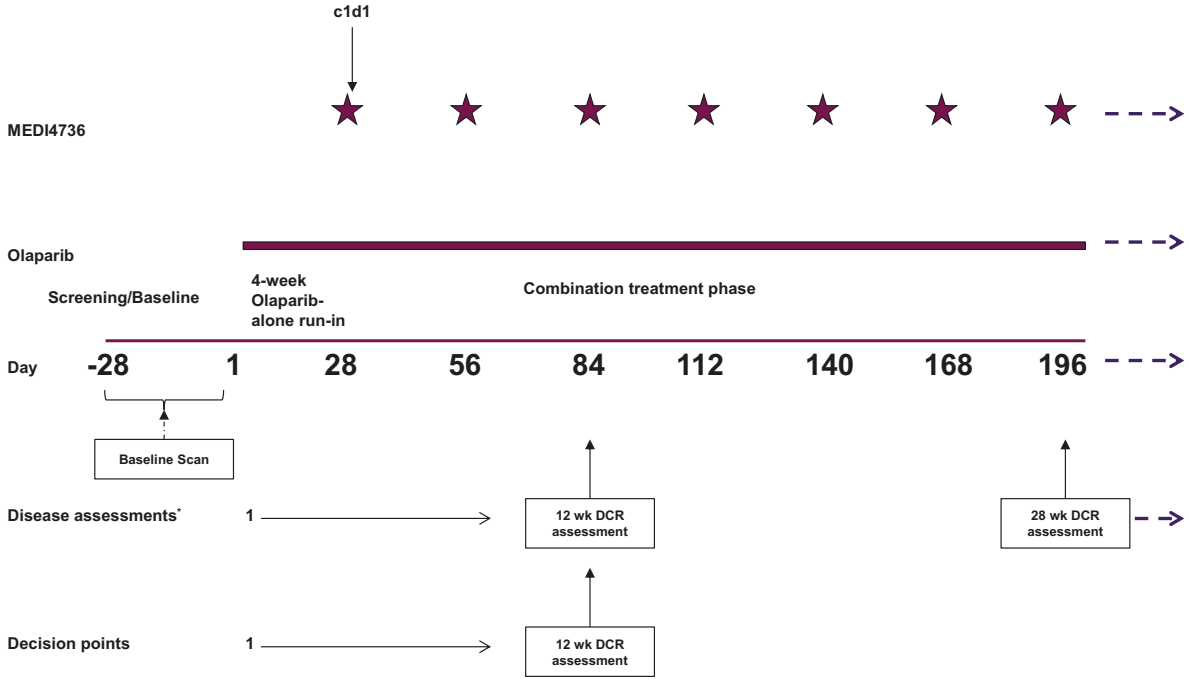
There will be a final data cut-off in each cohort defined as the time when all patients receiving investigational product (IP) have reached last patient first visit (LPFV) + 2 years and all 4 cohorts have observed a median value for PFS.

Formal evaluation of a cohort will end when all patients have either been treated for the specified time with the combination or have discontinued before this time (ie, the data cut-off for that cohort).

Thereafter, patients who are still on treatment may remain on treatment after the data cut-off for their cohort and individual patients will continue to be assessed for safety and efficacy as specified in the protocol. The clinical database will close when all cohorts have reached their final data cut-off. Because of the 4-week initial run-in period, the counting of weeks is different when referring to dosing and when referring to assessment for initial stage cohorts.

Refer to Figure 2 for clarification and reference.

Figure 2 Treatment plan schematic



wk=week

1.2.2 Second Stage Cohorts

In the second stage of the study, patients will be enrolled into 1 of 3 exploratory Second Stage Cohorts, which include patients with *BRCAm* Platinum-sensitive recurrent (PSR) ovarian cancer (*BRCAm* ovarian cancer expansion cohort), non *BRCAm* PSR ovarian cancer (ovarian cancer triplet cohort), and non *BRCAm* PSR ovarian cancer (ovarian cancer doublet cohort). In these cohorts there is no olaparib monotherapy run-in and all study drugs will be started on study Cycle 1/Day 1. CCI [redacted]

1.2.2.1 Ovarian cancer expansion cohort

Based on the results of the NCI study (see Section 1.2.3.1 of the Core Protocol) and the current study, patients in this *BRCAm* ovarian cancer expansion cohort will start a dose of olaparib at 300 mg bid + MEDI4736 1.5g Q4W (hereafter referred to as “Full Dose”).

In the final analysis, patients will be evaluated for ORR based on RECIST 1.1 as assessed by the investigator as the primary endpoint. Other endpoints will include DCR at 24 and 56 weeks, DoR, PFS, percentage change from baseline in tumor size at 24 and 56 weeks, best percentage change from baseline in tumor size, TDT, and OS following objective radiological disease progression according to RECIST 1.1 as assessed by the investigator. Thereafter, patients who are still on treatment may remain on treatment and individual patients will continue to be assessed for safety and efficacy as specified in the protocol. Scans will be

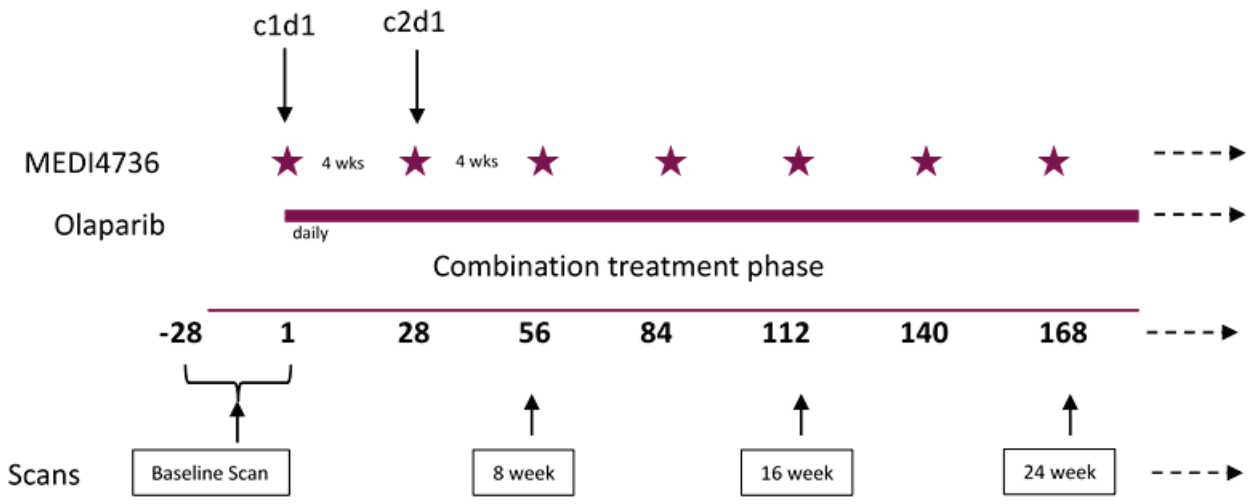
conducted every 8 weeks to assess the target lesions. In addition to investigator assessments of scans, scans will be sent for independent central review as described in CSP Section 5.1.3.

Scans will undergo a BICR assessment, and DCR at 24 and 56 weeks, ORR, DoR and PFS will be analyzed using BICR data.

All patients will be followed for disease progression and survival until the final data cut-off for the *BRCAm* ovarian cancer expansion cohort, which is the point at which the cohort has undergone the formal efficacy assessment. Patients are, however, permitted to continue to receive study treatment beyond this if, in the opinion of the investigator, they are continuing to receive benefit from treatment. Patients who remain on study treatment after this timepoint will be monitored according to routine clinical practice as defined by the Investigator.

Refer to Figure 3 for clarification and reference.

Figure 3 Treatment plan schematic for ovarian cancer expansion cohort



1.2.2.2 Ovarian triplet and doublet cohorts

In the final analysis, ovarian triplet and doublet patients will be evaluated for DCR at 24 and 56 weeks, ORR, DoR, PFS, percentage change from baseline in tumor size at 24 weeks and 56 weeks, best percentage change from baseline in tumor size, TDT, and OS following objective radiological disease progression according to RECIST 1.1 assessed by the investigator.

To ensure uniform decision making, a Bayesian predictive probability design will be consistently employed in the ovarian cancer triplet and doublet cohorts.

Disease Control Rate (defined as: complete response [CR] + partial response [PR] + stable disease [SD], evaluated at 24 weeks) and selected safety data will be reviewed after data from 15 evaluable patients are available, and then again at the maximum sample size (n=30). The Review Committee (see Section 1.4 of the Core Protocol) will be convened and will review

pre-specified safety and efficacy data at these time points. The Committee deliberations will consider safety and pertinent tumor assessment data (at a minimum from radiologic imaging studies but also other data, such as relevant physical exam findings, etc). All serious adverse events (SAEs), adverse events of special interest (AESI), discontinuations, dose reductions and dose interruptions will be reviewed, as well as any lesser-grade adverse events (AEs) that are considered by the study team to be of particular interest (based on emerging data from the ongoing safety monitoring and accumulating clinical experience and other data from external sources as indicated).

If the doses used in combination demonstrate evidence of antitumor activity based on DCR, and are considered safe and tolerable, then the alternative hypothesis can be accepted at the interim looks. If the DCR is such that the null hypothesis will not be able to be rejected at the end of the trial then additional screening activities for new patients into that cohort may be stopped. Figure 4 summarizes, in graphical form, the Bayesian predictive probability design for the ovarian cancer triplet and doublet cohorts.

Figure 4 Study design: Bayesian predictive probability design – ovarian cancer triplet and doublet cohorts

non *BRCAm* PSR OVARIAN CANCER

Doublet	**Triplet**
Target DCR 24 weeks 80%	**Target DCR 24 weeks 80%**
Treated with olaparib+MEDI4736 until objective radiological disease progression [a]	**Treated with olaparib +MEDI4736+Bevacizumab until objective radiological disease progression [a]**

Eval. Pts	Decision Futility	Decision Efficacy
15	≤9/15	≥13/15
30	≤21/30	≥22/30

Eval. Pts	Decision Futility	Decision Efficacy
15	≤9/15	≥13/15
30	≤21/30	≥22/30

DCR[b] reviewed after 15 evaluable patients and then at the maximum sample size. At each review, cohort may be stopped for futility or efficacy. If decision threshold not reached recruitment continues. Selected safety data included in initial review.

DCR=disease control rate; Eval. Pts=evaluable patients;

[a] Per RECIST 1.1 as assessed by the investigator or as long as, in the investigator's opinion, they are benefiting from treatment and they do not meet any other discontinuation criteria.

[b] DCR: defined as CR + PR + SD, evaluated at 24 weeks.

All patients will be followed for disease progression and survival until the final data cut-off for the ovarian cancer triplet and doublet cohorts, which is the point at which the cohort has undergone the formal efficacy assessment. Patients are, however, permitted to continue to receive study treatment beyond this if, in the opinion of the investigator, they are continuing to receive benefit from treatment. Patients who remain on study treatment after this timepoint will be monitored according to routine clinical practice as defined by the Investigator. See Section 9.3 of the Core Protocol for details.

Refer to Figure 5 and Figure 6 for clarification and reference for ovarian cancer triplet and doublet cohorts, respectively.

Figure 5 **Treatment plan schematic for the ovarian cancer triplet cohort**

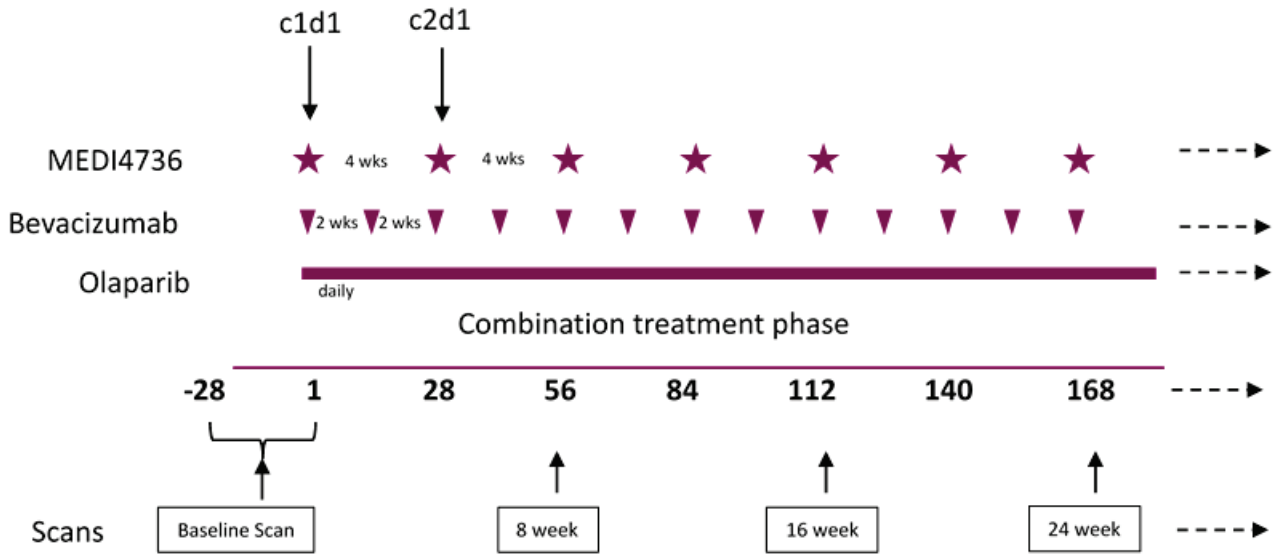
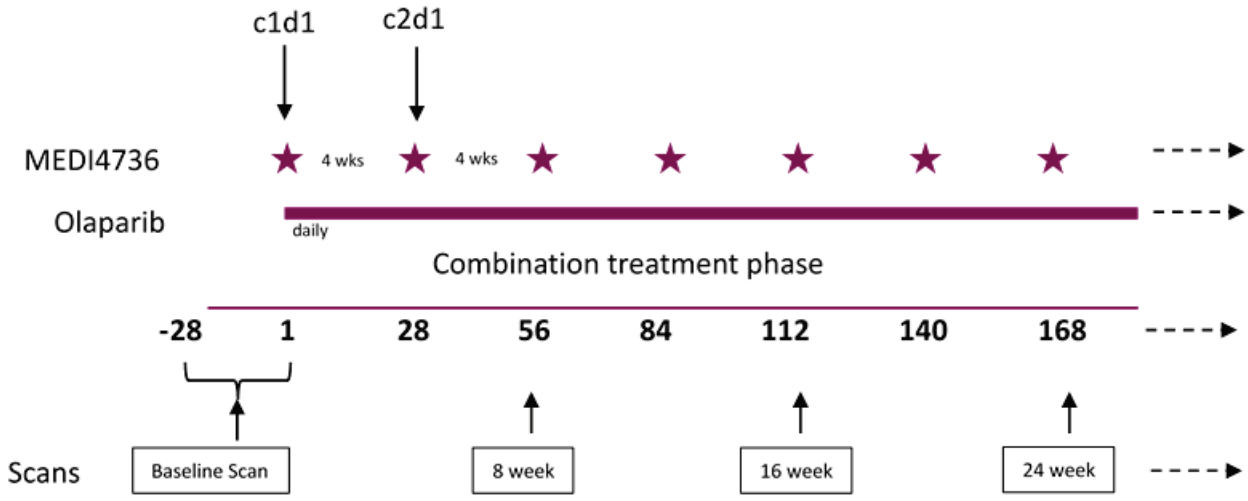


Figure 6 **Treatment plan schematic for the ovarian cancer doublet cohort**



1.3 Number of patients

As described in Section 1.2 the minimum number of patients to be included in each of the four Initial Stage Cohorts is 10, resulting in a minimum of 40 patients.

The maximum number of patients to be included in each cohort of the study is as follows:

Initial Stage Cohorts:

- Breast cancer: *gBRCAm* HER2-negative: 30 patients
- *gBRCAm* Ovarian cancer: 31 patients
- Gastric cancer: 34 patients,
- Small cell lung cancer: 38 patients.

Therefore, if each of the Initial Stage Cohorts proceeds to maximum number of patients in the Full Analysis Set, an additional 93 patients will be included, giving a maximum of 133 patients in the study. In order to reach the target for the number of tumor biopsies for analysis, the cohorts were allowed to be extended by a small number of patients, which resulted in the actual number of patients who were enrolled and who started study treatment to be greater than the planned maximum sample size in the breast, ovarian and gastric initial stage study cohorts.

The number of patients in the Second Stage *BRCAm* PSR ovarian cancer expansion is fixed at 80 patients. In the Second Stage ovarian cancer triplet and doublet cohorts the minimum number of patients to be included in each of the two cohorts is 15, resulting in 110 patients in all three Second Stage ovarian cohorts at minimum.

The maximum number of patients to be included in each of the Second Stage cohorts of the study is as follows:

Second Stage Cohorts:

- *BRCAm* PSR ovarian cancer expansion: 80,
- Ovarian cancer triplet: 30,
- Ovarian cancer doublet: 30.

The rationale for these minimum and maximum numbers of patients is as follows:

Each cohort included into the study, except the *BRCAm* ovarian cancer expansion cohort, will be considered as individual predictive probability designs as described by Lee and Liu 2008. These designs are based on Bayesian predictive probability and the minimax criterion. Predictive probability is obtained by calculating the probability of a positive conclusion

(rejecting the null hypothesis) should the trial be conducted to the maximum planned sample size given the interim observed data. In this framework, the chance that the trial will show a conclusive result at the end of the study, given the current information, is evaluated. Then, the decision to continue or to stop the trial can be made according to the strength of the predictive probability versus pre-specified decision rules. For example, if predictive probability is less than θ_L then the trial can be stopped for futility or if the predictive probability is greater than θ_U the null hypothesis can be rejected and the trial may be stopped for efficacy. If neither threshold is crossed the study continues. In each cohort in this study there is interest in decision making based on both futility and efficacy therefore both thresholds will be defined with θ_L set at 10% and θ_U at 90%.

Taking the predictive probability approach, in 6 of the 7 cohorts, it is assumed that the response (DCR) has a prior distribution of beta (0.5, 0.5) – a Jeffrey's non-informative prior. In the Initial Stage Cohorts, after evaluating DCR (at 12 weeks) and selected safety data from the first 10 patients in the cohort, DCR will be monitored every 5 patients until the maximum sample size is reached. In the ovarian cancer triplet and doublet cohorts, DCR and selected safety data from the first 15 patients in the cohort will be evaluated at 24 weeks. In each cohort the minimum sample size that results in type I and type II error rates under 0.10 and 0.20 respectively is selected based on the optimization criterion that maximizes the power under alternative hypothesis. The tumor types included and the target DCR in each case are given in Sections 1.3.1, 1.3.2.2 with the monitoring plans summarized in Figure 2 of the Core Protocol, Figure 1 of Appendix L, Figure 1 of Appendix M, and details in Appendix E.

In the Second Stage ovarian cancer triplet and doublet cohorts, where patients have no olaparib run-in treatment prior to start, DCR will be assessed at 24 weeks with a target of 80%. The DCR at 24 weeks will be reviewed after data from 15 evaluable patients from each cohort are available, and then again at the maximum sample size (n=30).

The primary efficacy endpoint for the *BRCAm* ovarian cancer expansion cohort is ORR, and this endpoint has been used to define the sample size.

For all cohorts except the *BRCAm* ovarian cancer expansion cohort, operating characteristics and monitoring plans were calculated using the Predictive Probability Calculation for Phase II (PID-535) Version 1.0 available from the biostatistics department at MD Anderson (https://biostatistics.mdanderson.org/SoftwareDownload/) (accessed August 7 2015).

1.3.1 Sample size estimation in the Initial Stage Cohorts

1.3.1.1 Small cell lung cancer

The median PFS in this cohort is estimated to be 4.4 months; this would suggest that approximately 60% of patients will be progression free after 12 weeks and therefore the target DCR will be 60% with a value of 40% or less considered undesirable. Given these figures and the specifications set out in Section 1.3, the maximum sample size for this cohort is 38 patients. The monitoring plan for futility and efficacy is given in Appendix E of the CSP.

1.3.1.2 Breast cancer: *gBRCAm* HER2-negative

The median progression free survival (PFS) in this cohort is estimated to be 7.5 months; this would suggest that approximately 75% of patients will be progression free after 12 weeks and therefore the target DCR will be 75% with a value of 55% or less considered undesirable. Given these figures and the specifications set out in Section 1.3, the maximum sample size for this cohort is 30 patients. The monitoring plan for futility and efficacy is given in Appendix E of the CSP.

1.3.1.3 Ovarian cancer: *gBRCAm*

The median PFS in this cohort is estimated to be 18.3 months; this would suggest that approximately 90% of patients will be progression free after 12 weeks and therefore the target DCR will be 90% with a value of 70% or less considered undesirable. Given these figures and the specifications set out in Section 1.3, the maximum sample size for this cohort is 31 patients. The monitoring plan for futility and efficacy is given in Appendix E of the CSP.

1.3.1.4 Gastric cancer

The median PFS in this cohort is estimated to be 5.5 months; this would suggest that approximately 70% of patients will be progression free after 12 weeks and therefore the target DCR will be 70% with a value of 50% or less considered undesirable. Given these figures and the specifications set out in Section 1.3, the maximum sample size for this cohort is 34 patients. The monitoring plan for futility and efficacy is given in Appendix E of the CSP.

1.3.2 Sample size estimation in the Second Stage Cohorts

1.3.2.1 *BRCAm* ovarian cancer expansion

When the sample size is n=80, a 2-sided 95.0% CI for a single proportion using the large sample normal approximation will extend 0.090 from the observed proportion for an expected proportion of 0.785.

1.3.2.2 Ovarian cancer triplet and doublet cohorts

The median PFS in these cohorts is estimated to be 17.7 months; this would suggest that approximately 80% of patients will be progression free after 24 weeks and therefore the target DCR will be 80% with a value of 60% or less considered undesirable. Given these figures and the specifications set out in Section 1.3, the maximum sample size for these cohorts is 30 patients. The monitoring plan for futility and efficacy is given in Appendix E of the CSP.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 Full analysis sets

The full analysis set (FAS) will include all patients who receive at least 1 dose of study treatment and have not been excluded from the study for administrative reasons, eg, failing important inclusion criteria.

The FAS will be used for all baseline, demography and efficacy analyses.

Reasons for exclusion from the FAS will be deviations 1 through 5 defined in Section 2.2.

2.1.2 Safety analysis set

The safety analysis set will include all patients who receive at least 1 dose of study treatment.

2.1.3 Pharmacokinetic analysis set

A total of 3 PK analysis sets are identified in this study.

Olaparib PK analysis set (all cohorts in monotherapy and combination therapy periods) will include all patients who receive at least 1 dose of olaparib and provide evaluable olaparib PK profile for at least 1 treatment period.

MEDI4736 PK analysis set (all cohorts in combination therapy period) will include all patients who receive at least 1 dose of MEDI4736 and provide evaluable MEDI4736 PK profile.

Bevacizumab PK analysis set (ovarian cancer triplet cohort) will include all patients who receive at least 1 dose of bevacizumab and provide evaluable bevacizumab PK profile.

If a patient has an important protocol deviation that affects the evaluability of the PK profile in a treatment period, then the patient will not form part of the PK analysis set for that period but may still be included in the PK analysis set for the other period.

2.2 Violations and deviations

The important protocol deviations will be listed and summarized by cohort and discussed in the Clinical Study Report (CSR) as appropriate for the study. The list of important protocol deviations with analysis sets the patients are excluded from is presented in Table 1.

Eligibility criteria deviations are deviations from the protocol inclusion and exclusion criteria. Post-entry deviations are deviations from the protocol that occurred after the patient was assigned to the study.

Table 1 List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets

Protocol deviations	The analysis sets the patients are excluded from
1. Patients who did not receive any of the study drugs: olaparib, MEDI4736 or bevacizumab.	FAS Safety
2. Patients who did not have histologically or cytologically confirmed progressive metastatic or recurrent solid tumor (as defined below for each tumor type). To be enrolled in this study, only the tumor types and settings described below are allowed: - Small cell lung cancer (CSP, Appendix G, Section 3.1, criterion 1) • Relapsed SCLC patients may have limited or extensive stage disease, and the disease should have relapsed >12 weeks following first-line platinum-based therapy. Should patients have received a second course of platinum-based therapy, then the same criterion (ie, the patient should have relapsed >12 weeks following the second course) applies. - *gBRCAm* HER2-negative metastatic breast cancer (CSP, Appendix H, Section 3.1, criterion 1) • g*BRCAm* HER2-negative breast cancer patients with metastatic or locally advanced disease, which is unresectable (or the patient is not a candidate for resection), may be a patient with no or up to two prior lines but all patients must meet the following specific criteria: o Must have confirmation of a germline mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). o Must have previously received treatment with an anthracycline (eg, doxorubicin, epirubicin) unless contraindicated and/or a taxane (eg, paclitaxel, docetaxel) in either a neo-adjuvant/adjuvant or metastatic setting.	FAS

Table 1 List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets

Protocol deviations	The analysis sets the patients are excluded from
○ Patients who have received prior platinum-based chemotherapy are eligible if platinum was given either as potentially curative treatment for a prior non-breast cancer (eg, ovarian cancer) with no evidence of disease for ≥5 years prior to study entry or as adjuvant/neo-adjuvant treatment for breast cancer provided at least 12 months have elapsed between the last dose of platinum-based treatment and enrollment. ○ Patients who have received platinum (cisplatin or carboplatin, either as monotherapy or in combination) for advanced breast cancer are eligible to enter the study provided there has been no evidence of disease progression during the platinum chemotherapy. ○ Patients with estrogen and/or progesterone receptor-positive disease must have received and progressed on at least one endocrine therapy (adjuvant or metastatic), or have disease that the treating physician believes to be inappropriate for endocrine therapy. ○ HER2-negative disease ○ Patients cannot have received more than 2 prior lines of cytotoxic chemotherapy for metastatic disease. Prior treatments with hormonal therapy and non hormonal targeted therapy are allowed and not counted as a prior line of cytotoxic chemotherapy. For the purposes of this protocol, the combination of an aromatase inhibitor and everolimus or palbociclib, are not considered cytotoxic chemotherapy. The number of prior lines of chemotherapy will be determined based on previous	

Table 1 List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets

Protocol deviations	The analysis sets the patients are excluded from
anti-cancer therapy treatment by the Study Physician. - g*BRCAm* ovarian cancer (CSP, Appendix I, Section 3.1, criterion 1) • g*BRCAm* ovarian cancer patients with recurrent disease must have previously received at least 1 previous courses of platinum-based therapy and must be considered to be platinum sensitive (relapsed at least 24 weeks after the administration of their last platinum treatment). • Patients must have confirmation of a germline mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). - Gastric cancer (CSP, Appendix J, Section 3.1, criterion 1) • Metastatic or recurrent gastric adenocarcinoma (including gastroesophageal junction adenocarcinoma) that has progressed following first-line therapy, confirmed by imaging modalities: o The first-line regimen must have contained at least a doublet 5-fluoropyrimidine and platinum based regimen. o Capecitabine is an acceptable 5-fluoropyrimidine-containing agent. o Relapse within 6 months of completion of adjuvant/neoadjuvant chemotherapy containing doublet 5-fluoropyrimidine and platinum based regimen is considered as first-line therapy. o Previous adjuvant/neoadjuvant chemotherapy is allowed, if completed	

Table 1 List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets

Protocol deviations	The analysis sets the patients are excluded from
more than 6 months prior to starting the first-line therapy. • HER2-positive and -negative patients are both eligible for entry into this study Patients with HER2-positive gastric cancer must have received a trastuzumab-containing regimen prior to study entry.	
3. Patients who did not have at least 1 measurable lesion that can be accurately assessed at baseline by computed tomography (CT) (or magnetic resonance imaging [MRI] where CT is contraindicated) and is suitable for repeated assessment as per RECIST 1.1	FAS
4. Baseline RECIST scan > 28 days before first dose of study drug	FAS
5. No baseline RECIST 1.1 assessment on or before date of first dose of study drug.	FAS
6. Patients who deviate other key entry criteria which are documented below	None
- Inclusion criteria: • Ability to swallow oral medications (capsules and tablets) without chewing, breaking, crushing, opening or otherwise altering the product formulation. Patients should not have gastrointestinal illnesses that would preclude the absorption of olaparib, which is an oral agent. • Ability of patient to understand and the willingness to sign a written informed consent document prior to any protocol related procedures, including screening evaluations. • Tissue samples must be available for testing for the initial stage cohorts. • Ovarian cancer triplet (CSP, Appendix L, Section 3.1, criterion 1) o High grade serous ovarian cancer (including patients with primary peritoneal and/or	

Table 1 List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets

Protocol deviations	The analysis sets the patients are excluded from
fallopian tube cancer) with recurrent disease and: ▪ Previously received 1 or 2 previous lines of chemotherapy, including ≥1 line of platinum-based therapy. NOTE: First-line agents include all agents administered to treat initial diagnosis, including adjuvant, neoadjuvant, maintenance, etc. Each subsequent line of chemotherapy includes all agents administered to treat relapse/progression, including maintenance. Switching drugs within a line of therapy to manage toxicities in the absence of PD does NOT count as a new line. Hormone therapy used as a single agent does not count as a line of chemotherapy. ▪ Must be considered to be platinum sensitive (relapsed ≥24 weeks after the administration of their last platinum treatment) o Patients must have documented evidence from the Myriad central laboratory that they do not have a germline mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Mandatory samples must be available for eligibility testing/confirmation as outlined in CSP, Table 1. Full details on BRCA status testing is provided in Appendix N of the CSP. • Ovarian cancer doublet (CSP, Appendix M, Section 3.1, criterion 1) o High grade serous ovarian cancer (including patients with primary peritoneal and/or	

Table 1 List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets

Protocol deviations	The analysis sets the patients are excluded from
fallopian tube cancer) with recurrent disease and: ▪ Previously received 1 or 2 previous lines of chemotherapy, including ≥1 line of platinum-based therapy. NOTE: First-line agents include all agents administered to treat initial diagnosis, including adjuvant, neoadjuvant, maintenance, etc. Each subsequent line of chemotherapy includes all agents administered to treat relapse/progression, including maintenance. Switching drugs within a line of therapy to manage toxicities in the absence of PD does NOT count as a new line. Hormone therapy used as a single agent does not count as a line of chemotherapy. ▪ Must be considered to be platinum sensitive (relapsed ≥24 weeks after the administration of their last platinum treatment) o Patients must have confirmation from the Myriad central laboratory that they do not have a germline mutation in BRCA1 or BRCA2 that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Mandatory samples must be available for eligibility testing/confirmation as outlined in CSP, Table 1. Full details on BRCA status testing is provided in Appendix N of the CSP. • *BRCAm* ovarian cancer expansion (CSP, Appendix K, Section 3.1, criterion 1) o High grade serous ovarian cancer (including patients with primary peritoneal and/or	

Table 1 List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets

Protocol deviations	The analysis sets the patients are excluded from
fallopian tube cancer) with recurrent disease and: ▪ Previously received 1 or 2 previous lines of chemotherapy, including ≥1 line of platinum-based therapy. NOTE: First-line agents include all agents administered to treat initial diagnosis, including adjuvant, neoadjuvant, maintenance, etc. Each subsequent line of chemotherapy includes all agents administered to treat relapse/progression, including maintenance. Switching drugs within a line of therapy to manage toxicities in the absence of PD does NOT count as a new line. Hormone therapy used as a single agent does not count as a line of chemotherapy (Investigators should discuss with the Study Physician if unsure regarding previous treatment lines when determining eligibility). ▪ Must be considered to be platinum sensitive (relapsed ≥24 weeks after the administration of their last platinum treatment) o Patients must have confirmation of a germline mutation in *BRCA1* or *BRCA2* that is predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function). Mandatory samples must be available for eligibility testing/confirmation as outlined in CSP, Table 1. Full details on *BRCA* status testing is provided in Appendix N of the CSP.	

- Exclusion criteria: • Prior chemotherapy or other systemic anticancer therapy within 4 weeks prior to start of olaparib treatment; 6 weeks for nitrosoureas or mitomycin • Concurrent use of any medications or substances that are strong inhibitors of cytochrome P450 (CYP) 3A (CYP3A) • Concomitant therapy with any other anticancer therapy or chronic use of systemic corticosteroids • Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ, Stage 1, grade 1 endometrial carcinoma, or other solid tumors including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 years. Patients with a history of localized breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than 3 years prior to registration and that the patient remains free of recurrent or metastatic disease. • Symptomatic or uncontrolled brain metastases. Patients with spinal cord compression unless considered to have received definitive treatment for this and evidence of clinically stable disease for 28 days. • Participation in another clinical study with an IP during the last 28 days or 5 half-lives of the drug, whichever is longer. • For g*BRCAm* ovarian cancer, *BRCA*m ovarian cancer expansion cohort and g*BRCAm* HER2-negative breast cancer cohort: o BRCA1 and/or BRCA2 variants that are considered to be non-detrimental (eg, "Variants of uncertain clinical significance" or "Variant of unknown significance" or "Variant, favor polymorphism" or "benign polymorphism" etc.). • For g*BRCAm* HER2-negative breast cancer cohort: o Patients with HER2-positive disease (3+ by immunohistochemistry [IHC] or in situ hybridization amplified ≥2.0). • For Small cell lung cancer cohort: o Patients with mixed small cell and NSCLC histology.	

Table 1 List of important protocol deviations (IPDs) including IPDs resulting in an exclusion of the patient from analysis sets

Protocol deviations	The analysis sets the patients are excluded from
• For Gastric cancer cohort: o For HER2-negative patients: More than 1 prior chemotherapy regimen (except for adjuvant/neoadjuvant chemotherapy with more than 6 months wash-out period) for the treatment of gastric cancer in the metastatic or recurrent setting. o For HER2-positive patients: More than 2 prior chemotherapy regimens (except for adjuvant/neoadjuvant with more than 6 months wash-out period) for the treatment of gastric cancer in the metastatic or recurrent setting.	
7. Received prohibited concomitant medications (including other anti-cancer agents). Please refer to the CSP Section 7.7 for those medications that are detailed as being 'excluded' from permitted use during the study. This will be used as a guiding principle for the physician review of all medications prior to database lock.	None
8. Patients who did not receive olaparib in combination with MEDI4736 ± bevacizumab.	None

The categorisation of these as important deviations is not automatic and will depend on duration and the perceived effect on efficacy.

In addition to the programmatic determination of the deviations above, monitoring notes or summaries will be reviewed to determine any important post entry deviations that are not identifiable via programming, and to check that those identified via programming are correctly classified.

For the analysis of PK data, the important protocol deviations will be listed and summarised. Those deviations include changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. Examples include, but may not be limited to, vomiting following oral dosing occurring within the timeframe of 2 times the median time to reach maximum plasma concentration (t_{max}), sample processing errors that lead to inaccurate bioanalytical results, incomplete dose administered, incomplete PK profile collected, and/or use of disallowed concomitant medication. Any PK data affected by one of those deviations will be excluded from the summaries and statistical analyses, but will still be reported in the study result listings. Important PK protocol deviations and eligibility of PK

profiles will be identified by the AstraZeneca clinical pharmacology scientist (CPS) and/or pharmacometrician.

The final classification of deviations will be made at a data review meeting (DRM) prior to database lock. Decisions made at the DRM will be documented and approved by AstraZeneca prior to analysis.

3. PRIMARY AND SECONDARY VARIABLES

Baseline for efficacy and safety summaries, with the exception of tumor and immune cell PD-L1 expression, is defined as the last assessment of the variable under consideration prior to or on the day of the intake of the first dose of olaparib for Initial Stage Cohorts, or Cycle 1 Day 1 for Second Stage Cohorts.

CCI baseline is defined as the screening assessment planned on day -28 or the archival sample taken prior to this. If the screening assessment and archival sample is missing then the latest assessment prior to or on the day of the intake of the first dose of study medication will be considered baseline.

Study day will be calculated as follows:

- Days prior to first dose: Study day=date – treatment first dose date.
- Days on or after first dose: Study day=date – treatment first dose date+1.

For the Initial Stage Cohorts treatment refers to the first dose of olaparib. In the Second Stage Cohorts first dose refers to either of the medications (olaparib+MEDI4736±bevacizumab).

In addition, study day within treatment period will be specified where necessary, for instance in the definition of visit windows relative to the start of each treatment period. See Section 3.3.1 for details.

3.1 Derivation of RECIST visit responses

For all patients, RECIST 1.1 (see further Appendix D of the CSP) tumor response data will be used to determine each patient's visit response. It will also be used to determine if and when a patient has progressed and also their objective response to treatment.

The scan used for baseline tumor assessment must be performed at screening unless it was performed within 28 days prior to the start of study treatment. Following the baseline tumor assessment the next tumor assessment will either be in 4 weeks in the Initial Stage Cohorts, or 8 weeks, in the Second Stage Cohort. Clinically stable patients, with objective radiological disease progression identified after olaparib monotherapy has started but before receiving combination therapy, may start combination therapy if the investigator believes they may derive benefit from study therapy.

The subsequent scans should be performed every 8 weeks (± 1 week) thereafter, up to objective radiological disease progression as determined by the investigator using RECIST 1.1. For patients in the Initial Stage Cohorts with objective radiological disease progression identified after olaparib monotherapy has started but before receiving combination therapy, who start combination therapy (see CSP Section 3.9) should be scanned at 12 weeks (8 weeks after start of combination therapy).

If a patient discontinues treatment (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until objective disease progression as defined by RECIST 1.1.

If an unscheduled assessment was performed and the patient had not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits. This schedule is to be followed in order to minimise any unintentional bias caused by some patients being assessed at a different frequency than other patients.

Additional assessments will be performed post objective disease progression for patients remaining on immunotherapy treatment, re-treatment, or until subsequent cancer therapy according to the CSP. In addition, all patients will be contacted in the week following data cut-off to confirm survival status.

At each visit for the site investigator data, an overall visit response will be determined programmatically - using the information from TLs, NTLs and new lesions.

For secondary analyses, overall visit responses determined from the BICR will be provided by the AstraZeneca appointed central Core Imaging Laboratory, together with supporting dates, measurements and assessments, and used to derive DCR at 12 and 28 weeks (for *gBRCAm* breast and ovarian cancer cohorts) and DCR at 24 and 56 weeks (*BRCAm* ovarian cancer expansion cohort), and ORR, DoR and PFS for *gBRCAm* breast and ovarian cancer cohorts and *BRCAm* ovarian cancer expansion cohort. For the investigator-assessed site data, overall visit responses will be calculated using the information provided in the eCRF.

3.1.1 Site Investigator Assessment Using RECIST 1.1: Target lesions

Measurable disease is defined as having at least 1 measurable lesion, not previously irradiated, which is ≥10 mm in the longest diameter (LD) (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and which is suitable for accurate repeated measurements.

A patient can have a maximum of 5 measurable lesions recorded at baseline with a maximum of 2 lesions per organ (including lymph nodes) representative of all lesions involved suitable for accurate repeated measurement) and these are referred to as TLs. If more than 1 baseline scan is recorded then measurements from the one that is closest to the date of first dose will be used to define the baseline sum of TLs. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

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

Measurable disease (ie, at least 1 TL) is one of the entry criteria for the study. However, if a patient with non-measurable disease is enrolled in the study, the evaluation of overall visit responses will be based on the overall NTL assessment and the absence/presence of new lesions (see Section 3.1.3 for further details). If a patient does not have measurable disease at baseline then the TL visit response will be not applicable (NA).

Table 2 TL Visit Responses

Visit Responses	Description
Complete Response (CR)	Disappearance of all target lesions since baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Not Evaluable (NE)	Only relevant if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a target lesion response.
Not Applicable (NA)	No target lesions 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 1 d.p. 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

If all TL measurements are missing then the TL visit response is not evaluable (NE). Overall visit response will also be NE, unless there is a progression of NTLs or new lesions, in which case the response will be PD.

If > 1/3 of TL measurements are missing then TL response will be NE, unless the sum of diameters of NTLs would result in PD (ie, 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 5 mm from nadir).

If ≤ 1/3 of the TL measurements are missing 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.

Example of scaling

Lesion	Longest diameter at nadir visit	Longest diameter at follow-up visit
1.	7.2	7.1
2.	6.7	6.4
3.	4.3	4.0
4.	8.6	8.5
5.	2.5	missing
Sum	**29.3**	**26**

Lesion 5 is missing at the follow-up visit.

The sum of lesions 1-4 at the follow-up is 26 cm. The sum of the corresponding lesions at nadir visit is 26.8 cm.

Scale up as follows to give an estimated TL sum of 28.4 cm:

$$\frac{26}{26.8} \times 29.3 = 28.4 cm$$

CR will not be allowed as a TL response for visits where there is missing data. Only PR, SD or PD (or NE) could be assigned as the TL visit response in these cases. However, for visits with ≤1/3 lesion assessments not recorded the scaled up sum of TLs diameters will be included when defining the nadir value for the assessment of progression.

Lymph nodes

For lymph nodes, if the size reduces to <10 mm 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 >0 mm the calculation of TL response should be over-written as a CR.

TL Visit responses subsequent to CR

A CR response can only be followed by CR, PD or NE. 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 (ie, 0 mm or <10 mm for lymph nodes) then response will be set to CR irrespective of whether the criteria for PD of TL is also met ie, if a lymph node LD increases by 20% but remains <10 mm

- Step 2: If some lesion measurements are missing but all other lesions meet the CR criteria (ie, 0 mm or <10 mm for lymph nodes) then response will be set to NE irrespective of whether when referencing the sum of TL diameters the criteria for PD is 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. 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 a value of 5 mm will be entered into the database and used in TL calculations, unless the radiologist has indicated and 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.

Irradiated lesions/lesion intervention

Previously irradiated lesions (ie, 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 tumors:

- 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 scale up as described previously as long as there remain ≤ 1/3 of the TLs with missing measurements. If the scaling results in a visit response of PD then the subject would be assigned a TL response of PD

- Step 3: If after both steps PD has not been assigned, then a scaled sum of diameters will be calculated, treating the lesion with intervention as missing, 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 <10 mm for lymph nodes) and the lesions that have been subject to intervention also has a value of 0 recorded.

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).

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 0 cm.

Change in method of assessment of target lesions

CT, 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. The TL visit response may still be evaluable if the number of missing TL measurements at a visit is ≤1/3 of the total number of TLs.

3.1.2 Site Investigator Assessment Using RECIST 1.1: Non-Target Lesions and new lesions.

Non-target lesion response will be derived based on the investigator's overall assessment of NTLs as follows:

Progressive disease:	Unequivocal progression of existing NTLs, which may be due to an important progression in 1 lesion only or in several lesions
Complete response:	Disappearance of all NTLs present at baseline with all lymph nodes non-pathological in size (<10 mm short axis)
Non-CR/Non-PD:	Persistence of 1 or more NTLs with no evidence of progression
Not evaluable:	Only relevant when 1 or some of the NTLs have not been assessed and in the investigator's opinion they are not able to provide an evaluable overall NTL assessment
Not applicable	Only relevant if there are no NTLs at baseline.

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 and should be treated as NE in the derivation of overall visit response.

3.1.3 Site Investigator Assessment Using RECIST 1.1: Overall visit response

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 Response

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD or NE	No	PR
SD	Non PD or NE	No	SD
NA	Non CR/Non PD	No	SD (Non CR/Non PD)
NE	Non PD or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no TL/NTLs at baseline).

3.1.4 Independent review

The BICR data will be used for the secondary analyses as specified in sections 1.2.1 and 1.2.2.1 for initial stage *gBRCAm* breast and ovarian cancer cohorts and *BRCAm* ovarian cancer expansion cohort respectively.

The independent review charter will contain the details of the BICR conducted by the AstraZeneca-appointed central Core Imaging Laboratory and will be developed in advance of the final data cut-off. The independent data review will provide RECIST measurements for each visit for each patient at the time of data cut-off (DCO).

For each patient, the independent reviewer will provide at each time point, TL and NTL responses with supporting measurements and assessments, location of new lesions and comments (if applicable), overall visit responses and the relevant scan dates. The overall visit response data as determined by the BICR will be used to derive the selected secondary endpoints.

To note, although the inclusion criteria require all patients to enter the study with at least one lesion (measurable and/or non-measurable) based on investigator assessment, it is possible in rare cases for an independent reviewer to assess the baseline scan and conclude that there is no evidence of disease (NED) (i.e. no TLs and no NTLs). In this scenario, RECIST 1.1 criteria

will be used and evaluation of overall visit responses will be based on absence/presence of new lesions. If no TLs and no NTLs are recorded at a visit, both the TL and NTL visit response will be recorded as NA and the overall visit response will be NED. An overall visit response of progression is possible based on the appearance of new lesions.

3.2 Outcome variables

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues investigational product (IP) or receives another anti-cancer therapy.

At each visit, patients will be programmatically assigned a RECIST visit response of CR, PR, SD, PD or NE depending on the status of their disease compared to baseline and previous assessments, using the overall visit responses and relevant dates from the investigator RECIST assessments.

Similarly the assessment of visit response will be performed based on the BICR data for patients in the *gBRCAm* breast and ovarian cancer cohorts and *BRCAm* ovarian cancer expansion cohort.

3.2.1 Primary efficacy endpoints

3.2.1.1 Disease control rate at 12 and 24 weeks

The primary endpoints of DCR are defined as follows:

- **Initial Stage Cohorts:** DCR at 12 weeks
  - The DCR is defined as the percentage of patients who have at least 1 visit response of CR or PR in the first 12 weeks (in the first 13 weeks to allow for a late assessment in the assessment window) or have demonstrated SD which is maintained until the RECIST 1.1 assessment at 12 weeks (ie who have SD for at least 11 weeks to allow for an early assessment within the assessment window). There is no requirement for the confirmation of DCR with a repeat visit before the 12 week assessment. Any patient that progressed in this time period cannot have controlled disease.
- **Ovarian cancer triplet and doublet cohorts:** DCR at 24 weeks
  - The DCR is defined as the percentage of patients who have at least 1 visit response of CR or PR in the first 24 weeks (in the first 25 to allow for a late assessment in the assessment window) or have demonstrated SD which is maintained until the RECIST 1.1 assessment at 24 weeks (ie who have SD for at least 23 weeks to allow for an early assessment within the assessment window). There is no requirement for the confirmation of DCR with a repeat visit before the 24 week assessment. Any patient that progressed in this time period cannot have controlled disease.

  Both endpoints are based on RECIST 1.1 assessed by investigators.

3.2.1.2 Objective response rate

The primary endpoint is objective response rate (ORR) for the following cohort:

- ***BRCAm* ovarian cancer expansion cohort:** ORR
  - Objective response rate is defined as the number (%) of patients with a best objective response of CR or PR, prior to progression or subsequent cancer therapy, as assessed by the investigator. There is no requirement for the confirmation of a visit response of CR or PR.

3.2.2 Secondary efficacy endpoints

3.2.2.1 Best objective response

Best objective response (BOR) is calculated based on the overall visit responses from each RECIST assessment, described in section 3.1.3. It is the best response a patient has had following the first study treatment dose, but prior to starting any subsequent cancer therapy and up to and including RECIST progression or the last evaluable assessment in the absence of RECIST progression. Categorisation of BoR will be based on RECIST using the following response categories: CR, PR, SD, NED (applies only to those patients entering the study with no disease at baseline), PD and NE. SD must be maintained for at least 11 weeks. Patients who discontinue treatment without progression, receive a subsequent anti-cancer therapy and then respond will not be included as responders in the BOR. The denominator used for analysis will be the number of patients who received at least 1 dose of investigational treatment for whom measurable disease is present at baseline and who were included in the FAS.

For patients who die in the absence of progression and have no evaluable visit responses prior to death, BOR will be set to PD.

3.2.2.2 Disease control rate at 12, 24, 28 and 56 weeks

Disease control rate, as defined in Section 3.2.1.1, as follows:

- **Initial Stage Cohorts :** DCR at 12 weeks and 28 weeks assessed by investigator for all cohorts, and by BICR for *gBRCAm* breast and ovarian cohorts
- ***BRCAm* ovarian cancer expansion cohort**: DCR at 24 weeks and 56 weeks, assessed by the investigator and assessed by BICR
- **Ovarian cancer triplet and doublet cohorts:** DCR at 56 weeks assessed by investigator

3.2.2.3 Progression free survival

Based on RECIST 1.1 as assessed by the investigator, PFS is a secondary endpoint for all cohorts. In the initial g*BRCAm* breast and ovarian cancer cohorts and the *BRCAm* ovarian

cancer expansion cohort, PFS based on RECIST 1.1 as assessed by BICR is also a secondary endpoint.

Progression-free survival is defined as the time from start of study treatment (Day 1; either the start of olaparib monotherapy for Initial Stage Cohorts or Cycle 1 Day 1 for Second Stage Cohorts) until the date of objective radiological disease progression according to RECIST 1.1 or death (by any cause in the absence of disease progression), regardless of whether the patient withdraws from therapy or receives another anticancer therapy prior to disease progression (ie date of event or censoring – date of study treatment + 1). Confirmation of disease progression after the initial progression is not required. Patients whose disease has not progressed or who have not died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progresses or dies after 2 or more missed visits, they will be censored at the time of the latest evaluable RECIST 1.1 assessment. If the patient has no evaluable visits or does not have a baseline assessment they will be censored at Day 1 unless they die within 2 tumor assessment visits of treatment start.

Two visits will be considered to have been missed if the number of days between scans is more than 2 times (the protocolled time between scans + the protocol allowed visit window) ie, 18 weeks, as the protocolled time between scans after the 1st tumor assessment visit is 8 weeks (for both Initial Stage cohorts in combination treatment phase and Second Stage Cohorts) and the visit window is 1 week. In the initial stage cohorts, the first two visits will be considered missed if the time between scans is more than 14 weeks (the first post-baseline scan is at week 4 and the following scan is 8 weeks after).

The PFS time will always be derived based on scan/assessment dates not visit dates. All scans will be taken into account for the assessment of PFS.

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

(a) For BICR assessments, 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 for either reviewer where both select PD as time point response and there is no adjudication for BICR data.

(b) For investigational site assessments, date of progression will be determined based on the earliest of the RECIST 1.1 assessment/scan dates of the component that triggered the progression

(c) For both BICR and investigational site assessments, when censoring a patient for PFS the patient will be censored at the latest of the RECIST 1.1 assessment/scan dates contributing to a particular overall visit assessment

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of PFS.

Objective progression is defined as at least a 20% increase in the sum of the diameters of the TLs (compared to previous minimum sum) and an absolute increase of >5 mm, or an overall NTL assessment of progression or a new lesion.

3.2.2.4 Overall survival

OS is defined as the time from the start of study treatment (Day 1; either the start of olaparib monotherapy for Initial Stage Cohorts or Cycle 1 Day 1 for Second Stage Cohorts) until death due to any cause (ie date of death or censoring – date of study treatment + 1). Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which they were known to be alive. See Section 3.10.2 of the CSP for the methods to be used to obtain vital status for patients who are no longer in the study.

Note: Survival calls will be made in the week following the date of Data Cut Off (DCO) for the analysis, and if patients are confirmed to be alive or if the death date is post the DCO date these patients will be censored at the date of DCO. The status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final OS analysis should be obtained by the site personnel by checking the patient's notes, hospital records, contacting the patient's general practitioner and checking publicly-available death registries. In the event that the patient has actively withdrawn consent to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly-available resources where it is possible to do so under applicable local laws.

3.2.2.5 Time to study treatment discontinuation or death

TDT is defined as the time from start of study treatment (Day 1; either the start of olaparib monotherapy for Initial Stage Cohorts or Cycle 1 Day 1 for Second Stage Cohorts) to the earlier of the date of study treatment discontinuation or death (ie date of event or censoring – date of study treatment + 1). Study treatment discontinuation during the combination therapy phase is the later of the date of last administration of MEDI4736, the date of last administration of olaparib, and the date of last dose of bevacizumab. Any patient not known to have died at the time of analysis and not known to have discontinued study treatment will be censored based on the last recorded date on which the patient was known to be alive. See Section 3.10.2 of the CSP for the methods to be used to obtain vital status for patients who are no longer in the study.

3.2.2.6 Objective response rate

The ORR for Initial Stage Cohorts and Ovarian cancer triplet and doublet cohorts is defined as for the in Section 3.2.1.2. For the initial g*BRCAm* breast and ovarian cancer cohorts and the expansion *BRCAm* ovarian cohort, ORR will also be evaluated using BICR data.

3.2.2.7 Duration of response

Duration of response (DoR) is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression, the end of response should coincide with the date of progression or death from any cause used for the PFS endpoint (ie date of event or censoring – date of first documented response + 1). The date

of the initial response will be defined as the latest of the dates contributing towards the first visit response of PR or CR. Data contributing to DoR assessment are the same as in Section 3.2.1.2.

If a patient does not progress or die following a response, then their DoR will use the PFS censoring time.

DoR based on investigator data will be evaluated using investigator data for all cohorts, and BICR data will also be used for the breast and ovarian Initial Stage Cohorts and *BRCAm* ovarian expansion cohort.

3.2.2.8 Percentage change in tumor size at 12 weeks and 28 weeks (Initial Stage Cohorts) or 24 and 56 weeks (Second Stage Cohorts)

The percentage change from baseline in tumor size at 12 weeks and 28 weeks (Initial Stage Cohorts) and the percentage change from baseline in tumor size at 24 and 56 weeks (Second Stage Cohorts) will be based on RECIST 1.1. TL measurements taken at baseline and at 12 and 28 weeks (Initial Stage Cohorts) or 24 and 56 weeks (Second Stage Cohorts). Tumor size is the sum of the longest diameters of the TLs. Target lesions are measurable tumor lesions. The percentage change in TL tumor size at each time point will be obtained for each patient taking the difference between the sum of the TLs at each time point and the sum of the TLs at baseline divided by the sum of the TLs at baseline times 100; ie, for week 12 (week 12 - baseline) / baseline * 100.

Patients who progress before the specified timepoint, eg week 12, should have had a tumor assessment performed at the time of progression prior to treatment discontinuation. The tumor size from their latest progression assessment will be used instead of the relevant timepoint, ie the week 12 assessment, for these patients.

Missing data imputation methods - Target lesion imputation

For patients who have less than or equal to one-third of TLs missing at a visit, assessment data from missing lesions may be scaled up proportionally to the sum of the corresponding lesions at baseline to give an estimated sum of diameters as described in the *missing TL data* subsection of Section 3.1.1.

Apply a window around the week X visit:

Whenever tumor size data for the week X visit (Note: or visit at which progression was documented if before week X) is available then this should be used in the analysis. A windowing rule will be applied and will follow the protocol allowed visit window; therefore any RECIST scan performed within ± 1 week of the protocol scheduled visit will be used for that visit. The windows around protocol scheduled visits are provided in Appendices G to M, Table 3 of the CSP.

3.2.2.9 Best percentage change in tumor size

The best percentage change from baseline in tumor size is based on RECIST 1.1 TL measurements taken at each RECIST 1.1 assessment. All measurements up until RECIST 1.1 progression or the last evaluable assessment in the absence of RECIST 1.1 progression will be included in the calculation.

3.2.2.10 Concordance between investigator and BICR

Disagreements between investigator and BICR assessment of RECIST progression and objective response will be presented for g*BRCAm* breast and ovarian cancer cohorts and the *BRCAm* ovarian cancer expansion cohort. The summaries will be provided for PFS, Overall objective response and Best objective response.

a) Concordance between investigator and BICR assessments for PFS

The summary will include the frequency and percentage of PFS events concordant between investigator and BICR reviews. The summary of concordant PFS events will further include the early discrepancy rate which is the frequency of investigator review progressions declared before the BICR (≥8 weeks earlier and including progressions declared by investigator but not BICR) as a proportion of all investigator review progressions, and the late discrepancy rate which is the frequency of investigator review progressions declared after the BICR (≥8 weeks later and including progressions declared by BICR but not investigator) as a proportion of all discrepancies (including early and late discrepancies).

In addition the summary will include the frequency and percentage of discordant PFS events and BICR confirmation rates:

- BICR confirmation rate in investigator declared progressions = "Concordant PFS event" / ("Concordant PFS event" + "PFS by investigator but not by BICR").

- BICR confirmation rate in investigator declared non-progressions = ("Concordant no PFS event") / ("Concordant no PFS event" + "PFS by BICR but not by investigator").

b) Concordance between investigator and BICR assessments for Overall radiological objective response

The summary will include the frequency and percentage of Objective response assessments concordant between investigator and BICR reviews. The summary of concordant objective responses will further include the early discrepancy rate which is the frequency of investigator review objective responses declared before the BICR (≥8 weeks earlier and including objective responses declared by investigator but not BICR) as a proportion of all investigator review objective responses, and the late discrepancy rate which is the frequency of investigator review objective responses declared after the BICR (≥8 weeks later and including objective responses declared by BICR but not investigator) as a proportion of all discrepancies (including early and late discrepancies).

In addition the summary will include the frequency and percentage of discordant objective responses.

Similar summary of agreements and disagreements will be provided for Best objective response using the responses categories as in section 3.2.2.1. The overall response concordance rate will be calculated as the total number of agreements between investigator and BICR divided by the total sample size, at the level of each type of response (total number of agreements for each type of response/non-response).

3.2.3 Supportive efficacy endpoints

3.2.3.1 Percentage change in tumor size at all visits

For supportive purposes, percentage change in tumor size will also be derived for all scheduled tumor assessment visits (not just week 12 and week 28 [Initial Stage Cohorts] or 24 and 56 weeks [Second Stage Cohorts]).

3.3 Safety

Safety and tolerability will be assessed in terms of adverse events (AEs) (including serious adverse events [SAEs]), deaths, laboratory data, vital signs, electrocardiograms (ECGs) and exposure. 'On treatment' will be defined as assessments between date of first dose of olaparib and 90 days following the latest of the last dose/infusion of olaparib or MEDI4736 for the Initial Stage cohorts. In the Second stage cohorts it will include assessments between the date of first dose of MEDI4736+olaparib, or MEDI4736+olaparib+bevacizumab, and 90 following the last dose/infusion.

The Safety analysis set will be used for reporting of safety data.

3.3.1 General considerations for safety assessments

Time windows will need defining for any presentations that summarize values by visit. The following conventions should also apply:

- The time windows should be exhaustive so that data recorded at any time point has the potential to be summarized. Inclusion within the time window should be based on the actual date and not the intended date of the visit
- All unscheduled visit data should have the potential to be included in the summaries
- For laboratory and vital signs data (measured during combination treatment period only) the window for the visits following screening will be constructed in such a way that the upper limit of the interval falls half way between the 2 visits. For the Initial Stage cohorts the lower limit of the first post-screening treatment visit will be Day 2 (relative to first dose in the monotherapy period) and the lower limit of the first post-dose visit in the combination treatment period will be Day 2 (relative to first dose in the combination treatment period). As there is no monotherapy run-in for the Second Stage cohorts the first post-screening treatment visit and first post-

dose visit will both be defined as Cycle 1 Day 2. If an even number of days exists between 2 consecutive visits then the upper limit will be taken as the midpoint value minus 1 day.

- The visit windows for the monotherapy treatment period in the Initial Stage Cohorts (days relative to start of monotherapy treatment) are:

Visit (Day of Monotherapy treatment period)	Window (days)
8 (Week 2)	2-11
15 (Week 3)	12-18
22 (Week 4)	19-start of combination treatment

- The visit windows for the combination treatment period (days relative to start of combination treatment) in the Initial Stage Cohorts and for treatment period in the Second Stage Cohorts are:

Visit (Day of Combination Therapy)	Window
1	From -1 to 1
8	2-11
15	12-18
22	19-25
29	26-35
43	36-49
57	50-70
85	71-98
113	99-126
141	127-154
169	155-182
197	183-210
225	211-238
253	239-266
281	267-294
309	295-322
337	323-351
End-of-treatment	N/A

- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval)

- Listings should display all values contributing to a time point for a patient

- For visit based summaries:
  - If there is more than 1 value per patient within a time window then the closest value to the scheduled visit date should be summarized, or the earlier in the event the values are equidistant from the nominal visit date. The listings should highlight the value for that patient that went into the summary table, wherever feasible. Note: in summaries of extreme values all post baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is closest to the scheduled visit date
- For summaries at a patient level, all values should be included, regardless of whether they appear in a corresponding visit based summary, when deriving a patient level statistic such as a maximum
- Baseline will be defined as the last non-missing measurement prior to or on the day of the first dose of study treatment. Where safety data are summarized over time, study day will be calculated in relation to date of first treatment.

Missing safety data will generally not be imputed. However, safety assessment values of the form of "< x" (ie, below the lower limit of quantification) or > x (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or ">x" in the listings.

3.3.2 Adverse events

Adverse events and SAEs will be collected throughout the study. Summaries will be produced for treatment emergent AEs, defined as any AE reported from the date of first dose of study treatment and until 90 days after the latest of the last dose of either olaparib, MEDI4736 or bevacizumab. The Medical Dictionary for Regulatory Activities (MedDRA) dictionary (using the latest or current MedDRA version) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE Version 4.03).

Olaparib and MEDI4736 adverse events of special interest

Adverse events of special interest (AESIs) for olaparib and MEDI4736 are events of scientific and medical interest specific to the further understanding of the olaparib and MEDI4736 safety profiles. An AESI may be serious or non-serious.

For olaparib these AESIs have been identified in the CSP (Section 6.7.3) as the Important Potential Risks of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), new primary malignancy (other than MDS/AML), pneumonitis and diffuse alveolar damage.

For MEDI4736 these AESIs have been identified in the CSP (Section 6.7.5) as Diarrhea/colitis and intestinal perforations, rash/dermatitis, nephritis, pneumonitis, hepatitis, endocrinopathy, pancreatitis, myocarditis, myositis/polymyositis, neuropathy/neuromuscular toxicity and other inflammatory responses that are rare/less frequent with a potential immune-

mediated etiology but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events.

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

The preferred terms associated with these AESIs will be provided to IQVIA biostatistics team by AstraZeneca in form of an external spreadsheet and will be listed in a separate appendix by IQVIA.

Bevacizumab adverse events of special interest

For the purposes of this study, there are no AESIs for bevacizumab that are currently known.

Immune-related adverse events

Immune-related AEs (irAE) are identified by the investigator and recorded on the CRF, as defined in CSP section 6.7.6.

3.3.3 Treatment exposure

For patients in the Initial Stage Cohorts, exposure will be defined separately for the monotherapy phase of treatment, the combination phase of treatment and for entire study treatment as follows:

Total (or intended) exposure of MEDI4736

- Total exposure = last dose date where dose > 0 mg and volume infused >0 mL– first dose date + 28, where 28 days represents the duration of one cycle of MEDI4736.

Actual exposure of MEDI4736

- Actual exposure = intended exposure – total duration of dose delays, where intended exposure will be calculated as above.

Dose delay is the deviation of the actual to the planned dosing day (relative to previous dosing date). The first dose of MEDI4736 is planned on Day 29 of the olaparib treatment (ie after the first dose of olaparib) +/- 1 day. Each next dose of MEDI4736 is received by intravenous infusion Q4W +/-3 days.

Total (or intended) exposure of olaparib during the monotherapy phase

- Total exposure = last dose date where dose > 0 mg prior to date of first MEDI4736 infusion– first dose date + 1

Actual exposure of olaparib during the monotherapy phase

- Actual exposure = intended exposure – total duration of dose interruptions during the monotherapy phase, where intended exposure will be calculated as above.

Dose interruption = date when dose was restarted with dose > 0 mg – the date of the first day of dose interruption ie when dose = 0 mg. When dose was not restarted within the phase, no interruption is calculated.

Total (or intended) exposure of olaparib during combination treatment

- Total exposure = last dose date where olaparib dose > 0 mg after first MEDI4736 infusion– first dose date where olaparib dose >0mg on or after first MEDI4736 infusion + 1

Actual exposure of olaparib during the combination treatment

- Actual exposure = intended exposure – total duration of dose interruptions during combination treatment, where intended exposure during combination treatment will be calculated as above

Dose interruption of olaparib during combination treatment will be calculated as shown above.

Total (or intended) exposure of olaparib during the study

- Total (or intended) exposure = last dose date where olaparib dose > 0 mg– first olaparib dose date + 1

Actual exposure of olaparib during the study

- Actual exposure = intended exposure – total duration of dose interruptions during the study, where intended exposure will be calculated as above.

Dose interruption of olaparib during the study will be calculated as shown above.

Total (or intended) exposure of study drug (olaparib+MEDI4736) during the study

- Total (or intended) exposure = max(last dose date where olaparib dose > 0 mg + 1, last dose date where MEDI4736 dose > 0 mg and volume infused >0 mL + 28) – min(first olaparib dose date, first MEDI4736 dose date)

Actual exposure of study drug (olaparib+MEDI4736) during the study

- Actual exposure = intended exposure – total duration of any dose interruptions of olaparib and dose delays of MEDI4736 during the study, where intended exposure will be calculated as above.

Dose interruption of olaparib and delays of MEDI4736 during the study will be calculated as shown above.

For patients in the Second Stage Cohorts, exposure will be defined for entire study treatment as MEDI4736, bevacizumab and olaparib (study drug) all start of the same day (Day 1) +/-1 day. The total and actual exposure for bevacizumab will be calculated as follows:

Total (or intended) exposure of bevacizumab

- Total exposure = last dose date where dose > 0 mg and volume infused >0 mL– first dose date + 14, where 14 days represents the duration of bevacizumab dosing.

Actual exposure of bevacizumab

- Actual exposure = intended exposure – total duration of dose delays, where intended exposure will be calculated as above.

Dose delay is the deviation of the actual to the planned dosing day (relative to previous dosing date). The first dose of bevacizumab is planned on Cycle 1/Day 1. Each next dose of bevacizumab is received by intravenous infusion Q2W +/-3 days.

Total and actual exposures will be derived as follows:

Total (or intended) exposure of study drug during the study

- Total (or intended) exposure = max(last dose date where olaparib dose > 0 mg + 1, last dose date where MEDI4736 dose > 0 mg and volume infused >0 mL + 28, last dose date where bevacizumab dose > 0 mg and volume infused >0 mL + 14) – min(first olaparib dose date, first MEDI4736 dose date, first bevacizumab dose date)

Actual exposure of study drug during the study

- Actual exposure = intended exposure – total duration of any dose interruptions of olaparib and dose delays of MEDI4736 and bevacizumab during the study, where intended exposure will be calculated as above.

Dose interruption of olaparib and delays of MEDI4736 and bevacizumab during the study will be calculated as shown above.

The actual exposure calculations are based on duration and make no adjustment for any dose reductions that may have occurred.

Patients who permanently discontinue during a dose interruption

If a patient permanently discontinues study treatment during a dose interruption or dose delay, then the date of treatment discontinuation used in programming will the same as the date of last dose/last infusion recorded.

3.3.4 Dose intensity

For patients in the Initial Stage Cohorts: for olaparib dose intensity will be derived separately for the monotherapy phase, for the combination treatment phase and for the entire study treatment period. MEDI4736 dose intensity is only applicable to the combination treatment phase.

For patients in the Second Stage Cohorts: for MEDI4736, bevacizumab and olaparib dose intensity will be derived for the entire study treatment period.

Relative dose intensity (RDI) is the percentage of the actual dose intensity delivered relative to the intended dose intensity through to treatment discontinuation. Percentage intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose through to progression or treatment completion. Both will be derived using study treatment data up to 12 months or until the date of objective disease progression (if this is earlier) as defined by RECIST using the investigator site assessments. If the investigator considered that it was in the patient's best interest to continue study treatment past this time, this was not included in the derivation of dose intensity.

RDI and PID will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the earlier of progression (or death) or the actual last day of dosing and D is the intended cumulative dose up to the earlier of progression (or death) or the actual last day of dosing plus the protocol-defined post-dose rest period. The protocol-defined post-dose rest period is 27 days for MEDI4736 and 0 days for olaparib and 13 days for bevacizumab.

- PID = 100% * d/D, where d is the actual cumulative dose delivered up to progression (or death) or the actual last day of dosing (if treatment is completed) and D is the intended cumulative dose up to progression (or death) or the actual last day of dosing (if treatment is completed). D is the total dose that would be delivered, if there were no modification to dose or schedule.

3.3.5 Laboratory data

Laboratory data will be collected throughout the study, from screening to the follow-up visits as described in Tables 2, 3 and 3 of the CSP each of appendices G-M. The hematology and clinical chemistry variables to be collected are described in Sections 5.2.1.1 – 5.2.1.3 of the CSP. For derivation of post baseline visit values considering visit window and how to handle multiple records, derivation rules as described in Section 3.3.1 will be used.

Change from baseline in hematology and clinical chemistry variables will be calculated for each post-dose visit on treatment. CTC grades will be defined at each visit according to the CTC grade criteria using local or project ranges as required, after conversion of lab result to corresponding SI units. The following parameters have CTC grades defined for both high and

low values: Potassium, Sodium, Magnesium, Glucose and Corrected calcium so high and low CTC grades will be calculated.

Corrected calcium will be derived during creation of the reporting database using the following formulas:

Corrected calcium = Total calcium (mmol/L) + ([40 –Albumin (G/L)] x 0.02)

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

The maximum or minimum on-treatment value (depending on the direction of an adverse effect) will be defined for each laboratory parameter as the maximum (or minimum) post-dose value at any time.

Local reference ranges will be used for the primary interpretation of laboratory data at the local laboratory. Project reference ranges will be used throughout for reporting purposes. The denominator used in laboratory summaries of CTC grades will only include evaluable patients, in other words those who had sufficient data to have the possibility of an abnormality.

For example:

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

3.3.6 ECGs

Resting 12-lead ECGs will be recorded at screening, on Day 1 (either Day 1 of combination treatment phase for Initial Stage Cohorts or Cycle 1 Day 1 for Second Stage Cohorts), and as clinically indicated throughout the study.

All ECGs will be assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the electronic case report form (eCRF).

3.3.7 Vital signs

Vital signs data obtained up until 30 days from date of last dose of study treatment will be used for reporting. Change from baseline in vital signs variables will be calculated for each post-dose visit on treatment. For derivation of post baseline visit values considering visit window and to handle multiple records, derivation rules as described in Section 3.3.1 will be used.

3.4 ECOG performance status

Eastern Cooperative Oncology Group (ECOG) performance status will be recorded at screening, Day 1 (either Day 1 of combination treatment phase for Initial Stage Cohorts or Cycle 1 Day 1 for Second Stage Cohorts) and at timepoints as described in Table 4 of appendices G-M in the CSP.

3.5 Biomarkers

CCI [redacted]

3.6 Pharmacokinetics and immunogenicity

The olaparib sample bioanalysis will be performed by Covance and is the responsibility of the clinical pharmacology scientist at AstraZeneca. The plasma concentration data listings and summary will be the responsibility of the IQVIA biostatistics team, see section 4.2.14.

The creation of a dataset suitable for non-linear mixed effects modeling (NONMEM) will be the responsibility of the AstraZeneca programmer and pharmacometrician. The NONMEM analysis will be the responsibility of the pharmacometrician and clinical pharmacology scientist at AstraZeneca.

Samples for determination of MEDI4736 concentrations in serum will be analyzed by a designated third party on behalf AstraZeneca/MedImmune. The serum concentration data listings and summary will be the responsibility of the IQVIA biostatistics team, see section 4.2.14.

Samples for determination of bevacizumab concentrations in serum will be analyzed by a designated third party on behalf AstraZeneca/MedImmune for the ovarian cancer triplet cohort only. The serum concentration data listings and summary will be the responsibility of the IQVIA biostatistics team, see section 4.2.14.

3.6.1 Population PK and exposure-response/safety analysis

The olaparib plasma, MEDI4736 serum and/or bevacizumab serum concentration-time data may be analyzed by non-linear mixed effects modeling in order to quantify variability in the PK, identify demographic or pathophysiological covariates which may explain the observed variability and explore exposure-response relationships. The population PK/pharmacodynamic modeling methodology may be described in a modeling analysis plan and the results and conclusions will be reported separately from the CSR.

Concentration data listings and summary of the plasma (olaparib) and serum (MEDI4736 and bevacizumab) concentrations will be the responsibility of the Quintiles biostatistics team, see section 4.2.14.
Note: In this study, no non-compartmental PK analysis is planned and hence no PK parameters will be provided for olaparib, MEDI4736 and bevacizumab (only the concentration data).

3.6.2 Immunogenicity analysis

Immunogenicity will be assessed via MEDI4736 anti-drug antibodies (ADAs).

4. ANALYSIS METHODS

Generally, all analyses and reporting will be separated for each cohort.

4.1 General principles

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

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarized by the number of observations, mean, standard deviation, minimum, Q1, median, Q3, and maximum. For log transformed data it is more appropriate to present geometric mean, geometric standard deviation, coefficient of variation (CV), median, minimum and maximum. Categorical variables will be summarized by frequency counts and percentages for each category
- Unless otherwise stated, percentages will be calculated out of the population total and for each cohort
- For continuous data the mean, median and quartiles will be rounded to 1 additional decimal place compared to the original data. The standard deviation will be rounded to 2 additional decimal places compared to the original data. Minimum and maximum will be displayed with the same accuracy as the original data
- For categorical data, percentages will be rounded to 1 decimal place
- SAS® version 9.2 or higher will be used for all analyses.

Efficacy data will be summarized and analyzed by cohort on the FAS. Safety data will be summarized by cohort and across cohorts combined based on the safety analysis set. Study population, demography will be summarized by cohort and across cohorts combined based upon the FAS.

4.2 Analysis methods

All efficacy analyses will be performed on the FAS for each of the Initial and Second Stage Cohorts. In addition, for the initial stage *gBRCAm* ovarian cancer cohort and the BRCAm ovarian cancer expansion cohort, as a key sensitivity to the main analyses of PFS, DoR and ORR, analyses of these endpoints will be performed in those patients whose *gBRCAm* status is determined using a sponsor designated central laboratory (such as Myriad). Key demographics, patient and disease characteristics, and safety data including AEs and laboratory data, will also be presented for this subgroup. The subset of data reports to be repeated for patients with *gBRCAm* status determined by Myriad will be identified prior to database lock.

Table 4 Formal Statistical Analyses to be Conducted

Endpoint Analysed	Notes
DCR	**Initial Stage cohorts** Primary analysis – mean (90% credible interval), median, SD of the posterior distribution, exact 90% CI and 1-sided p-value INV @12wks - Initial Stage cohorts[a] Secondary analysis INV @28wks – Initial Stage cohorts[c] BICR @12 wks – Initial breast and ovarian cohorts[a] BICR @28wks – Initial breast and ovarian cohorts[c]
	Second Stage cohorts Primary analysis – mean (90% credible interval), median, SD of the posterior distribution, exact 90% CI and 1-sided p-value INV @24wks - triplet and doublet cohorts[b] Secondary analysis INV @24wks – Ovarian expansion cohort[b] BICR @24wks – Ovarian expansion cohort[b] INV @56wks - Second Stage cohorts[d] BICR @56wks – Ovarian expansion cohort[d]
ORR	**Initial Stage cohorts** Secondary analysis - 95% CI for the number of patients with a single visit response of CR or PR[e] INV – Initial Stage cohorts BICR – Initial breast and ovarian cohorts

Table 4 Formal Statistical Analyses to be Conducted

Endpoint Analysed	Notes
	Second Stage cohorts Primary analysis - 95% CI for the number of patients with a single visit response of CR or PR[e] INV - Ovarian expansion cohort Secondary analysis INV – Triplet and doublet cohorts BICR – Ovarian expansion cohort
PFS	**Initial Stage cohorts** Secondary analysis – KM plots and summary of number (percent) of patient experiencing an PFS event, and PFS rates every 6 months[f] INV – Initial stage cohorts BICR – Initial breast and ovarian cohorts
	Second Stage cohorts Secondary analysis – KM plots and summary of number (percent) of patient experiencing an PFS event, and PFS rates every 6 months[f] INV – Ovarian expansion, triplet and doublet cohorts BICR – Ovarian expansion cohort
OS	**Initial Stage cohorts** Secondary analysis – as for PFS[g] Initial stage cohorts
	Second Stage cohorts Secondary analysis – as for PFS[g] Ovarian expansion, triplet and doublet cohorts
TDT	**Initial Stage cohorts** Secondary analysis – as for PFS[h] Initial stage cohorts
	Second Stage cohorts Secondary analysis – as for PFS[h] Ovarian expansion, triplet and doublet cohorts
DoR	**Initial Stage cohorts** Secondary analysis – KM plots and median duration[i] INV – Initial stage cohorts BICR – Initial breast and ovarian cohorts

Table 4 Formal Statistical Analyses to be Conducted

Endpoint Analysed	Notes
	Second Stage cohorts Secondary analysis – KM plots and median duration[i] INV – Ovarian expansion, triplet and doublet cohorts BICR – Ovarian expansion cohort
%chg - Percentage change from baseline in tumor size	**Initial Stage cohorts** Secondary analysis – summary statistics[j] @ 12, 28wks – Initial Stage cohorts Supportive analysis @ all visits – Initial stage cohorts
	Second Stage cohorts Secondary analysis – summary statistics[j] @ 24, 56wks – Ovarian expansion, triplet and doublet cohorts Supportive analysis @ all visits – Ovarian expansion, triplet and doublet cohorts
Best percentage change from baseline in tumor size	**Initial Stage cohorts** Secondary analysis – summary statistics[j] Initial Stage cohorts
	Second Stage cohorts Secondary analysis – summary statistics[j] Ovarian expansion, triplet and doublet cohorts
BOR	**Initial Stage cohorts** Secondary analysis[k] INV – Initial Stage cohorts BICR – Initial breast and ovarian cohorts
	Second Stage cohorts Secondary analysis[k] INV – Ovarian expansion, triplet and doublet cohorts BICR – Ovarian expansion cohort

a See section 4.2.1 for details
b See section 4.2.2 for details
c See section 4.2.3 for details
d See section 4.2.4 for details
e See section 4.2.9 for details
f See section 4.2.5 for details
g See section 4.2.6 for details
h See section 4.2.7 for details
i See section 4.2.10 for details
j See section 4.2.11 for details
k See section 4.2.8 for details

4.2.1 Disease control rate at 12 weeks

The primary efficacy variable, DCR at 12 weeks for the Initial Stage Cohorts will be summarized (ie, number of patients, %) in each tumor group. Patients who do not complete the DCR assessment at week 12 (for example, due to drop out prior to the assessment) will be considered as a treatment failure. The mean and median of the posterior distribution along with the standard deviation and a 90% credible interval around the mean (based on the highest posterior density (Lee 1997)) will be presented. An exact 90% confidence interval (CI) and 1-sided p-value will also be presented.

If a patient has died before 12 weeks, DCR will be programmed as not applicable (NA) at 12 weeks.

If a patient progresses at 12 weeks or before, DCR will be programmed as 'No'.

CCI [redacted]

4.2.2 Disease control rate at 24 weeks

Disease control rate at 24 weeks is the primary efficacy variable for the Ovarian cancer triplet and doublet cohorts (primary) and secondary for the ovarian expansion cohort, and will be summarized and analyzed as per DCR at 12 weeks.

4.2.3 Disease control rate at 28 weeks

Disease control rate at 28 weeks, for the Initial Stage Cohorts, will be summarized and analyzed as per DCR at 12 weeks.

4.2.4 Disease control rate at 56 weeks

Disease control rate at 56 weeks, for the Second Stage Cohorts, will be summarized and analyzed as per DCR at 12 weeks.

4.2.5 Progression-free survival

Kaplan-Meier plots of PFS will be presented for each cohort. Summaries of the number and percentage of patients experiencing a PFS event, and the type of event (RECIST 1.1 or death) will be provided along with median PFS for each cohort.

The estimated PFS rates at 3 months, and then subsequently by every three months (at month 6, 9, 12, 15, 18, 21 and 24), will be presented for each cohort, using the Kaplan-Meier estimates at these timepoints. The PFS analysis will include median follow-up which is defined as time from the first dose of the study drug until the date of event or censoring.

Kaplan-Meier plots of PFS and the estimated PFS rates by CCI [redacted]

In addition, for the initial stage breast and ovarian cancer cohorts and the *BRCAm* ovarian cancer expansion cohort Kaplan-Meier plots of PFS and the estimated PFS rates will be presented by subgroup of prior lines of chemotherapy.

4.2.6 Overall survival

Overall survival will be summarized and presented in an identical manner to PFS.

4.2.7 Time to study treatment discontinuation or death

Kaplan-Meier plots of TDT will be presented for each cohort. Summaries of the number and percentage of patients experiencing a TDT event will be provided along with median time to study treatment discontinuation or death.

In addition, a swimmer plot will be presented for each cohort, grouped by best objective response and number of prior lines of chemotherapy.

4.2.8 Best objective response

Summaries for the Initial and Second Stage Cohorts, will be produced that present the number and percentage of patients for each category (CR, PR, SD, PD, NE, NED).

4.2.9 Objective response rate

The ORR will be summarized with 95% confidence intervals for the number of patients with a single visit response of CR or PR, for the Initial and Second Stage Cohorts.

CCI [redacted]

In addition, for the initial stage breast and ovarian cancer cohorts and the *BRCAm* ovarian cancer expansion cohort ORR and confirmed ORR will be summarized by subgroup of prior lines of chemotherapy.

A confirmed response of CR/PR means that a response of CR/PR is recorded at one visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.

4.2.10 Duration of response

Kaplan-Meier plots of DoR will be presented for each cohort. Median DoR (presented in months, where a month is defined as 365.25/12=30.4375 days) will also be summarized calculated from the Kaplan-Meier (KM) curve.

CCI [redacted]

In addition, for the initial stage *gBRCAm* breast and ovarian cancer cohorts and the *BRCAm* ovarian cancer expansion cohort Kaplan-Meier plots of DoR and median DoR will be presented by subgroup of prior lines of chemotherapy.

4.2.11 Percentage change in tumor size

The absolute values and percentage change in TL tumor size from baseline will be summarized using descriptive statistics and presented at all timepoints for each cohort. The best percentage change in TL tumor size from baseline, (where best change in TL size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction) will also be summarized and presented for each cohort.

Tumor size will also be presented graphically using waterfall plots for each cohort, to present each patient's best percentage change in tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease. Reference lines at the +20% and –30% change in tumor size levels will be added to the plots, which correspond with the definitions of progression and partial response respectively.

Additional waterfall plots showing percentage change in tumor size at specific timepoints may be produced if it is felt that these are warranted to provide greater clarity. The number and percentage of patients in each treatment group whose week 12 and week 28 (Initial Stage Cohorts) or 24 and 56 weeks (Second Stage Cohorts) data is imputed will also be presented.

In addition, a waterfall plot by subgroup of prior lines of chemotherapy will be presented for each cohort for best objective change from baseline in tumor size. Percentage change in target lesion size will be presented using spider plot grouped by prior lines of chemotherapy and also by best objective response.

4.2.12 Safety

Safety data will be summarized only. No formal statistical analyses will be performed on the safety data. All safety and tolerability data will be presented for each cohort and also for all cohorts combined using the safety population.

Summaries for safety data will be provided for entire study (not broken down by monotherapy treatment period and combination treatment period). Listings of AE data will include indication of the study treatment period of onset (monotherapy, combination treatment, follow-up, or post follow-up, ie more than 90 days post last-dose of study treatment).

The following sections describe the planned safety summaries for AEs, vital signs, laboratory parameters and ECG.

Adverse Events

All AEs, both in terms of current MedDRA preferred term and CTCAE grade, will be summarized descriptively by count (n) and percentage (%). The current MedDRA dictionary will be used for coding. Any AE occurring before study treatment start (Day 1; either the start of olaparib monotherapy for Initial Stage Cohorts or Cycle 1 Day 1 for Second Stage Cohorts)

will be included in the AE listings, but will not be included in the summary tables (unless otherwise stated). These will be referred to as 'pre-treatment'.

Adverse events observed up until 90 days following discontinuation of the latest of study treatment, without taking subsequent therapy into account, will be used for reporting of all of the AE summary tables. This approach is intended to capture more long-term safety events that may be related to study treatment.

Any data post 90 days last dose will be presented in a separate summary that presents any pre-treatment AEs or AEs starting more than 90 days after discontinuing study treatment.

All reported AEs will be listed along with the date of onset, date of resolution (if AE is resolved) and investigator's assessment of severity and relationship to study drug. Frequencies and percentages of patients reporting each preferred term will be presented (ie, multiple events per patient will not be accounted for apart from on the episode level summaries).

In addition, the following summary tables will be presented:

- Summary of number (%) of patients who had at least one AE in any category (Any AE, any causally related AE, any AE of CTCAE grade 3 or higher, any causally related AE of CTCAE grade 3 or higher, any AE with outcome = death, any causally related AE with outcome=death, any SAE (including events with outcome = death), any causally related SAE (including events with outcome = death), any SAE causing discontinuation of IP (olaparib, bevacizumab or MEDI4736)), any causally related SAE causing discontinuation of IP, any AE leading to discontinuation of investigational product (IP).

- In addition, a similar summary of number (%) of AEs in any category (episode level) will also be presented

- Summary of number (%) of patients who had at least 1 AE by preferred term, arranged by system organ class

- Summary of number (%) of patients who had at least 1 AE by system organ class and preferred term presented by maximum reported CTCAE grade

- Summary of number (%) of patients who had at least 1 AE with CTCAE grade 3 or higher by system organ class and preferred term

- Summary of number (%) of patients who had at least 1 causally related AE by preferred term

- Summary of number (%) of patients who died, summary of number (%) of patients with an AE with outcome = death. In addition, a listing of deaths, and a listing of key information for AEs with outcome = death will be presented

- Summary of number (%) of patients with SAEs by preferred term, arranged by system organ class. In addition, a listing of key information for SAEs, and a listing of key information for SAEs with outcome other than death will be presented
- Summary of number (%) of patients who had at least 1 causally related SAE by preferred term
- Summary of number (%) of patients with AESIs by the grouped terms defined in Section 3.3.2
- Summary of number (%) of patients with immune-mediated AEs by preferred term, arranged by system organ class
- Summary of number (%) of patients with infusion reaction AEs by preferred term, arranged by system organ class
- Summary of number (%) of patients who had an AE leading to discontinuation of any study treatment, by system organ class and preferred term. In addition, a listing of key information for AEs leading to discontinuation of study treatment will be presented.
- Summary of number (%) of patients who had an AE causally related to study treatment leading to discontinuation of study treatment, by system organ class and preferred term
- Summary of number (%) of patients with an AE leading to olaparib dose reduction / interruption, by system organ class and preferred term
- Summary of number (%) of patients with an AE leading to MEDI4736 dose interruption, by system organ class and preferred term
- Summary of number (%) of patients with an AE leading to bevacizumab dose interruption, by system organ class and preferred term

Summary of number (%) of patients who had an AE which started prior to study treatment or more than 90 days after last dose of study treatment, by system organ class and preferred term. Causally related AEs will be summarized separately by whether they are related to 'any treatment' (any out of olaparib, bevacizumab, MEDI4736) or each individual treatment olaparib, bevacizumab or MEDI4736.

AEs leading to discontinuation of IP will be summarized separately for discontinuation of olaparib, bevacizumab, MEDI4736, any treatment or all study drugs olaparib, MEDI4736 and bevacizumab as warranted. 'Any treatment' includes either or all study drugs (olaparib, MEDI4736 and bevacizumab).

Related AEs leading to discontinuation of IP will be summarized separately for discontinuation of olaparib, bevacizumab, MEDI4736, any treatment or all study drugs (olaparib, MEDI4736 and bevacizumab). 'Any treatment' includes either or all study drugs (olaparib, MEDI4736 and bevacizumab). 'Related' includes AEs related to either or all study drugs (olaparib, MEDI4736 and bevacizumab).

An overall summary of the number and percentage of patients in each category will be presented, as will an overall summary of the number of episodes in each category. In addition, a truncated AE table of most common AEs, showing all events that occur in at least 10% of patients in any cohort will be summarized by preferred term, by decreasing frequency. This cut-off may be modified after review of the data and depending on the number of patients in each cohort. When applying a cut-off (ie, x %), the raw percentage should be compared to the cut-off, no rounding should be applied first (ie, an AE with frequency of 9.9% will not appear if a cut-off is 10%). Summary statistics showing the time to onset and the duration of the first AE will also be presented as appropriate.

AEs will be assigned CTCAE grades (National Cancer Institute (NCI) CTCAE version 4.03) and summaries of the number and percentage of patients will be provided by maximum reported CTCAE grade, system organ class, preferred term and cohort.

A summary of deaths will be provided with number and percentage of, categorised as:

- Related to disease under investigation,
- AE outcome=death only,
- AE with outcome=death > 90 days after last treatment dose,
- Deaths > 90 days after last treatment dose, unrelated to AE or disease under investigation, and
- Patients with unknown reason for death.

Laboratory assessments

Data obtained up until the 90 days following discontinuation of study treatment, without taking subsequent therapy into account, will be used for reporting. This approach is intended to capture more long-term safety events that may be related to study treatment. Any data post 90 days last dose will not be summarized.

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

Scatter plots (shift plots) of baseline to maximum value on treatment (ie, on-treatment is defined as data collected between the start of treatment and 90 days following the last dose of study treatment) will be produced for: alanine aminotransferase (ALT), aspartate

aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, corrected calcium, magnesium, sodium, potassium, glucose, creatinine, and urea nitrogen.

Scatter plots (shift plots) of baseline to minimum value on treatment will be produced for: haemoglobin, lymphocyte (count, absolute); neutrophils (count, absolute); platelet count; albumin, total protein, corrected calcium, magnesium, sodium, potassium and glucose.

Box-plots of absolute values by week, and box-plots of change from baseline by week, will be presented for haemoglobin; neutrophil count, absolute; lymphocyte count, absolute; platelet count; AST; ALT; ALP; Total bilirubin; albumin; total protein; corrected calcium, sodium; potassium; creatinine and urea nitrogen.

Shift tables for laboratory values by worst CTC grade will be produced, and for specific parameters separate shift tables indicating hyper- and hypodirectionality of change will be produced. The laboratory parameters for which CTC grade shift outputs will be produced are:

- Haematology: Haemoglobin, Leukocytes, Lymphocytes, absolute count, Neutrophils, absolute count, Platelets
- Clinical chemistry: ALT, AST, Alkaline Phosphatase (ALP), Total bilirubin, Albumin, Magnesium – hypo and – hyper, Sodium – hypo and – hyper, Potassium – hypo and – hyper, Corrected calcium – hypo and – hyper, Glucose –hypo and – hyper, Bicarbonate, Creatinine.

For the parameters with no CTCAE grading that are listed in the CSP, shift tables from baseline to worst value on-treatment will be provided.

Hy's law

The following summaries will include the number (%) of patients who have:

- Elevated ALT, AST, and Total bilirubin during the study
    - ALT ≥3x –≤5x, > 5x –≤10x and > 10x Upper Limit of Normal (ULN) during the study
    - AST ≥3x –≤5x, > 5x –≤10x and > 10x ULN during the study
    - Total bilirubin ≥2x ULN during the study

Narratives will be provided in the CSR for patients who have ALT ≥3x ULN plus Total bilirubin ≥2x ULN or AST ≥3x ULN plus Total bilirubin ≥2x ULN at any visit.

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

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

ECGs

ECG data will only be listed.

Vital signs

Box plots for absolute values and change from baseline in systolic blood pressure, diastolic blood pressure, pulse rate, temperature, respiration rate and weight will be presented.

A shift table comparing baseline to maximum value on treatment will be summarized for each of the above listed vital signs except weight. The normal range for each parameter will be confirmed by Study Physician before database lock.

Time to Subsequent Therapy from discontinuation of MEDI4736

Descriptive summaries will be produced for time to subsequent therapy from discontinuation of study treatment.

Physical examination

Physical examination data will not be summarized.

4.2.13 ECOG performance status

All ECOG performance status data be summarized over time for the FAS.

4.2.14 PK Data

PK Summaries

All plasma olaparib concentration and serum MEDI4736 and bevacizumab concentration will be presented in data listings, and summaries will be presented for patients in the respective PK analysis set specific to each study drug. Data from patients excluded from the specific PK analysis set will be included in the data listings, but not in the summaries. Extra measurements (such as unscheduled or repeat assessments) will also not be included in summary tables, but will be included in patient listings.

Summaries of plasma concentration of olaparib, serum concentration of MEDI4736, serum bevacizumab (for the triplet cohort only) will be by study drug and by cohort.

Descriptive statistics will include n, arithmetic mean, standard deviation, coefficient of variation (%CV), geometric mean, geometric standard deviation and geometric %CV (%GCV), median, minimum and maximum values. The geometric mean is calculated as the

exponential of the arithmetic mean calculated from data on a log scale. The %GCV is calculated as $100 \cdot \sqrt{(\exp(s^2)-1)}$ where s is the standard deviation of the data on a log scale.

For all concentration data descriptive statistics will be presented in summary tables and by-patient listings as described in Table 5.

Table 5 Reporting accuracy of pharmacokinetic data

Variable / Parameter	Data	Mean	SD	Geometric Mean	Geometric SD	%CV & %GCV	Median	Min	Max
Plasma concentrations	As reported	+1sf	+1sf	+1sf	+1sf	1dp	+1sf	3sf	3sf

NA Not Applicable.
sf Significant figures.
dp Decimal places.

For descriptive statistics of plasma/serum concentrations, non-quantifiable (NQ) values of concentrations will be handled as follows:

- If, at a given time point, 50% or less of the plasma/serum concentrations are NQ, the mean, standard deviation, geometric mean, geometric standard deviation, %CV, and %GCV will be calculated by substituting the limit of quantification (LOQ) for values which are NQ

- If more than 50%, but not all, of the concentrations are NQ, the mean, geometric mean, standard deviation, geometric standard deviation, %CV, and %GCV will be reported as not calculable (NC)

- If all the concentrations are NQ, the geometric mean and mean will be reported as NQ and the standard deviation, geometric standard deviation, %CV, and %GCV as NC.

Specific PK summaries

Summaries of plasma/serum concentration data will be provided for each study treatment based on the respective PK analysis set and cohort:

- Olaparib PK from the initial stage cohorts: Plasma concentration summary of the pre-dose and 1 hr post dose samples taken on Day 1 and 22 during the olaparib monotherapy period and the pre-dose samples taken on Day 15 during the combination therapy phase

- Olaparib PK from the initial stage cohorts: Ratio of steady state pre-dose observed plasma concentration of combination treatment (combination therapy phase Day 15) and olaparib alone (olaparib monotherapy Day 22)

- Olaparib PK from the second stage cohorts: Plasma concentration summary of the pre-dose and 1 hr post dose samples taken on Day 15 during the combination therapy phase

- MEDI4736 PK from the initial stage cohorts: Plasma concentration summary of the pre-dose and end infusion taken on Day 1 and 113

- MEDI4736 PK second stage cohorts: Plasma concentration summary of the pre-dose and end infusion taken on Day 1 and 85

- Bevacizumab (for the ovarian triplet cohort): Plasma concentration summary of the pre-dose and end infusion taken on Day 1 and 85

Specific PK plots

In addition, the PK data will be explored graphically. The following plots will be presented separately for each cohort unless otherwise specified:

- Individual patient plots of concentration versus time. Time on the x-axis with linear scale, concentration on the y-axis with log scale. There will be 1 plot per patient per treatment/metabolite. ie, one plot for olaparib (alone and when dosed in combination with MEDI4736) and one plot for MEDI4736 and bevacizumab. Olaparib concentrations will appear as separate lines on the same page

- The above plots repeated with concentration on the y-axis with linear scale

- Geometric mean (± geometric standard deviation, if appropriate) or combined individual line plots of plasma concentration versus time. There will be one plot for olaparib (alone [Day 1 and Day 22, pre-dose and 1h post-dose] and when dosed in combination with MEDI4736 [Day 15]) and one plot for MEDI4736 and bevacizumab. The geometric mean will be presented for MEDI4736 and bevacizumab. Combined individual line plots for olaparib plasma concentration will appear with different symbols for the sampling dates and treatment (alone or when dosed in combination with MEDI4736) on same page. Time on x-axis with linear scale and concentration on y-axis with log scale

- The above plots repeated with concentration on y-axis with linear scale

- Scatter plot of olaparib steady state pre-dose observed plasma concentration on separate plots per cohort presenting ratio of combination treatment (combination phase day 15) and olaparib alone (olaparib monotherapy day 22) with patient number denoted on x-axis.

The geometric standard deviation will be derived as $\text{sqrt}(\exp(s^2)-1)*\exp(m)$, where m and s are the mean and standard deviation on the log scale (respectively).

4.2.15 Immunogenicity analysis

A summary of immunogenicity results will be provided showing the number and percentage of patients who develop detectable ADAs to MEDI4736/Bevacizumab based on the patients in the safety analysis set who have non-missing baseline ADA and at least one non-missing post-baseline ADA results. The output will be produced by the Quintiles biostatistics team.

4.2.16 sPD-L1 analysis

CCI

[redacted]

4.2.17 Demographic and baseline characteristics data

The following will be summarized for all patients in the FAS (unless otherwise specified) by cohort and also for all cohorts combined:

- Patient disposition (all patients including screening failures and reason for screening failure)
- Important protocol deviations
- Inclusion in analysis populations (all enrolled patients)
- Demographics (age, age group[<50, 50-< 65, ≥65 years], sex, race and ethnicity)
- Patient characteristics at baseline (height, weight, body mass index [BMI])
- Patient recruitment by country and centre
- Previous disease-related treatment modalities
- Number of lines of previous chemotherapy at baseline
- Previous disease-related chemotherapy treatments
- Previous lung cancer therapy
- Disease characteristics at screening/diagnosis* (ECOG performance status, primary tumor location*, histology type, tumor grade, AJCC stage*/FIGO stage*, BRCA

mutation type (breast and ovarian cancer cohorts only), best response to previous therapy and overall disease classification (metastatic or locally advanced)

- Extent of disease at baseline (site of disease by extent of disease)
- TNM classification at baseline
- Time from most recent disease progression to start of olaparib monotherapy (Initial Stage Cohorts) or combination treatment (Second Stage cohorts)

4.2.18 Concomitant medications

The following summaries will be produced for each cohort for the FAS:

- Disallowed concomitant medications during study treatment
- Allowed concomitant medications during study treatment.

The AZ drug dictionary (AZDD) will be used for concomitant medication coding.

4.2.19 Treatment exposure

The following summaries related to study treatment will be produced for the safety analysis set by cohort and also for all the Initial Stage cohorts combined:

- Total olaparib treatment duration during the monotherapy phase
- Actual olaparib treatment duration during the monotherapy phase
- Total olaparib treatment duration during the combination treatment phase
- Actual olaparib treatment duration during the combination treatment phase
- Total olaparib treatment duration during the monotherapy and combination treatment phases
- Actual olaparib treatment duration during the monotherapy and combination treatment phases
- Total MEDI4736 treatment duration during the combination treatment phase
- Actual MEDI4736 treatment duration during the combination treatment phase
- Total study drug treatment (olaparib+MEDI4736) duration
- Actual study drug treatment (olaparib+MEDI4736) duration
- Number of dose delays of MEDI4736 including reasons for delays

- Number of dose interruptions, number of dose reductions and duration of interruptions of olaparib. In addition, interruptions due to AEs and due to reasons other than AEs will be summarized separately
- Number of cycles of MEDI4736
- PID and RDI of olaparib (during each of monotherapy, combination and entire study treatment period)
- PID and RDI of MEDI4736.

The following summaries related to olaparib and MEDI4736 will be produced for the safety analysis set by cohort for all the Second Stage cohorts combined:

- Total olaparib treatment duration
- Actual olaparib treatment duration
- Total MEDI4736 treatment duration
- Actual MEDI4736 treatment duration
- Total study drug (olaparib+MEDI4736) treatment duration[a]
- Actual study drug (olaparib+MEDI4736) treatment duration[a]
- Number of dose delays of MEDI4736 including reasons for delays
- Number of dose interruptions, number of dose reductions and duration of interruptions of olaparib. In addition, interruptions due to AEs and due to reasons other than AEs will be summarized separately
- Number of cycles of MEDI4736
- PID and RDI of olaparib
- PID and RDI of MEDI4736.

[a] Applicable to ovarian expansion and doublet cohorts.

The following summaries related to bevacizumab will be produced for the safety analysis set for the triplet cohort:

- Total bevacizumab treatment duration
- Actual bevacizumab treatment duration

- Total study drug (olaparib+MEDI4736+bevacizumab) treatment duration
- Actual study drug (olaparib+MEDI4736+bevacizumab) treatment duration
- Number of dose delays of bevacizumab including reasons for delays
- Number of cycles of bevacizumab
- PID and RDI of bevacizumab

4.2.20 Subsequent Therapy

Post-discontinuation disease related anti-cancer therapy will be summarized (number of patients and regimens).

5. INTERIM ANALYSES

Within each of the Initial Stage Cohorts, an initial review of DCR and selected safety data will take place when 10 patients have been evaluated at 12 weeks. This review will be performed by the Safety and Tumor Cohort Review Group (STCRG).

Subsequent to the first 10 patients, DCR and safety data will be monitored every time 5 patients become evaluable, until the maximum sample is reached.

The primary responsibility of the STCRG is to regularly monitor the overall safety of patients in D081KC00001. The STCRG will provide recommendations regarding stopping, modifying or continuing the trial.

Further details on the STCRG and details of the summaries to be provided to the STCRG are provided in a separate document, the STCRG Operating Procedure. The subset of the data reports used for the STCRG is specified in Appendix A.

The safety of the “triplet” treatment regimen will be assessed once n=10 patients have reached 4 weeks of treatment in the ovarian cancer triplet cohort.

In addition, for ovarian cancer triplet and doublet cohorts, an initial review of DCR and selected safety data will take place when 15 patients have been evaluated at 24 weeks. Patients who do not complete the DCR assessment (for example, due to drop out prior to the assessment) will be considered as a treatment failure.

Subsequent to the first 15 patients, the DCR will be monitored again once 30 patients (full cohort) become evaluable.

In the ovarian expansion cohort, an initial review of ORR, PFS [including % progression free at landmark time points] and DoR will take place when all 80 patients have been followed for

24 weeks. Subsequent, the above listed efficacy endpoints will be analysed at Week 40, 56, 80 and 104 in the ovarian expansion cohort.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Best objective response (BOR), as described in Section 3.2.2.1 was added to the SAP after the CSP was signed off. The rationale for this is due to DOR becoming an endpoint of interest internally for ongoing MEDIOLA ovarian and breast cancer data, to assess whether the effects are seen longer term.

BICR DCR assessment at 12 weeks has been added as an endpoint for the initial stage breast and ovarian cohorts.

Removed any reference to confirmation of progression or response from the SAP and to modified RECISIT criteria as this is no longer planned to be incorporated in the efficacy analysis.

Modified section 2.2 to refer to documented evidence of a germline mutation in BRCA1 or BRCA2 by Myriad rather than confirmation as the testing is considered as an independent verification of the BRCA status. The note for ovarian expansion cohort for previously received 1 or 2 previous lines of chemotherapy, including ≥1 line of platinum-based therapy. is specified as: “NOTE: First-line agents include all agents administered to treat initial diagnosis, including adjuvant, neoadjuvant, maintenance, etc. Each subsequent line of chemotherapy includes all agents administered to treat relapse/progression, including maintenance. Switching drugs within a line of therapy to manage toxicities in the absence of PD does NOT count as a new line. Hormone therapy used as a single agent does not count as a line of chemotherapy (Investigators should discuss with the Study Physician if unsure regarding previous treatment lines when determining eligibility).”

7. REFERENCES

Lee 1997
Lee PM. Bayesian statistics: an introduction. 1997. New York: John Wiley & Sons.

Lee and Liu 2008
Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clin Trials. 2008;5(2):93-106.

APPENDIX A SUBSET OF DATA REPORTS USED FOR STCRG

Demography tables

Patient disposition (All patients)

Important protocol deviations (Full analysis set)

Demographic characteristics (Full analysis set)

Patient baseline characteristics (Full analysis set)

Previous disease-related chemotherapy treatments (Full analysis set)

Medical history (Full analysis set)

Extent of Exposure tables and listings

Tables:

Duration of exposure of olaparib during the monotherapy and combination treatment phases (Safety analysis set)

Duration of exposure of MEDI4736 (Safety analysis set)

Treatment interruptions and dose reductions for olaparib (Safety analysis set)

Delays of MEDI4736 (Safety analysis set)

Treatment cycles received of MEDI4736 (Safety analysis set)

Listings:

Study drug administration - olaparib (Safety analysis set)

Study drug administration - MEDI4736 (Safety analysis set)

Efficacy table and listings

Table:

Disease control at 12 weeks (Full analysis set)

Listings:

Disease control status (Full analysis set)

Progression events (Full analysis set)

Duration of RECIST response (Full analysis set)

Adverse Events tables

Adverse Events in any category - patient level (Safety analysis set)

Adverse Events in any category - episode level (Safety analysis set)

Adverse Events, patients with at least one adverse event by system organ class and preferred term (Safety analysis set)

Adverse Events by system organ class, preferred term and maximum reported CTCAE grade (Safety analysis set)

Adverse Events causally related to olaparib, by system organ class and preferred term (Safety analysis set)

Adverse Events causally related to MEDI4736, by system organ class and preferred term (Safety analysis set)

Listing:

Adverse events (1) (Safety analysis set)

Adverse events of special interest tables

Olaparib adverse events of special interest by CTCAE grade (Safety analysis set)

MEDI4736 adverse events of special interest by CTCAE grade (Safety analysis set)

Olaparib adverse events of special interest presented by outcome (Safety analysis set)

MEDI4736 adverse events of special interest presented by outcome (Safety analysis set)

Deaths tables

All Deaths (Full analysis set)

Adverse Events with outcome of death by system organ class and preferred term (Safety analysis set)

Serious adverse events tables

Serious adverse events by system organ class and preferred term (Safety analysis set)

Serious adverse events causally related to olaparib, by system organ class and preferred term (Safety analysis set)

Serious adverse events causally related to MEDI4736, by system organ class and preferred term (Safety analysis set)

Immune-mediated adverse events by system organ class and preferred term (Safety analysis set)

Labs, vital signs and physical examination tables and figure

Tables:

Haematology and clinical chemistry laboratory variables over time (Safety analysis set)

Haematology and clinical chemistry, change from baseline and percentage change from baseline (Safety analysis set)

Haematology laboratory data, box plot of absolute values (Safety analysis set)

Haematology and clinical chemistry, CTCAE grade change from baseline to maximum on treatment (Safety analysis set)

Vital signs variables over time (Safety analysis set)

Vital signs variables, change from baseline and percentage change from baseline over time (Safety analysis set)